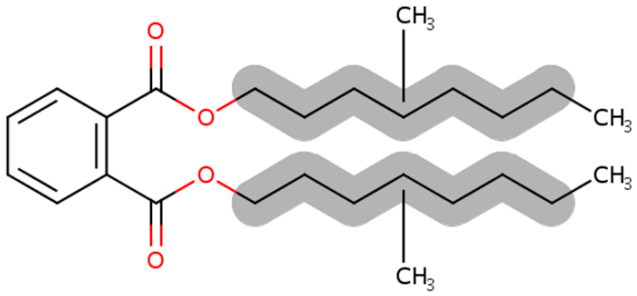
United States
Environmental Protection Agency

January 2025
Office of Chemical Safety and
Pollution Prevention

Data Quality Evaluation Information for Human Health Hazard Epidemiology for Diisononyl Phthalate (DINP)

Systematic Review Support Document for the Risk Evaluation

CASRNs: 28553-12-0 and 68515-48-0



January 2025

This supplemental file contains the data quality evaluation results for epidemiology data sources that met the PECO screening criteria and further filtering criteria for the *Human Health Hazard Assessment for Diisononyl Phthalate (DINP)*. EPA conducted data quality evaluation based on author-reported descriptions and results; additional analyses (*e.g.*, statistical analyses performed during data integration into the risk evaluation) potentially conducted by EPA are not contained in this supplemental file. EPA used the TSCA systematic review process described in the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (also referred to as '2021 Draft Systematic Review Protocol'). Any updated steps in the systematic review process since the publication of the 2021 Draft Systematic Review Protocol are described in the *Risk Evaluation for Diisononyl Phthalate (DINP) - Systematic Review Protocol*.

Table of Contents

Study Citation:	Bamai, Ait, Y., Araki, A., Nomura, T., Kawai, T., Tsuboi, T., Kobayashi, S., Miyashita, C., Takeda, M., Shimizu, H., Kishi, R. (2018). Association of filaggrin gene mutations and childhood eczema and wheeze with phthalates and phosphorus flame retardants in house dust: The Hokkaido study on Environment and Children's Health. Environment International 121(Pt 1):102-110.
Health Outcome(s) Assessed:	Lung/Respiratory- Wheeze, Non-cancer
Chemical:	Diisononyl Phthalate- Parent compound
HERO ID:	4829235

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	Recruitment is properly reported in this study. This cross-sectional study examined the associations between exposure to phthalates, phosphorus flame retardants (PFRs) and mite allergens in house dust with outcomes of age 7 eczema and wheeze in Japanese children. Participants were limited to children recruited for the Hokkaido study on Environment and Children's Health (Hokkaido cohort), with specific recruitment details reported in previous studies. Authors provide a detailed inclusion and exclusion criteria, which included children who reached the age of 7 by March of 2013, mothers who received and returned the follow-up questionnaire for 7-year old children, mothers who collected and returned household dust samples, and children who had cord blood FLG mutation assessments. There is uncertainty as this limited the initial 20,926 children enrolled in the Hokkaido study to 296 children, however the demographic and building characteristics of the children within the original cohort and those included within the current study were reported within Supplemental material and were comparable with respect to most factors other than building age, maternal smoking and household income.
Domain 2: Exposure Characterization			

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Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Low	This study assessed exposure to DiNP, DEHP, and DiBP through single household dust samples collected by the mothers of children (at age seven) in the Hokkaido cohort at the time of the questionnaire survey. Mothers were provided with a polyethylene dust bag and instructions for collecting the samples with a vacuum cleaner. These dusts were sieved with a 300 μm filter to removed any unwanted floor substances in the dust samples. Quantification of phthalates utilized gas chromatography–mass spectrometry (GC–MS) in signal-to-ion mode. Limits of quantification (LOQ) and percent of samples greater than the LOQ (100% for DiNP) were reported. Percent greater than the LOQ for DEHP (99.8%), DiBP (79%), DnBP (99.5%) and BBzP (95.2%) were reported. Median (25th, 75th percentile) concentrations were reported for DiNP as 63.91 μg/g (30.72, 152.50), DEHP as 1350.26 μg/g (940.94, 2254.32), DiBP as 4.50 μg/g (2.08, 8.30), DnBP as 47.45 μg/g (26.66, 89.35), and BBzP as 1.31 μg/g (0.38, 3.73). Quality assurance and quality control methods of sample analyses were described within previous work (Ait Bamai et al., 2013 (HERO ID 2215426). There is uncertainty in the use of a single dust sampling to represent the intensity, duration and potential peak phthalate exposures responsible for the initiation of the outcomes of interest. There is additional uncertainty in the use of household dust, rather than urinary metabolites, to assess exposure to phthalates which might have sources (dietary, personal care product use, etc.) other than through indoor household exposures. Finally, sampling was conducted only within the living room, rather than the child's bedroom, of the household, although the time children spend in living rooms typically is less than that of their bedrooms.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	The allergic disease outcomes in this study (eczema/wheeze) were defined via self-administered questionnaires, which the mothers filled out with information about the children at age seven. The study utilized the Japanese version of the validated International Study of Asthma and Allergies in Childhood (ISAAC) core questionnaire. Eczema was defined as "Having an itchy rash that comes and goes for at least 6 months" or "Having the aforementioned itchy rash at any time during the last 12 months", or "Having the aforementioned itchy rash affect one or several of the following areas: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes". Wheeze was determined by answering the question, "Has your child had wheezing or whistling in the chest in the last 12 months?". Authors note that while the ISAAC questionnaire has been validated, the severity of allergic outcomes cannot be captured in the questionnaire. There is uncertainty due to the use of parental report for classification of outcomes.
	Metric 3B:	Selective Reporting	High	Authors properly report analyses in the study, and are consistent in reporting results in text and tables.
Domain 4: Potential Confounding / Variability Control				

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Health Outcome(s) Assessed:	Lung/Respiratory- Wheeze, Non-cancer
Chemical:	Diisononyl Phthalate- Parent compound
HERO ID:	4829235

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	Medium	The strategy for selection of potential confounding factors was described as utilizing literature review and a greater than 10% change in the estimate of the model. Final models were adjusted for sex, household income, maternal smoking, paternal history of allergies, and filligrin (FLG) gene mutation. The method of obtaining data regarding confounding factors was not detailed but could be assumed to have been gathered through questionnaire at the time of sampling. Due to the cross-sectional design of the study, authors could not consider additional covariates, such as history of eczema, medical treatments, or use of moisturizer. Missing covariate data was not detailed. Distributions of confounding factors was presented across outcome categories.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Multivariate logistic regression was utilized to determine the relationships between phthalates, PFRs, or mite allergen levels and outcomes of eczema or wheeze. Results were presented as odds ratios with corresponding 95 percent confidence intervals. Gene-environment interactions were explored through the use of interaction terms and stratification to assess effects of filligrin (FLG) gene mutations. Sensitivity analyses were conducted excluding children who lived in their current house for less than 12 months.
	Metric 5B:	Sensitivity	Low	Although the sample size for the current study (n=296) was relatively low, phthalate levels were described as similar to or only slightly higher than previous studies. 100 percent of DiNP samples, 99.8% of DEHP samples, 99.5% of DnBP, 95.2% of BBzP and 79% of DiBP samples were greater than the LOQ. There is uncertainty in the use of a single vacuum dust sample within the living room rather than the child's bedroom, the use of household dust rather than urinary metabolites to assess exposure to phthalates which might have sources (dietary, personal care product use, etc.) other than through indoor household exposures, and the use of parental report for collection of data regarding outcomes of interest.

Additional Comments: This cross-sectional study included a relatively small sample size (n=296). There is uncertainty in the outcome ascertainment (eczema and wheeze within the past 12 months, assessed by parent report at child age 7) and exposure measurements assessed by a single parent-obtained dust vacuum sampling, rather than biomonitoring, within the living room of the home. Authors report no significant associations in models with continuous exposure variables between wheeze or eczema and DiNP, DEHP, DnBP, BBzP or DiBP, but an association between eczema and DiNP in house dust within categorical models [Figure 1, positive dose-response relationships were found between DiNP levels and eczema (Q1 vs. Q4 p for trend=0.060) overall, as well as among children without FLG mutation (Q1 vs. Q4 p for trend=0.011).

Overall Quality Determination — Medium

Study Citation:	Kishi, R., Ketema, R. M., Bamai, Y. A., Araki, A., Kawai, T., Tsuboi, T., Saito, I., Yoshioka, E., Saito, T. (2018). Indoor environmental pollutants and their association with sick house syndrome among adults and children in elementary school. Building and Environment 136:293-301.
Health Outcome(s) Assessed:	Lung/Respiratory- Sick home syndrome: self-reported weekly mucosal symptoms., Non-cancer
Chemical:	Diisononyl Phthalate- Parent compound
HERO ID:	4728476

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Low	This cross-sectional study in Sapporo, Japan examined associations between several indoor pollutants measured in the home environment and the prevalence of sick house syndrome. The sample was drawn from a large 2008 survey distributed to children in 12 Sapporo elementary schools (4408 of 6393 or 68.9% participation). This study included a total of 128 child dwellings (2.9% of the 4,408 surveyed), after excluding incomplete questionnaires, children no longer in elementary school, or households where a home visit could not be arranged. The analysis sample included 184 children under age 12 years (from 128 homes), and 283 family members aged >= 13 (parents, siblings) co-residing in 128 homes. One concern is that while the proportion of included vs. excluded dwellings was similar in terms of single vs. multi-family buildings (53.1% vs. 54.7%), there was a considerably higher prevalence of visible mold (76.6% vs. 35.2%) and condensation (71.9% vs. 52.5%) (Ait Bamai et al, 2014 HEROID 2215426). The proportion of children with atopic dermatitis (32.4% vs. 16.7%) was also higher than in the parent study (Ukawa et al, 2013 HEROID 2560019). 75% of participants reported a parental history of allergies. The authors did not discuss examining evidence of bias, such as whether factors associated with atopic dermatitis were similar in the parent study and analysis sample. However, there was no direct evidence of bias.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Several phthalate esters were measured in house dust samples. These included di(isobutyl) phthalate (DiBP), butyl benzyl phthalate (BBP), di(2-ethylhexyl) phthalate (DEHP), and di(isononyl) phthalate (DiNP), and di(n-butyl) phthalate (DBP). Dust was collected from floors and several surfaces >35cm (e.g., shelves, TV sets) in the living room. Children's bedrooms were not sampled. Dust was collected with hand-held vacuums carefully cleaned by ultrasound and with ethanol to avoid cross-contamination. Laboratory glass tubes and stainless-steel equipment were also ultrasonicated and rinsed in acetone (Ait Bamai et al, 2215426). Dust was weighed after removing unwanted substances (e.g., human and animal hair), samples extracted using acetone and analyzed using gas chromatography in selective ion mode. Recovery rates for phthalates ranged from 97% to 121.7%. Detection rates for the phthalates of interest in dust samples ranged from 93.0% to 100% for phthalates with the exception of BBP (68% in floor dust, 85.2% in multi-surface dust). The authors did not mention how values below LOD were handled: failure to impute values below LOD is a potential concern for BBP in floor dust. Variability in dust measures of all phthalates was high (e.g. for DiNP median, 25th-75th percentile 139, 66- 276 μg/g floor dust; 203, 99.7-443 μg/g dust in multi-surface dust).
Domain 3: Outcome Assessment				

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Health Outcome(s) Assessed:	Lung/Respiratory- Sick home syndrome: self-reported weekly mucosal symptoms., Non-cancer
Chemical:	Diisononyl Phthalate- Parent compound
HERO ID:	4728476

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Self-administered questionnaires were administered during visits for dust sampling in 2009 and 2010 (Ait Bamai et al, 2215426). Sick building syndrome (SBS) was characterized based on responses to published standardized questionnaires for children and adults developed in Sweden and translated to Japanese. Parents were asked to complete questionnaires for children aged <=12 years. Questionnaires asked about the frequency of three types of symptoms during the past three months: dermal (e.g., dry or itching hands, dry facial skin), mucosal (e.g., runny nose, eye irritation) and general (e.g., fatigue, headache) symptoms, reported as occurring weekly, sometimes, or never. Respondents were also asked whether they believed the symptoms were due to the home environment. Sick home syndrome was limited to symptoms that occurred weekly and were attributed to the home environment. Binary outcomes were defined based on reporting of at least one dermal symptom (6% and 4.6% of children and teens/adults), mucosal symptom (17.4% and 12.3%), or any type (including general, 20.6% and 15.1%). Given the small numbers of cases (N=11 to 38 and N=13 to 42 in children and teens/adults, variable severity based on number of symptoms was not considered. Questionnaires were administered in October–November to limit seasonal variation in symptoms. Validity and reliability in Japanese populations for the questionnaires and definitions used was not discussed (e.g., bias associated with allergies), but there is no evidence of error or bias.
	Metric 3B:	Selective Reporting	Medium	The authors described their primary (and secondary) analyses in the methods section and results were reported for all primary analyses.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Low	Confounders were selected a priori, and included age, gender, diagnosed allergies, parental history of allergies, a dampness index (0-5 for presence of condensation, moldy odor, visible mold, water leakage, bathroom humidity), and environmental tobacco smoke. Parental history of allergies was omitted from models for adults and adolescents, raising the possibility of residual confounding among adolescents. However, a sensitivity analysis excluded junior high school children from the adult/adolescent group. The authors stated that correlations among different categories of chemicals were low (data were not shown). However, the authors did not discuss confounding or modification by variables such as duration at the current residence, or by sociodemographic factors such as household income or parental education. Lower household income was associated, albeit not significantly, with increased odds of any vs. no symptoms in both children and adults [OR (95% CI) 2.12 (0.38,12.3) and 4.4 (0.63,35.1) for <5 vs >=8 million yen per year. Potential residual confounding is a concern.
Domain 5: Analysis				

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Health Outcome(s) Assessed:	Lung/Respiratory- Sick home syndrome: self-reported weekly mucosal symptoms., Non-cancer
Chemical:	Diisononyl Phthalate- Parent compound
HERO ID:	4728476

Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Low	Multivariate adjusted logistic regression was used to analyze associations between log-10 transformed exposure variables and reporting of any, dermal, or mucosal symptoms. Separate models were run for children <= age 12 years and for adolescents and adults combined. Non-independence of multiple respondents from the same household was not discussed (n=128 homes, 184 children and 283 adolescents/adults). Results of a sensitivity analysis excluding junior high participants (perhaps up to age 16) were described as not influencing significant associations; analyses excluding all adolescents were not mentioned. The number of hours per day spent at home (mean $\pm$ sd 15.2 $\pm$1.5 children, 15.0 $\pm$ 4.9 in teens/adults) was associated with dermal symptoms in children [odds ratio (95% CI) = 1.65 (0.96-2.92)] but was not discussed as a potential modifier. An important concern is that cleaning patterns –which may affect dust-based exposure measures – may be associated with the prevalence of symptoms attributed to contaminants in the home environment (reverse causation). For example, cleaning frequency was significantly higher in households with teens/adults with any symptoms. Associations with cleaning frequency were not shown for most exposures, but there was a negative correlation with DiNP. However, cleaning frequency was not evaluated as a confounder or modifier.
	Metric 5B:	Sensitivity	Medium	The sample size and number of cases were small. However, variability in exposure variables was large, and several associations were statistically significant, albeit not always in the hypothesized direction.

Additional Comments: This cross-sectional study in Sapporo, Japan examined associations between reported "sick house syndrome" symptoms during the last three months and measured indoor pollutants in household dust and air. Several phthalates, including DiNP, DiBP, DBP, BBP and DEHP, were measured in floor and surface dust. Sick home syndrome was characterized based on weekly symptoms in several domains - mucosa, dermal, and any including more general symptoms - that were attributed by participants to the house environment. The sample, selected from over 4,000 households in a parent survey, included 128 households; analyses included 184 children <= 12 years and 283 teen/adult residents. Associations between phthalates in dust and sick home syndrome outcomes were heterogeneous and largely non-significant. However, DiNP in floor dust was associated with significantly lower odds of mucosal symptoms in adolescents/adults. While there was no direct evidence of selection bias, the sample for this study included considerably more households with visible mold, condensation, and children with atopic dermatitis than the parent study. Residual confounding by factors such as socioeconomic status is also potential concern. Analyses did not examine whether including multiple residents from the same household was influential, or whether number of hours in the home modified associations. Finally, reverse causation cannot be ruled out. The authors did not discuss whether participant cleaning patterns, which may have affected dust levels and dust contaminant content, may have reflected efforts by participants to reduce their symptoms, and analyses were not stratified by cleaning frequency.

Overall Quality Determination — Low

Study Citation:	Wan, Y., North, M. L., Navaranjan, G., Ellis, A. K., Siegel, J. A., Diamond, M. L. (2021). Indoor exposure to phthalates and polycyclic aromatic hydrocarbons (PAHs) to Canadian children: the Kingston allergy birth cohort. Journal of Exposure Science & Environmental Epidemiology 32(1):69-81.
Health Outcome(s) Assessed:	Sensitization- Skin prick testing (allergy), Non-cancer
Chemical:	Diisononyl Phthalate- Parent compound
HERO ID:	7613166

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Study participants included 45 prenatally included children and 34 postnatally included children who were recruited from the KABC. The prenatally recruited children were identified in out-patient ObGyn clinics, family physician offices, midwifery clinics, and labor/delivery wards of Kingston hospital and were from 18 months to 3 years old. Post-natally recruited children ranged in age from 18 months to 14 years and consented to skin prick testing at hospital. Exclusion criteria were not discussed further and missing data also not described.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	DINP, DIDP, DBP, DiBP, DEHP, and BBP were measured in floor dust samples from the 79 children bedrooms that were collected from June 24, 2014 to February 25, 2015. Dust samples were collected from carpeted and uncarpeted floors in the center of a child's room using a conventional vacuum cleaner with a nylon bag inserted. Dust samples were dry sieved and extracted in 3 mL dichloromethane and repeated three times. Samples were analyzed using GS-MS. LOD for DINP is 1.04E+00 µg/g, for DIDP is 6.25E-01 µg/g, for DiBP is 5.48E-03 µg/g, for DBP is 5.90E-03 µg/g, for BBP is 5.71E-03 µg/g, and for DEHP is 2.47E-02 µg/g. Values below detection were substituted with half of the method detection limit.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Low	Authors reported performing skin prick tests on 34 postnatal children testing for 14 allergens and were conducted at the Kingston general hospital. Mothers were also tested with a panel of 9 common environmental allergens. No further information provided. Only 21% of children demonstrated a positive skin prick test with at least one of the allergens tested.
	Metric 3B:	Selective Reporting	Medium	No concerns for selective reporting. The authors described their primary analyses in the methods section and results were reported for all the analyses.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Confounders assessed including sex, household income (for SES), presence of mold, level of cigarette smoke exposure, maternal atopy, paternal history of allergy, prenatal smoking, gestational age, and breastfeeding status at 3 months of age. Confounders were included in the model if the OR changed by at least 10%.
Domain 5: Analysis				

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Study Citation:	Wan, Y., North, M. L., Navaranjan, G., Ellis, A. K., Siegel, J. A., Diamond, M. L. (2021). Indoor exposure to phthalates and polycyclic aromatic hydrocarbons (PAHs) to Canadian children: the Kingston allergy birth cohort. Journal of Exposure Science & Environmental Epidemiology 32(1):69-81.
Health Outcome(s) Assessed:	Sensitization- Skin prick testing (allergy), Non-cancer
Chemical:	Diisononyl Phthalate- Parent compound
HERO ID:	7613166

Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Medium	Logistic regression was conducted to assess association between phthalate exposure and allergic sensitization and 95% CIs shown. Log-transformed phthalate data was tested for normality, but concentrations were not normally distributed so performed analysis on untransformed data. Concentrations grouped into tertiles, but not defined further. Only performed statistical analysis on chemicals with more than 50% detection frequency. Results were considered statistically significant at $p<0.05$ but no significant results were found after adjusting for confounders. Missing data were not described but there seems to be no data missing.
	Metric 5B:	Sensitivity	Low	Very small sample size (n = 34) results in a low statistical power. Exposure range is adequate for DIDP from <MDL to 3350 ug/g, for DINP from 22 to 7330 ug/g, for DiBP from 3.06 to 942 ug/g, for DBP from 1.10 to 49.0 ug/g, for BBP from 4.12 to 75400 ug/g, and for DEHP from 26.7 to 1160 ug/g.

Additional Comments: Overall study quality is low because of the very small sample size of 34 children tested for allergies and homes tested for phthalates in dust. In addition, only 21% of the tested children displayed a positive skin prick testing, lowering the statistical power to detect any association between phthalate exposure and allergic sensitization. These limitations impact the results and validity of the study.

Overall Quality Determination Low

Study Citation:	Wang, C. W., Chen, S. C., Wu, D. W., Chen, H. C., Lin, H. H., Su, H., Shiea, J. T., Lin, W. Y., Hung, C. H., Kuo, C. H. (2021). Effect of dermal phthalate levels on lung function tests in residential area near a petrochemical complex. Environmental Science and Pollution Research 28(21):27333-27344.
Health Outcome(s) Assessed:	Lung/Respiratory- Spirometry measurements (FEV1, FVC, FEV1% predicted, FVC% predicted), Non-cancer
Chemical:	Diisononyl Phthalate- Parent compound
HERO ID:	7502437

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Participants were n=397 subjects from the Dalinpu Community for Health Care cohort (2016-2018, total n = 405). Participants were recruited from a village in close proximity to multiple industrial facilities. No information on recruitment methods or participation rates was provided. Inclusion criteria for the current study were: age > 20 years, willingness to receive spirometry testing and forehead skin wipes, and ability to complete provided questionnaires. Exclusion criteria were history of asthma, neuromuscular disease, abnormalities of the chest wall or pleura, or ascites. It is not clear if there were additional inclusion/exclusion criteria for the larger cohort. While there was a lack of information on some aspects of participant selection, the information provided does not raise substantial concerns about selection bias. Additionally, while study participants were members of a cohort study, the information provided suggests that this study was a cross-sectional analysis of baseline characteristics; as such, loss to follow-up is not a concern.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Dermal phthalates were measured using skin wipes of participants' foreheads. Measurements were obtained via linear ion trap mass spectrometry coupled to a TD-ESI source. The timing of sample collection relative to outcome measurement was not stated, although the participant recruitment text implies this was an analysis of baseline measurements taken in a larger cohort (i.e., a cross-sectional analysis with both exposure and outcome measured at the same time point).
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	The outcomes of interest in this study were lung function measurements (FEV1, FVC) assessed via spirometry. Spirometry testing by a single trained technician. Three consecutive measurements meeting quality criteria standards were taken for each participant, and the best measurement was recorded and included in analysis. Measurements were divided by reference standards to yield calculated endpoints of FEV1 and FVC percent predicted. No information was provided on whether participants or the technician were blinded as to exposure status, but this is not a major concern given the set of exposures and outcomes measured in this study.
	Metric 3B:	Selective Reporting	Medium	The authors described their primary and secondary analyses in the methods section and results were reported for all primary and secondary analyses.
Domain 4: Potential Confounding / Variability Control				

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Study Citation:	Wang, C. W., Chen, S. C., Wu, D. W., Chen, H. C., Lin, H. H., Su, H., Shiea, J. T., Lin, W. Y., Hung, C. H., Kuo, C. H. (2021). Effect of dermal phthalate levels on lung function tests in residential area near a petrochemical complex. Environmental Science and Pollution Research 28(21):27333-27344.
Health Outcome(s) Assessed:	Lung/Respiratory- Spirometry measurements (FEV1, FVC, FEV1% predicted, FVC% predicted), Non-cancer
Chemical:	Diisononyl Phthalate- Parent compound
HERO ID:	7502437

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	Medium	Potential confounders were selected based on prior literature as well as based on significant bivariate associations with the exposures and outcomes. Variables included in final regression models were: age, gender, BMI, smoking, exercise, and education. It appears that DiDP and DiNP models were also adjusted for face mask use, but it is not fully clear that this is the case from the description provided. It is also not clear whether models were adjusted for other measured phthalates. Study participants were recruited from an area with multiple industrial facilities, but no discussion of potentially co-occurring chemical exposures was provided.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	The association between each phthalate and the measured and calculated lung function outcomes was estimated using multiple linear regression. Phthalate concentrations were log-transformed prior to analysis due to a skewed distribution. Samples below the LOD were replaced with half of the LOD. Regression models were constructed for the whole study population (n=397) as well as for participants age 60+ only (n=54). No information on handling of missing values (if any) was provided. No sensitivity analyses were described.
	Metric 5B:	Sensitivity	Medium	The sample size was adequate (n=397). For all phthalates, a large proportion of samples were below the limit of detection (detection rate 47.1% for DiDP, 62.0% for DiNP, 39.0% for DBP, 48.9% for BBP, 50.6% for DEHP). However, among samples with detectable levels, the exposure range was large.

Additional Comments: This study of participants in the Dalinpu Community for Health Care cohort had an adequate sample size and used appropriate exposure assessment, outcome assessment, and analytic methods. Minor concerns include a lack of detail on some elements of the study design (e.g., the timing of exposure and outcome assessment) as well as the large proportion of samples below the LOD. In the full study population (n=397), a one-unit increase in log-transformed DiNP was associated with lower FEV1% predicted (β = − 2.17; 95% CI − 4.26, − 0.08), FVC (− 0.08; 95% CI − 0.15, − 0.02), and FVC% predicted (β = − 3.16; 95% CI − 5.21, − 1.10). There were no associations between DiDP and any of the outcomes in the full study population. DBP, BBP, and DEHP were inversely associated with FVC and FVC% predicted.

Overall Quality Determination Medium

Study Citation:	Sarigiannis, D. A., Papaioannou, N., Handakas, E., Anesti, O., Polanska, K., Hanke, W., Salifoglou, A., Gabriel, C., Karakitsios, S. (2021). Neurodevelopmental exposome: The effect of in utero co-exposure to heavy metals and phthalates on child neurodevelopment. Environmental Research 197:110949.
Health Outcome(s) Assessed:	Neurological/Behavioral- Cognitive development, language development, motor development, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-isononyl phthalate (MiNP)
HERO ID:	8351761

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Individuals in this analysis were a subset of participants from the Polish Mother and Child Cohort, which was established in 2007. Inclusion criteria for this broader cohort included: single pregnancy up to 12 weeks of gestation, no assisted conception, no pregnancy complications, and no chronic diseases as specified in the study protocol. Participants were followed-up with three times throughout the pregnancy, once during each trimester, and again after delivery. The subset of participants in the current study were 148 mother-child pairs "for whom most of the parameters of interest were available." No information is provided on which parameters were used to identify this subset, what proportion of the total study population the subset represents, or whether the subset is similar to the overall cohort. While information on the study population was limited, the information that was available does not raise serious concerns regarding selection bias.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Relevant phthalate metabolites (7-OH-MiNP, 7-oxo-MiNP, MEHP, and MiBP) were measured in maternal and child urine samples. Details of the exposure assessment are provided in Polanska et al. 2014 (HERO ID 2347467). Spot urine samples were collected from mothers during the 3rd trimester of pregnancy as well as from children at approximately 24 months of age. Phthalates were measured using HPLC-MS/MS. For 7-OH-MiNP, the LOD was 0.1 ug/L and 90% and 99% of samples were above the LOD for prenatal and postnatal samples, respectively. For 7-oxo-MiNP, the LOD was 0.03 ug/L and 62% and 74% of samples were above the LOD for prenatal and postnatal samples, respectively. For MEHP, the LOD was 0.03 ug/L and 66% and 14% of samples were above the LOD for prenatal and postnatal samples, respectively. For MiBP, the LOD was 0.03 ug/L and 86% and 97% of samples were above the LOD for prenatal and postnatal samples, respectively. Samples below the LOD were assigned a value of one half the LOD. Maternal samples were adjusted for creatinine. It is unclear whether single spot urine samples at two time points adequately represent exposure over the relevant time period. Postnatal samples taken at 24 months of age are taken after the first time point at which the outcome is assessed (1 year of age).
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	The outcome of interest was child neurodevelopment, assessed among children at ages 1 and 2 using the Bayley Scales for Infant Development (Bayley-III). Endpoints examined in this assessment were cognitive function, language development and motor development. The authors detail that these assessments were performed by a pediatrician as well as a psychologist/child development specialist. The Bayley Scales for Infant Development is a commonly used assessment tool for neurodevelopmental outcomes, and there are no major concerns of validity for this assessment tool.

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Study Citation:	Sarigiannis, D. A., Papaioannou, N., Handakas, E., Anesti, O., Polanska, K., Hanke, W., Salifoglou, A., Gabriel, C., Karakitsios, S. (2021). Neurodevelopmental exposome: The effect of in utero co-exposure to heavy metals and phthalates on child neurodevelopment. Environmental Research 197:110949.
Health Outcome(s) Assessed:	Neurological/Behavioral- Cognitive development, language development, motor development, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-isononyl phthalate (MiNP)
HERO ID:	8351761

Domain	Metric		Rating	Comments
	Metric 3B:	Selective Reporting	Medium	The results reported in the study align with the analyses described within the methods section. However, there is some lack of clarity around the number of phthalates exposures and exposure time points included in this environment-wide association study (EWAS). Table 1 provides a summary of associations only for exposures and exposure time points with statistically significant results.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Low	There are some concerns about potential confounding in this environment-wide association study (EWAS). While the authors discuss adjusting for gender in logistic regression models, they do not discuss or provide information on other potential confounders of the association between phthalates and child neurodevelopment. In the authors' discussion of the EWAS, they mention that one of the coefficients in the logistic regression model equation is "adjusted by other variables," but they are not described further. Given the limited information presented, the potential for residual confounding cannot be ruled out.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	The association between phthalate metabolites and child neurodevelopment was assessed as part of a larger environment-wide association study (EWAS). This analysis involved the development of logistic regression models to evaluate associations between environmental factors (including phthalates) and neurodevelopmental outcomes. The use of logistic regression suggests that outcomes were treated as dichotomous variables, but this is not described. The description of the analysis also suggests some continuous exposure variables may have been categorized, but the specific variables are not stated. The study states that non-monotonic relationships were detected using scatterplots, so "Hoeffding's D-statistics (Hoeffding, 1948) was used to examine a wide variety of dependence structures beyond merely the associations." The Benjamini-Hochberg step-down approach was used to false discovery rate (FDR) was used to estimate the false discovery rate. No information was provided on the handling of missing values (if any), although the study population was limited to mother-infant pairs with limited missing data. In general, methods appear appropriate but additional detail on modeling choices would provide greater confidence in this domain.
	Metric 5B:	Sensitivity	Low	The sample size was relatively small (n=148). The exposure distribution was reported in Polanska et al. 2014 (HERO ID 2347467). Mean (SD) 7-OH-MiNP = 4.5 (12.0) ug/L in prenatal samples, 9.3 (20.0) ug/L in postnatal samples. Mean (SD) 7-oxo-MiNP = 0.4 (0.4) ug/L in prenatal samples, 0.5 (1.4) ug/L in postnatal samples. Mean (SD) MiBP = 73.8 (141.9) ug/L in prenatal samples, 5.8 (8.8) in postnatal samples. Mean (SD) MEHP = 0.4 (0.5) ug/L in prenatal samples, 1.7 (14.7) in postnatal samples. There is some concern for limited sensitivity due to narrow exposure ranges particularly for 7-oxo-MiNP. There is also some concern about the high number of postnatal samples for MEHP that fell below the LOD.

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Health Outcome(s) Assessed:	Neurological/Behavioral- Cognitive development, language development, motor development, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-isononyl phthalate (MiNP)
HERO ID:	8351761

Domain	Metric	Rating	Comments

Additional Comments: This study examined a subset of mother-child pairs (n=148) from the Polish Mother and Child Cohort. Major concerns include the lack of information on how potential confounding was addressed and limited sensitivity due to relatively narrow exposure ranges. Other concerns include the relatively small sample size and the potential for selective reporting of only statistically significant results. The authors noted that exposure to DiNP, DEHP, and DiBP metabolites in child urine samples was associated with language development in the second year of life, but did not provide a quantitative measure of association.

Overall Quality Determination **Low**

Study Citation:	Jankowska, A., Polańska, K., Koch, H. M., Pälmke, C., Waszkowska, M., Stańczak, A., Wesołowska, E., Hanke, W., Bose-O'Reilly, S., Calamandrei, G., Garí, M. (2019). Phthalate exposure and neurodevelopmental outcomes in early school age children from Poland. Environmental Research 179(Pt B):108829.
Health Outcome(s) Assessed:	Neurological/Behavioral- Child behavioral and emotional problems at age 7 years, child cognitive and psychomotor development, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isononyl phthalate (cx-MiNP)
HERO ID:	5932896

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This cross-sectional included 250 mother-child pairs from the Polish Mother and Child Cohort study (REPRO_PL) recruited in maternity units 2007 with inclusion criteria specified as first trimester of healthy singleton pregnancy not assisted with reproductive technology and exclusion criteria of spontaneous abortions, women with serious chronic diseases like diabetes, hypertension, nephropathy, epilepsy, and cancer, as well as suspicion of serious child malformations., (HERO ID: 2092850 Polanska et al., 2009). The current study investigated phthalate exposure and neuropsychological outcomes in early school age children (age 7). The current assessment focused on n=250 out of 407 (61%) children from the REPRO_PL cohort. There were no statistically significant differences between the subset of children included and not included in current analyses except for age at examination (7.2 ± 0.23 years vs. 7.5 ± 1.1 years; $p < 0.05$).
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Child spot urine samples were collected at the REPRO_PL age 7 follow-up examination for analysis of 21 metabolites of 11 phthalate compounds using on-line high performance liquid chromatography coupled to tandem mass spectrometry (HPLC-MS/MS) with isotope dilution for quantification. Additional details regarding sampling results can be found within Gari et al., 2019 (HEROID 5540505). The current analysis focused upon 18 metabolites above the Limit of Quantification (LOQ) in more than 90% of analyzed samples. A total of 8 parent phthalates were considered for study. Limits of quantification were reported for each metabolite as 0.2 ug/L. Detection frequencies for each phthalate metabolite were reported in the referenced study (Gari et al., 2019 (HEROID 5540505)). Details regarding handling of concentrations below the limit of detection and sample storage prior to analysis were lacking.
Domain 3: Outcome Assessment				

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HERO ID:	5932896

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	High	Child behavioral and emotional problems at 7 years of age were assessed by the Strengths and Difficulties Questionnaire (SDQ) which was filled out by the mothers. The 25 items in the SDQ consist of five scales (conduct problems, hyperactivity/inattention problems, emotional symptoms, peer relationship problems and prosocial behavior) of five items each. In the current study, the outcomes were assessed both as continuous (score) variables and as dichotomized, according to a clinically relevant cut-off (normal vs. clinical). Child cognition and psychomotor development were assessed by a Polish adaptation of the Intelligence and Development Scales (IDS). The IDS allows assessing general intellectual ability (Fluid and Crystallized intelligence) and six developmental domains and included scales regarding cognition, mathematical skills, language skills, and psychomotor skills. Reliability and validity values of the IDS for Polish population were reported as satisfactory and the correlation with the Wechsler Intelligence Scale for Children (WISC-R) was about 0.80. These tests were administered by trained psychologists according to standard procedures.
	Metric 3B:	Selective Reporting	Medium	No significant concerns for selective reporting.

Domain 4: Potential Confounding / Variability Control

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HERO ID:	5932896

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	High	Potential confounders were defined a priori based upon previous literature. Details regarding source of data for potential confounders was lacking but assumed to be part of the REPRO_PL cohort procedures. The following variables related to child characteristics were initially considered: child's sex and age at the neurodevelopmental assessment, prenatal exposure to tobacco smoke (with 10 ng/ml as cut off point for cotinine level in maternal saliva) and postnatal tobacco smoke exposure (with 2,1 ng/ml as cut off point for cotinine level in child urine collected at examination), traumatic events (including death of close family member or parental divorce) experienced by the child (yes/no), child age when he/she has started school education (at age of 6 years/at age of 7 years), child body mass index (BMI) based on height and weight measured by trained staff at child examination, breastfeeding duration (0–2 months/2–6 months/>6 months) and number of siblings (0/1/≥2). The parental factors included were maternal age at childbirth, parental educational level at child examination (years of completed education: ≤9/10–12/>12), socio-economic status (SES) of the family (very poor and poor/good/very good), household status (parents living together/single parent household) and place of residence (urban/rural).Confounding factors within final analysis of Behavioral scales (SDQ) outcomes: childs sex and age at examination, age at school attendance, household status, SES, parental educational level, maternal age at birth, traumatic events, children's BMI, place of residence, number of siblings, exposure to tobacco during pregnancy and in children's at 7 years of age. Confounding factors within final analysis of Intelligence and development scales (IDS) outcomes: child's sex and age at examination, age at school attendance, examiner, household status, SES, parental educational level, maternal age at birth, breastfeeding duration, place of residence, number of siblings, exposure to tobacco during pregnancy and in children at 7 years of age. Additional covariates not considered included the quality of home environment and parental IQ, although SES and parental education were regarded as reliable proxies.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Multivariate linear regression models were used to assess the neurodevelopmental outcomes (both SDQ and IDS) and phthalate concentrations. Phthalate metabolite concentrations (ng/ml) were transformed into the natural logarithm form normalization. Details of alternative multivariate logistic modeling for SDQ outcomes with categorization of the outcome variables into normal versus clinical groups, as well as additional multivariate linear regression models using confirmatory factor analysis (CFA) was provided within supplemental materials. Consideration for effect modification by gender was lacking.

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Health Outcome(s) Assessed:	Neurological/Behavioral- Child behavioral and emotional problems at age 7 years, child cognitive and psychomotor development, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isononyl phthalate (cx-MiNP)
HERO ID:	5932896

Domain	Metric	Rating	Comments
	Metric 5B: Sensitivity	Medium	The analytic sample size (n=250) was adequate, but limited when considering potential for analyses of effect modification. Ranges of metabolites were adequate as reported in referenced study (Gari et al., 2019 (HEROID 5540505)). Given the short half-life of phthalates, it is unclear if a single spot urine at age 7 adequately represents the intensity, frequency and potential peak exposures responsible for initiation and development of the outcomes of interest.

Additional Comments: This cross-sectional study included a fairly large (n=250) sample size and relatively high-quality exposure assessment methodology of an extensive set of phthalate metabolites. Given the short half-life of phthalates, it is unclear if a single spot urine at age 7 adequately represents the intensity, frequency and potential peak exposures responsible for initiation and development of the age 7 behavioral and cognitive/psychomotor outcomes of interest. Overall high phthalate exposures were noted for this population of Polish children. Negative associations in peer relationship problems were noted for sumDiNP metabolites, and lower IDS scores were generally positively associated with higher phthalate concentrations.

Overall Quality Determination Medium

Study Citation:	Muerköster, A. P., Frederiksen, H., Juul, A., Andersson, A. M., Jensen, R. C., Glintborg, D., Kyhl, H. B., Andersen, M. S., Timmermann, G., C.A., Jensen, T. K. (2020). Maternal phthalate exposure associated with decreased testosterone/LH ratio in male offspring during mini-puberty. Odense Child Cohort. Environment International 144:106025.
Health Outcome(s) Assessed:	Reproductive/Developmental- hormone levels:testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), androstenedione (adione), 17 alpha-hydroxyprogesterone (17-OHP), dehydroepiandrosterone (DHEAS), testosterone/LH ratio, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: MiNP, MHiNP, MOiNP, MCiOP
HERO ID:	7978907

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	From 2010-2012, all pregnant women residing in Odense, Denmark (N=4017) were invited to participate in the Odense Child Cohort study; of these, 2874 were enrolled. 374 dropped out, and exclusions included twins (n=52), women without phthalate measurements (n=1605), offspring without hormone measurements (n=364), leaving 479 mother/child pairs with prenatal phthalate measurements and reproductive hormone measurements during mini-puberty. All pregnant women were invited; there is no indication that participation was influenced by knowledge of phthalate or hormone measurements, and participation is clearly described at all stages. However, there was a large proportion of enrolled participants with incomplete data who were subsequently excluded from the analysis; the authors do not address this or provide information comparing demographic or other factors between those who were included vs. excluded. Descriptive data on exposure and outcome is presented stratified by demographic characteristics.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Urine was obtained from mothers at gestational week 28 and analyzed for phthalate metabolites using standard methodology (enzymatic deconjugation, followed by solid phase extraction and liquid chromatography-tandem mass spectrometry.) Limits of detection (LODs) were provided. Urinary osmolality was measured by the freezing point depression method and was used to adjust for urinary dilution; this is a preferred method of adjustment. Phthalate measurements below LOD were not osmolarity adjusted but substituted with LOD divided by square root of 2. Exposure measurement would not be affected by knowledge of or presence of the outcome since outcome was measured in infants after birth.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	High	Hormone measurements from children at 3-4 months of age were analyzed using standard methodology (LH and FSH were analyzed with automated immunoassay system, and testosterone, androstenedione, 17-OHP, and DHEAS were analyzed by LC-MS/MS); LOQs were provided for each. Concentrations below LOD were substituted with LOD/2. Outcome measures unaffected by exposure knowledge since exposure was assessed from mothers prior to childbirth. Inter-day relative standard deviation was given and appeared acceptable.
	Metric 3B:	Selective Reporting	Medium	Results were reported consistently with analyses described in the methods section.
Domain 4: Potential Confounding / Variability Control				

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Health Outcome(s) Assessed:	Reproductive/Developmental- hormone levels:testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), androstenedione (adione), 17 alpha-hydroxyprogesterone (17-OHP), dehydroepiandrosterone (DHEAS), testosterone/LH ratio, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: MiNP, MHiNP, MOiNP, MCiOP
HERO ID:	7978907

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	Medium	Confounders were selected a priori based on their associations with reproductive hormones and phthalate exposure and included parity (nulliparous or multiparous), post-conceptional age (continuous variable), and individual age- and sex-specific standard deviation score for child BMI (BMI z-score, continuous variable). There was a detailed and thoughtful discussion of the rationale for including each of these. Analyses were also stratified by child sex, as there are hormonal differences by sex, and phthalates have been shown to have different affects based on sex.
Domain 5: Analysis				
	Metric 5A:	Analysis	High	When phthalate and hormone concentrations were non-normally distributed, medians and percentiles were compared and appropriate statistical tests for non-normally distributed data were used. Multiple linear regression was used to assess associations between prenatal phthalates and hormones in children at 3-4 months of age, controlling for confounders described previously. Hormone concentrations were adjusted using the natural logarithm when continuous and were also analyzed in tertiles. Statistical models were validated using several methods (residual plots, Whites test, checking for multicollinearity and linearity). Analyses were stratified by sex as discussed previously. Percent change and 95% CI were presented in tables. Percent of urine samples with phthalate metabolites and hormone measurements above LOD, as well as associations between hormones and confounders/descriptive variables (age at examination and post-conceptional age at examination, BMI, maternal age, parity, education, etch) are described in supplemental tables.
	Metric 5B:	Sensitivity	Medium	The study has a large sample size (479 mother/child pairs) and assessed a large number of phthalate metabolites and hormones. Prenatal measurements of phthalate exposure preceded outcome measurement of child hormone levels. The study measured hormone levels during mini-puberty, a brief time period during the first 6 months of postnatal life that may reflect later reproductive development. The study did not measure exposure during the male programming window during the first trimester (when androgens act to masculinize all components of the reproductive tract and allow their later complete development), so it is possible that assessing exposure during this key window may have been better, although it is unclear if this is the case in populations with low exposure (as this cohort was). A single spot urine sample was used to assess exposure, which has limitations, and women were fasting at the time of collection, which could impact phthalate measurements. Not all infants were assessed at 3-4 months at age, although that was adjusted for in the analysis.

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Health Outcome(s) Assessed:	Reproductive/Developmental- hormone levels:testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), androstenedione (adione), 17 alpha-hydroxyprogesterone (17-OHP), dehydroepiandrosterone (DHEAS), testosterone/LH ratio, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: MiNP, MHiNP, MOiNP, MCiOP
HERO ID:	7978907

Domain	Metric	Rating	Comments
Additional Comments:	This cohort study of 479 mother/child pairs assessed associations between prenatal phthalate metabolites measured around 28 weeks gestation and child reproductive hormone levels measured around 3-4 months of age. The study was strong in all components, with some limitations, and found that maternal exposure to the phthalate MnBP was association with significantly reduced testosterone in boy at mini-puberty, while maternal exposure to anti-androgenic phthalates (sum of MBP and DiNP metabolites) was associated with a significantly reduced testosterone/LH ratio in boys at mini-puberty; exposure to MnBP was associated with an increase in DHEAS, and the sum of DiNP metabolites was associated with a decrease in FSH in boys at mini-puberty. No clear pattern was found in girls.		

Overall Quality Determination Medium

Study Citation:	Henrotin, J. B., Feigerlova, E.,va, Robert, A., Dziurla, M., Burgart, M., Lambert-Xolin, A. M., Jeandel, F., Weryha, G. (2020). Decrease in serum testosterone levels after short-term occupational exposure to diisononyl phthalate in male workers. Occupational and Environmental Medicine 77(4):214-222.
Health Outcome(s) Assessed:	Reproductive/Developmental- Total testosterone (TT), free testosterone (FT), estradiol (E2), follicle stimulating hormone (FSH), and leutenizing hormone (LH), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: MiNP: Mono-oxo-isononyl phthalate (oxo-MiNP), Mono-hydroxy-isononyl phthalate (OH-MiNP), Mono-carboxy-isononyl phthalate (cx-MiNP)
HERO ID:	7978431

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	Male French factory workers from six factories in the plastics industry were recruited from 2015-2018. The six factories were located between four different French regions: North, Center, Paris, and South-East. Authors provided details regarding the specific factory productions (PVC compounds, plastisol coating on bottles, coated fabrics). Authors provided clear inclusion criteria: " aged 18 years and older; do not have any disease related to low serum testosterone level; have been working for at least 1year; a French speaker; and did not work at night (00:00–05:00) in the 10 days before the first blood sample was taken." Participation rate and excluded participant rates were not reported, resulting in a medium/adequate rating. Overall, 97 workers met the inclusion criteria.
Domain 2: Exposure Characterization			

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Chemical:	Diisononyl Phthalate- Metabolite: MiNP: Mono-oxo-isononyl phthalate (oxo-MiNP), Mono-hydroxy-isononyl phthalate (OH-MiNP), Mono-carboxy-isononyl phthalate (cx-MiNP)
HERO ID:	7978431

Domain	Metric	Rating	Comments
	Metric 2A: Exposure Measurement	High	Di-isononyl phthalate (DINP) and di-2-ethylhexyl phthalate (DEHP) exposure was measured by urinary sampling of mono-4-methyl-7-oxo-octyl phthalate (OXO-MINP), mono-4-methyl-7-hydroxy-octyl phthalate (OH-MINP), mono-4-methyl-7-carboxyheptylphthalate (CX-MINP) and mono(2-ethylhexyl) phthalate (MEHP), mono (2-ethyl- 5-hydroxyhexyl) phthalate (OH-MEHP), mono(2-ethyl- 5-oxohexyl) phthalate (OXO-MEHP) and mono(2-ethyl- 5-carboxypentyl) phthalate (MCEPP) . Workers recruited from the six plastics factories provided two urinary samples, one pre-shift at the beginning of the work week (with two work-free days before collection), and a post-shift sample after three days of working. This design was used to reflect within-subject changes in occupational exposure for the short longitudinal study. Urinary samples were collected in 250mL bottles and sent for analysis. Urinary DINP and DEHP metabolites were measured by two-dimensional high-performance liquid chromatography coupled with tandem mass spectrometry (HP-LC/MS-MS). Workers were described as wearing gloves while handling, mixing liquid plasticizer but working without special personal protective equipment for all other activities. All factories were described as equipped with local exhaust systems, however workstation-specific exhaust was not detailed. Two study groups of participants with DINP metabolite urinalysis were identified. The ‘exposed’ group (n=55) was defined as workers exposed to DINP at the workstation for the 3 days of the follow-up period. The group ‘less exposed’ (n=42) was defined as workers not directly exposed to DINP at the workstation (those working in administration offices). Limits of detection were reported. DINP metabolites were detected in 97% of the samples from the ‘exposed’ group and 90.2% of the samples from the ‘less exposed’ group. Although pre- and post-shift urine sampling for exposure was conducted, given the relatively short half-life of phthalates it is unclear if the concentrations adequately represented the intensity and potential peak exposures responsible for initiation of outcomes of interest.

Domain 3: Outcome Assessment

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HERO ID:	7978431

Domain	Metric	Rating	Comments
	Metric 3A: Outcome Ascertainment	Medium	Total and free testosterone levels were analyzed from non-fasting blood samples collected. Each worker provided two blood samples, (1) on the first day and (2) on the fourth day, each between 7:45 and 11:00. Serum levels of total testosterone (TT), oestradiol (E2), follicle-stimulating hormone (FSH) and luteinising hormone (LH) were measured by the University Hospital Laboratory of Nancy (France), and free testosterone (FT) levels were measured by a commercial laboratory in Nancy. The radioimmunoassay technique was used to measure TT, E2, FSH, LH and FT. Limits of detection (LOD) and coefficients of variation (CV) were reported. Limits of detection (LOD) and coefficients of variation (CV) were 0.05ng/mL and 4.3% for TT, 20pg/mL and 21% for E2, 0.2 mUI/mL and 4.3%–5.6% for FSH, 0.2 mUI/mL and 4.3%–6.4% for LH, and 0.1pg/mL and 5.7%–11.4% for FT. Indirect estimation of aromatase activity was calculated as the ratio of TT to E2." Serum bone turnover biomarkers of bone formation (serum procollagen type I N propeptide, P1NP) and one marker of bone resorption (serum C terminal cross-linking telopeptide of type I collagen, CTX) were also measured. Sexual health was quantified using the International Index of Erectile Function (IIEF-5), and Androgen Deficiency in Aging Males (ADAM) instruments. Authors note some uncertainty with the methods used to measure free testosterone (radioimmunoassay technique) as alternative methods such as dialysis or ultrafiltration are known to present more accurate levels.
	Metric 3B: Selective Reporting	Medium	Results are well reported by study authors. There is consistency in the reporting of the results throughout the abstract, results and discussion section.
Domain 4: Potential Confounding / Variability Control			
	Metric 4A: Potential Confounding	Medium	Confounders related to serum testosterone levels were sourced from previous literature: age $\geq$50 years and abdominal diameter ($\geq$102cm). As the study divided participants into "exposed" and "less exposed" groups, authors included an "exposed" binary variable for DEHP adjustments. Overall, the study provided adjustments in analyses for important confounders. Authors excluded a number of covariates following a sensitivity analysis: a given factory, hard physical work, some lifestyle habits, some medical history, age $>$50 years, abdominal perimeter $>$102cm and summer period.
Domain 5: Analysis			

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Study Citation:	Henrotin, J. B., Feigerlova, E.,va, Robert, A., Dziurla, M., Burgart, M., Lambert-Xolin, A. M., Jeandel, F., Weryha, G. (2020). Decrease in serum testosterone levels after short-term occupational exposure to diisononyl phthalate in male workers. Occupational and Environmental Medicine 77(4):214-222.
Health Outcome(s) Assessed:	Reproductive/Developmental- Total testosterone (TT), free testosterone (FT), estradiol (E2), follicle stimulating hormone (FSH), and leutenizing hormone (LH), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: MiNP: Mono-oxo-isononyl phthalate (oxo-MiNP), Mono-hydroxy-isononyl phthalate (OH-MiNP), Mono-carboxy-isononyl phthalate (cx-MiNP)
HERO ID:	7978431

Domain	Metric	Rating	Comments
	Metric 5A: Analysis	High	The difference in serum testosterone between T1 and T2 as an outcome with the difference in DINP metabolite T1 and T2 as exposure was examined within linear mixed regression models nested within a factory variable cluster. To investigate the low dose effects, differences in DINP metabolites according to a cut-off of "less than median" or "greater than or equal to median" were also analyzed. Exposed binary variables were adjusted within models for each DEHP metabolite. Sensitivity analyses excluded variables of factory, hard physical work, lifestyle habits, some medical history, age greater than 50 years, abdominal perimeter greater than 102 cm and summer period. Additional analyses were described as conducted examining the effect of oxo-MINP on FSH and LH, on TT:E2, and on P1NP and CTX. Indicators of sexual health as measured by the IIEF-5 and ADAM were also compared between exposed and less exposed groups.
	Metric 5B: Sensitivity	Medium	Authors note that the sample size is small due to the limitations in finding factories and workers, which introduces bias into the results. The longitudinal design is appropriate for measuring short-term occupational exposures to oxidized DiNP metabolites, which have short half-lives. Although pre- and post-shift urine sampling for exposure was conducted, given the relatively short half-life of phthalates it is unclear if the concentrations adequately represented the intensity and potential peak exposures responsible for initiation of outcomes of interest.

Additional Comments: This occupational short longitudinal study observed the three-day changes in levels of total and free testosterone and oxidized MiNP exposure in male factory workers. Limitations included a smaller sample size and potential bias through the measurement methods of free testosterone. The study also had strength in testing for robustness with multiple sensitivity analyses and knowledge that the workers selected controlled their own work, increasing the statistical power of the study.

Overall Quality Determination Medium

Study Citation:	Zettergren, A., Andersson, N., Larsson, K., Kull, I., Melen, E., Georgelis, A., Berglund, M., Lindh, C., Bergstrom, A. (2021). Exposure to environmental phthalates during preschool age and obesity from childhood to young adulthood. Environmental Research 192:10249-10249.
Health Outcome(s) Assessed:	Nutritional/Metabolic- Obesity: overweight/obesity, body mass index (BMI), waist circumference (WC), body fat %, and trunk fat %., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono(oxo-iso-nonyl) phthalate (MOiNP); Mono carboxyisooctyl phthalate (MCiOP); Mono(hydroxy-iso-nonyl) phthalate (MHINP)
HERO ID:	7978414

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Participants in this longitudinal study are a sub-sample of the Swedish birth cohort, BAMSE (Swedish abbreviation for Children, Allergy, Milieu, Stockholm, Epidemiology) which enrolled 4,089 participants born in Stockholm in 1994-1996. Follow-up occurred at 2 months, and at 1, 4, 8, 12, 16, and 24 years of age. This analysis includes a sub-sample of 100 participants selected for a time trend analysis of preschool phthalates exposure. Eligible BAMSE participants had questionnaires at baseline, 4 and 16 years, and urine samples at age 4y (n=720); selection for urine sampling at age 4 was based on allergy prevalence (n=933, 684 with symptoms). The sub-sample of 50 girls and 50 boys was selected to have an equal number of each sex with/without symptoms. The sample was similar to the parent cohort in terms of parental occupation, breastfeeding duration, and maternal smoking in pregnancy. Attrition was modest (n=100 at 4 and 16y, n=91 at 8y, n=71 at 24y). There was no evidence of biased selection (i.e., associated with both phthalates and obesity). The authors stated there was no significant difference in phthalate concentrations for participants with vs without allergy symptoms (data not shown). The authors did not discuss whether there was an association between allergy prevalence and obesity measures within the sub-sample, as observed in some childhood studies.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	DiNP metabolites mono(hydroxy-isononyl) phthalate (MHiNP), mono(oxo-isononyl) phthalate (MOiNP) and mono(carboxy-isooctyl) phthalate (MCiOP) were measured in a single urine sample collected at age 4 years. The molar sum of the three metabolites was used as a measure of DiNP; this measure was converted back to ng/ml multiplying by the average molar mass of each metabolite. Liquid chromatography tandem mass spectrometry (LC-MS/MS) was used to analyze the samples. The laboratory conducting analyses participates in a European QA/QC and is certified as qualified for analysis of these phthalate metabolites. The authors stated that 100% of samples were above detection limits. Specific gravity was used to correct for urine dilution. The authors acknowledged that due to high within-person variability and short half-lives, use of a single spot urine sample collected at random times of day may to some extent misclassify habitual DiNP exposure. However, there was no evidence of differential misclassification.
Domain 3: Outcome Assessment				

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Study Citation:	Zettergren, A., Andersson, N., Larsson, K., Kull, I., Melen, E., Georgelis, A., Berglund, M., Lindh, C., Bergstrom, A. (2021). Exposure to environmental phthalates during preschool age and obesity from childhood to young adulthood. Environmental Research 192:10249-10249.
Health Outcome(s) Assessed:	Nutritional/Metabolic- Obesity: overweight/obesity, body mass index (BMI), waist circumference (WC), body fat %, and trunk fat %., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono(oxo-iso-nonyl) phthalate (MOiNP); Mono carboxyisooctyl phthalate (MCiOP); Mono(hydroxy-iso-nonyl) phthalate (MHINP)
HERO ID:	7978414

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Outcomes of overweight/obesity at ages 4-24 and body mass index (BMI), waist circumference (WC), body fat % and trunk fat % at age 24 years were assessed for analysis with age 4 urinary phthalate metabolite concentrations. Overweight/ obesity ages 4-24 based on BMI was assessed using repeated measures over time; at age 24 y additional measures were obtained. Height and weight measures were obtained at ages 4, 8, 16, and 24. The International Obesity Task Force (childhood) and WHO standards (age 24y) were used to classify participants as overweight and obese. Height was measured to the nearest 0.1 cm, and weight to the nearest 0.1 kg. At age 24y, waist circumference was measured (nearest 0.1cm) and body fat percentages (total and trunk fat) were estimated using bioelectrical impedance analysis (BIA, Tanita MC-708 MA P). The use of multiple. longitudinal BMI measures, and of more direct measures of body fat amounts and distribution at age 24y, are an important strength. However, BIA based estimates of body fat are not a gold standard; estimates are based on prediction equations that may have substantial error.
	Metric 3B:	Selective Reporting	Medium	The authors presented all analyses reported in the methods and results sections adequately.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Covariates were identified based on previous literature. Models exploring the association between phthalate metabolite levels at age 4 years with repeated measures of BMI category outcomes of overweight/obesity versus thin/normal were adjusted for gender, baseline parental socioeconomic status (SES) based on parental education and occupation, maternal smoking during pregnancy, exclusive breastfeeding duration, total energy intake at 8 years, participation in organized physical activity at 8, 16 and 24 years, puberty stage at 16 years, smoking at 16 and 24 years and urinary cotinine. Associations between urinary phthalate concentrations and BMI, WC, body fat % and trunk fat % at age 24 years were adjusted for gender, parental socioeconomic status, maternal smoking during pregnancy, duration of exclusive breastfeeding, physical activity and smoking at age 24 years and urinary cotinine. Information on potential confounders came from questionnaires completed by both parents and participants. Models did not adjust for allergy, which may be a downstream effect of obesity. The authors noted residual confounding by dietary factors at age 4 (the time of exposure assessment) as a limitation. Other potential sources of residual confounding include changes in SES over time and measures of diet quality at age 8y beyond energy intake (measured with error in food frequency questionnaires). Co-exposure confounding by other phthalates was not evaluated, however, the authors analyzed both individual DiNP metabolites and their sum.
Domain 5: Analysis				

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Study Citation:	Zettergren, A., Andersson, N., Larsson, K., Kull, I., Melen, E., Georgelis, A., Berglund, M., Lindh, C., Bergstrom, A. (2021). Exposure to environmental phthalates during preschool age and obesity from childhood to young adulthood. Environmental Research 192:10249-10249.
Health Outcome(s) Assessed:	Nutritional/Metabolic- Obesity: overweight/obesity, body mass index (BMI), waist circumference (WC), body fat %, and trunk fat %., Non-cancer
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HERO ID:	7978414

Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Medium	Descriptive data on participant characteristics, outcome measures, and phthalates exposures were presented. Analysis methods were appropriate. Phthalate metabolite measures were log-transformed for analyses. Associations between phthalates exposures at age 4y and repeated measures of overweight/obesity status were analyzed using generalized estimating equations with a logit link. Exposure by age interaction terms were used to estimate age-specific associations. Associations between phthalates and measures of BMI, waist circumference, body fat percentage and trunk fat percentage at age 24 years were estimated using multiple linear regression. Effect estimates were reported as odds ratios or beta coefficients with 95% confidence intervals. Stratified analyses (e.g., by gender) were not discussed. The authors did not mention conducting sensitivity analyses to assess the robustness of findings. However, robustness was observed in terms of consistent associations for associations at multiple ages and multiple outcome measures.
	Metric 5B:	Sensitivity	Medium	There was substantial variability in both individual DiNP metabolites and their sum (DINP mean $\pm$ sd =34.5 $\pm$ 47.4 ng/mL). The prevalence of overweight was adequate for analysis: 20% at age 4y and 23.9% at age 24y. Statistical power was increased by the availability of repeated measures for some outcomes. However, the relatively small sample size (n=71 to 100) means that power was likely limited for stratified analyses.

Additional Comments: This longitudinal cohort study analyzed associations between phthalates exposure at age 4 and obesity measures through age 24y in a subset of 100 participants in the Swedish BAMSE cohort. Cohort members were born in 1994-1996. DiNP metabolites mono(hydroxy-isononyl) phthalate (MHiNP), mono(oxo-isononyl) phthalate (MOiNP), and mono(carboxy-isooctyl) phthalate (MCiOP), along with DEHP metabolites, were measured in urine samples at 4 years of age. Overweight status was measured at ages 4, 8, 12, 16, and 24 years. In addition, waist circumference, and BIA based body fat percentage and trunk fat percentage were analyzed at age 24y. The study found significant associations between increases in DiNP metabolites at age 4y and obesity measures obtained at ages 8 and above. The cross-sectional association between DiNP and obesity at age 4, as well as associations between DEHP metabolites and obesity at all ages, were null. The long follow-up and multiple obesity measures are strengths of this study. However, sample size was small. An additional potential limitation is residual confounding, in particular by dietary factors, which were not assessed at age 4y.

Overall Quality Determination — Medium

Study Citation:	Agier, L., Basagaña, X., Maitre, L., Granum, B., Bird, P. K., Casas, M., Oftedal, B., Wright, J., Andrusaityte, S., Castro, de, M., Cequier, E., Chatzi, L., Donaire-Gonzalez, D., Grazuleviciene, R., Haug, L. S., Sakhi, A. K., Leventakou, V., Mceachan, R., Nieuwenhuijsen, M., Petraviciene, I., Robinson, O., Roumeliotaki, T., Sunyer, J., Tamayo-Uria, I., Thomsen, C., Urquiza, J., Valentin, A., Slama, R., Vrijheid, M., Siroux, V. (2019). Early-life exposome and lung function in children in Europe: an analysis of data from the longitudinal, population-based HELIX cohort. The Lancet Planetary Health 3(2):e81-e92.
Health Outcome(s) Assessed:	Lung/Respiratory- Forced Expiratory Volume in 1s as % predicted value (FEV1%), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-4-methyl-7- oxooctyl phthalate (OXOMiNP); Mono-4-methyl-7- hydroxyoctyl phthalate (OH-MINP)
HERO ID:	5043613

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This study analyzed associations between early life exposures and lung function using data from the European Human Early-Life Exposome (HELIX) cohort. HELIX comprises 1033 mother-child pairs drawn from 6 prospective, general population birth cohorts in Europe (France, Greece, Lithuania, Norway, Spain, and the UK). Eligible participants (criteria: age 6-11 years, sufficient stored blood and urine samples from pregnancy for analysis, complete address history, no serious health problems) were randomly selected from each sub-cohort and invited to participate. Participating children were singletons born between 2003 and 2009, had an array of prenatal and postnatal exposure measures, and a valid spirometry test at age 6-12 years. Participation rates were not reported. HELIX children had similar mean birthweight and gestational ages as the parent cohort population, though sub-cohort mothers were slightly older and slightly more educated than the parent cohort (Le Maitre et al 2018, HEROID 8414108). Across study sites, sample sizes ranged from 147 to 242 children, and mean ages ranged from 6.5 to 10.8 years. There was no evidence of bias (i.e., that inclusion was associated with exposures or outcomes).
Domain 2: Exposure Characterization				

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Study Citation:	Agier, L., Basagaña, X., Maitre, L., Granum, B., Bird, P. K., Casas, M., Oftedal, B., Wright, J., Andrusaityte, S., Castro, de, M., Cequier, E., Chatzi, L., Donaire-Gonzalez, D., Grazuleviciene, R., Haug, L. S., Sakhi, A. K., Leventakou, V., Mceachan, R., Nieuwenhuijsen, M., Petraviciene, I., Robinson, O., Roumeliotaki, T., Sunyer, J., Tamayo-Uria, I., Thomsen, C., Urquiza, J., Valentin, A., Slama, R., Vrijheid, M., Siroux, V. (2019). Early-life exposome and lung function in children in Europe: an analysis of data from the longitudinal, population-based HELIX cohort. The Lancet Planetary Health 3(2):e81-e92.
Health Outcome(s) Assessed:	Lung/Respiratory- Forced Expiratory Volume in 1s as % predicted value (FEV1%), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-4-methyl-7- oxooctyl phthalate (OXOMiNP); Mono-4-methyl-7- hydroxyoctyl phthalate (OH-MINP)
HERO ID:	5043613

Domain	Metric	Rating	Comments
	Metric 2A: Exposure Measurement	Medium	Prenatal and childhood phthalates were among the array of exposome variables analyzed in this study. Prenatal phthalates were quantified in a single maternal spot urine sample. A limitation is that trimester of collection varied (means of 14 to 34 weeks gestation) across cohorts. Maternal urine was not available in one cohort that was excluded from analyses of prenatal exposure (Lithuania). Childhood phthalate measures. available for all cohorts, also captured a single time point but used pooled previous night and morning spot urine samples on the day of the clinical examination (Haug et al 2018, HEROID 4965808). Use of pooled samples aimed to reduce misclassification due to the short half-life of these metabolites. The phthalate metabolites measured in urine samples from mothers and children included: two metabolites of DiNP (oxo-MiNP and oh-MiNP), one DiBP metabolite (MiBP), one DBP metabolite (MnBP), and four DEHP metabolites (MEHP, MEHHP, MEOHP and MECPP). While analyzing urine samples collected at a single point in time is a limitation, the half-lives of the oxo- and hydroxy- metabolites used to estimate exposure to DiNP have been reported to persist longer than primary metabolites (Saravanabhavanet al, 2012 PMID 22505951). Phthalate metabolites were measured principally by the by the Norwegian Institute of Public Health (NIPH) using liquid chromatography-gas spectrometry with standards and quality controls (Haug et al 2018, HEROID 4965808). For the INMA cohort (Spain), with the exception of ox-MiNP and oh-MiNP which were analyzed at the NIPH, other phthalates were measured previously using ultra-performance liquid chromatography – mass spectrometry (Valvi et al 2014, HEROID 2804030). Duplicate measures in a subsample analyzed at the NIPH to evaluate consistency were highly correlated. LODs were provided for each metabolite; detection rates ranged from 92.6% to 100% (Haug 4965808; Valvi 2804030). Values below LOD or otherwise missing (15-29%, see Appendix Tables 1 and 2) were singly imputed using quantile regression for left-truncated data. Urinary creatinine was used to adjust for dilution. Phthalate concentration measures varied across cohorts; there was also substantial variability for all phthalates within each cohort (Haug 4965808).

Domain 3: Outcome Assessment

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Study Citation:	Agier, L., Basagaña, X., Maitre, L., Granum, B., Bird, P. K., Casas, M., Oftedal, B., Wright, J., Andrusaityte, S., Castro, de, M., Cequier, E., Chatzi, L., Donaire-Gonzalez, D., Grazuleviciene, R., Haug, L. S., Sakhi, A. K., Leventakou, V., Mceachan, R., Nieuwenhuijsen, M., Petraviciene, I., Robinson, O., Roumeliotaki, T., Sunyer, J., Tamayo-Uria, I., Thomsen, C., Urquiza, J., Valentin, A., Slama, R., Vrijheid, M., Siroux, V. (2019). Early-life exposome and lung function in children in Europe: an analysis of data from the longitudinal, population-based HELIX cohort. The Lancet Planetary Health 3(2):e81-e92.
Health Outcome(s) Assessed:	Lung/Respiratory- Forced Expiratory Volume in 1s as % predicted value (FEV1%), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-4-methyl-7- oxooctyl phthalate (OXOMiNP); Mono-4-methyl-7- hydroxyoctyl phthalate (OH-MINP)
HERO ID:	5043613

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	High	Lung function was measured during the clinical exam using a rigorous standardized protocol. The measure analyzed was forced expiratory volume in 1s as a percent of predicted values (FEV%). Children were examined once between the ages of 6 and 12 years using a common standardized protocol. Spirometry was measured by trained technicians. The protocol required at least three acceptable measures (e.g., no hesitation, coughing) that were reproducible (within 200 mL) which were further examined for validity (e.g., all highest values within 150 mL or 5%; subset reviewed in detail by trained investigators). Reference curves from the Global Lung Initiative were used to calculate predicted values standardized by age, height, sex, and ethnicity; any extreme values (FEV_1 <60% or >140% likely due to measurement error in young children) were excluded from the analysis. Mean (SD) FEV1% was 98·8 (13·2).
	Metric 3B:	Selective Reporting	High	Results were presented for all analyses and aims described. Methodologic information as well as very detailed results were included in an extensive appendix.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	High	Confounders were selected a priori and included: study center, child sex, age, height, parental country of birth, breastfeeding duration, season of conception, older siblings, parental education, maternal age, maternal pre-pregnancy BMI, postnatal passive smoking, prenatal maternal active and passive smoking. Models included a family affluence scale. Asthma was excluded as a potential intermediate. Sensitivity analyses adjusted for birth mode, gestational age, and child BMI which were omitted from primary models as potential intermediates; other sensitivity analyses excluded child age, sex and height which were incorporated in the FEV1% metric. Birth weight and prenatal birth were not discussed as potential confounders; these variables are also potential intermediates. Co-exposure confounding was explored in a multivariate linear regression by adjusting for all exposure variables associated with FEV1% with p<0.20 except those that were too highly correlated (absolute correlation coefficient >0·90) . The covariate selection strategy and variables included were appropriate.
Domain 5: Analysis				

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Study Citation:	Agier, L., Basagaña, X., Maitre, L., Granum, B., Bird, P. K., Casas, M., Oftedal, B., Wright, J., Andrusaityte, S., Castro, de, M., Cequier, E., Chatzi, L., Donaire-Gonzalez, D., Grazuleviciene, R., Haug, L. S., Sakhi, A. K., Leventakou, V., Mceachan, R., Nieuwenhuijsen, M., Petraviciene, I., Robinson, O., Roumeliotaki, T., Sunyer, J., Tamayo-Uria, I., Thomsen, C., Urquiza, J., Valentin, A., Slama, R., Vrijheid, M., Siroux, V. (2019). Early-life exposome and lung function in children in Europe: an analysis of data from the longitudinal, population-based HELIX cohort. The Lancet Planetary Health 3(2):e81-e92.
Health Outcome(s) Assessed:	Lung/Respiratory- Forced Expiratory Volume in 1s as % predicted value (FEV1%), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-4-methyl-7- oxooctyl phthalate (OXOMiNP); Mono-4-methyl-7- hydroxyoctyl phthalate (OH-MINP)
HERO ID:	5043613

Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Medium	The analytic approach was hypothesis-free, consistent with the objectives of an exposome study, which are to consider a large set of exposures simultaneously, which can help to limit selective reporting. The study examined 85 prenatal and 125 postnatal exposures. Exposure variables were transformed to approximate normality, multiple imputation was used to address missing values (<5% for variables with significant associations), and exposures were standardized as interquartile ranges to facilitate comparisons. Phthalates were log2 transformed. FEV% was analyzed as a continuous variable. Statistical analyses compared results from two approaches: a deletion-substitution-addition (DSA) algorithm that considered all exposures simultaneously, and an exposome-wide association study (ExWAS) that considered exposures independently. DSA is an iterative linear regression model search in which variables are iteratively removed, substituted, or added. Two-way interactions were tested as part of the analysis. Using DSA, the final model minimizes the root mean squared error of predictions using five-fold cross-validated data. The DSA was fitted 100 times, and exposure retained if selected in at least 5% of the runs. The ExWAS approach estimated exposure-outcome associations in independent linear regression models for each exposure variable and examined results after correcting for multiple hypothesis testing. Adjustments for co-exposures were also examined. As the authors noted, in simulation studies, DSA has been found to reduce false positive associations at the cost of sensitivity, while ExWAS has been found to increase sensitivity at the cost of false positives. Between-cohort heterogeneity was examined by running cohort-specific models. Sensitivity analyses excluded children who reporting a cold at the time of testing and children ever diagnosed with asthma. The authors also presented a detailed comparison of children included vs. excluded due to non-valid FEV1 values; besides child age and height which varied a priori, few differences were notable or significant; these were addressed as confounders. The authors did not discuss examining non-linear dose response, sex differences, or age group differences. Nonetheless, analyses were extensive, and the methods selected and their implementation seemed appropriate.
	Metric 5B:	Sensitivity	Medium	The pooled sample size was large (N=1033) and there was variability in both exposure measures and outcomes. However, power to detect associations that were significant after correcting for multiple comparisons was limited by the large number of exposures examined (n=85 prenatal, n=125 postnatal). Statistical power was likely limited in subcohort specific analysis, and to detect any interactions.

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Study Citation:	Agier, L., Basagaña, X., Maitre, L., Granum, B., Bird, P. K., Casas, M., Oftedal, B., Wright, J., Andrusaityte, S., Castro, de, M., Cequier, E., Chatzi, L., Donaire-Gonzalez, D., Grazuleviciene, R., Haug, L. S., Sakhi, A. K., Leventakou, V., Mceachan, R., Nieuwenhuijsen, M., Petraviciene, I., Robinson, O., Roumeliotaki, T., Sunyer, J., Tamayo-Uria, I., Thomsen, C., Urquiza, J., Valentin, A., Slama, R., Vrijheid, M., Siroux, V. (2019). Early-life exposome and lung function in children in Europe: an analysis of data from the longitudinal, population-based HELIX cohort. The Lancet Planetary Health 3(2):e81-e92.
Health Outcome(s) Assessed:	Lung/Respiratory- Forced Expiratory Volume in 1s as % predicted value (FEV1%), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-4-methyl-7- oxooctyl phthalate (OXOMiNP); Mono-4-methyl-7- hydroxyoctyl phthalate (OH-MINP)
HERO ID:	5043613

Domain	Metric	Rating	Comments
Additional Comments:	This exposome study used data from six European birth cohorts to examine associations between lung function assessed by spirometry and prenatal (n=85) and concurrent postnatal (n=125) exposure variables in 1,033 children aged 6-11 years. The array of exposures analyzed included metabolites of DiNP, DEHP, DiBP, DBP and BBP, along with other pollutants, dietary, social and community variables. Mean concentrations of DiNP metabolites were higher in children than in prenatal maternal samples (e.g. oxo-MiNP 6.2 vs 2.0 ug/g creatinine, reflecting that DiNP use is increasing in Europe as a substitute for DEHP. Prenatal and postnatal means for the sum of the four DEHP metabolites measured were similar (108.4 vs. 99.4 ug/g creatinine). Associations with maternal phthalate measures during pregnancy did not reach significance. The nine postnatal exposures significantly associated with poorer lung function as measured by lower FEV1% included five phthalate metabolite variables (MECPP, MEHHP, MEOHP, oxo-MiNP, and the sum of DEHP metabolites. However, no ExWAS associations remained significant at the multiple comparison threshold accounting for the large number of exposures; the moderate sample size may have limited statistical power. No exposure variables were selected for inclusion using the agnostic deletion-substitution-addition (DSA) models. While this study was a prospective cohort, significant associations were cross-sectional, based on concurrent measures of children's lung function and urinary phthalates. An important strength of this study was consideration of a wide array of exposures, and the use of extensive statistical analyses that included agnostic exposome statistical approaches to identify variables associated with children's lung function. Study cohort-specific as well as overall results were shown. However, sex-stratified results were not discussed. FEV1% was assessed by trained technicians using a rigorous standardized protocol, and variables were further evaluated for validity. Phthalates metabolites were measured in urine samples collected at a single time point; for children, however, evening and morning spot urine samples were pooled in an effort to strengthen exposure estimation given the short half-lives of phthalate metabolites in urine. It is also of note that the oxo- and hydroxy- metabolites used to estimate DiNP exposure have been found to persist longer than primary metabolites (Saravanabhavanet al, 2012 PMID 22505951).		

Overall Quality Determination High

Study Citation:	Balalian, A. A., Whyatt, R. M., Liu, X., Insel, B. J., Rauh, V. A., Herbstman, J., Factor-Litvak, P. (2019). Prenatal and childhood exposure to phthalates and motor skills at age 11 years. Environmental Research 171:416-427.
Health Outcome(s) Assessed:	Neurological/Behavioral- Age 11 motor skills, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5039985

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	The participants within this prospective evaluation of maternal prenatal and child age 3, 5 and 7 postnatal phthalate exposures with motor skills at age 11 were selected from participants in an ongoing longitudinal birth cohort study of 727 mothers and newborns conducted by the Columbia Center for Children's Environmental Health (CCCEH). The original CCEH cohort was restricted to nonsmoking African American or Dominican women ages 18-35 years residing in northern Manhattan or the South Bronx in New York City for at least 1 year before pregnancy and who delivered between 1999 and 2006. Women who used illicit drugs, had diabetes, hypertension or known HIV or had their first prenatal visit after the 20th week of pregnancy were excluded. Women with active smoking during pregnancy verified by maternal and/or umbilical cord plasma cotinine greater than 15 ng/mL at delivery (n=30), insufficient or no prenatal urine for measurement of phthalate metabolites (n=286), and those lost to follow-up prior to child age 11 years (n=202) were also excluded. Finally, a total of 209 mother-child pairs with spot urines collected during the third trimester and age 11 child completion of the short form of the Burininks-Oseretsky Test of Moror Proficiency-2 (BOT-2) were selected for study. The 209 study women reportedly did not differ significantly from the 147 women whose children had BOT-2 scores but who did not have prenatal phthalate measures in terms of basic demographics (race/ethnicity, prenatal marital status, education level, household income, and proportion on Medicaid or other public assistance). Children who did and did not complete the BOT-2 also had reportedly similar birth outcomes. However, there is uncertainty for selection bias given a total of 209 participants were selected out of an original cohort of 727, a total of n=202 were lost to follow-up for age 11 motor skills assessment, and data for prenatal MCOP metabolite analyses were only available for n=72 women (34 girls and 38 boys) due to the described lack of initial analyses (described below) for mono-carboxy-isooctyl phthalate (MCOP, a DiNP metabolite).
Domain 2: Exposure Characterization				

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Health Outcome(s) Assessed:	Neurological/Behavioral- Age 11 motor skills, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5039985

Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Medium	Quantification of prenatal and child age 3, 5 and 7 urinary metabolites of 6 phthalates (di(n-butyl) phthalate (DnBP), butylbenzyl phthalate (BBzP), di-isobutyl phthalate (DiBP), diethyl phthalate (DEP), diisononyl phthalate (DiNP), and di-2-ethyl hexyl phthalate (DEHP)) was conducted utilizing automated sample preparation and on-line preconcentration/high-performance liquid chromatography/tandem mass spectrometry. Quantification of DiNP metabolites was introduced only after the commencement in 2009 of Centers for Disease Control and Prevention (CDC) measurements such that only 34% of the prenatal samples had mono-carboxy-isooctyl phthalate (MCOP, a DiNP metabolite) measurements, but all child age 7 samples had MCOP measures. Results were adjusted for specific gravity to correct for urinary dilution. Limits of detection (LOD) and percent less than the LOD were reported, with concentrations below the LOD assigned a value of the LOD divided by the square root of 2. The percent of samples below the limit of detection was generally low, except for prenatal MCOP (percent $<$ LOD: 13.9%) and prenatal, age 3, and age 5 MEHP (percent $<$ LOD: 16.7%, 21.08%, and 20.82%, respectively). Concentrations were natural log transformed within analyses. There is uncertainty with MCOP analyses as only n=72 (34%) out of n=209 participants had prenatal MCOP measures, and only n=113 out of n=166 participants had age 3 MCOP measures, however 100% of samples had analyses for MCOP at ages 5 (n=199) and 7 (n=156). Given the short half-life of phthalates, it is unclear if a single spot urine measure adequately represents the intensity, frequency and potential peak exposures during the prenatal period responsible for initiation and development of outcomes of interest.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Age 11 motor function in terms of total, fine and gross motor composite point scores was assessed using the short form of the Bruininks-Oseretsky Test of Motor Proficiency, 2nd edition (BOT-2). The BOT-2 is a widely used individually administered test that measures a wide range of motor skills in children and young adults, and was standardized on a U.S. nationally representative sample of $>$ 1500 individuals 4–21 years of age. The short form of the BOT-2 was utilized, with good to excellent reliability in terms of test-retest and interrater reliability reported. There is uncertainty in the lack of clinical developmental coordination disorder diagnoses to validate below average BOT-2 scores, as well as the lack of refinement in motor skills outcomes able to be assessed due to the use of the short form of the BOT-2.
	Metric 3B:	Selective Reporting	Medium	There were no concerns for selective reporting.
Domain 4: Potential Confounding / Variability Control				

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Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	Medium	Final total and sex-stratified models were adjusted for specific gravity, maternal ethnicity, prenatal maternal demoralization, prenatal maternal alcohol exposure, quality of the home environment (HOME score), child BMI z-score at age 11, and child's age in months at BOT-2 administration. Data for potential confounders was obtained using questionnaires administered to the mother during pregnancy, at postnatal intervals and by review of maternal and infant medical records. The strategy for selection of potential confounders utilized directed acyclic graphs based upon previous literature suggesting the variables were associated with phthalate exposure and/or with motor outcomes. Potential confounders were included within the final models if their inclusion changed the estimated regression coefficient of the main phthalate predictor more than 0.5 standard errors of the coefficient estimate. Missing covariate data was reported. Missing values for maternal prenatal demoralization (n=3), HOME scale (n=9), and child BMI z-score at age 11 (n=9) were imputed using linear regression. There is uncertainty as covariate data was obtained from maternal self-report, and answers to questions associated with social stigma, such as maternal prenatal alcohol consumption and psychosocial factors (maternal self-report of hardship during pregnancy), may have had less accuracy in participants with potentially differing exposure and outcome status.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Multivariate generalized linear models analyzed the association between prenatal, child age 3, child age 5, and child age 7 urinary phthalate metabolite concentrations and age 11 BOT-2 total motor composite, fine motor composite, and gross motor composite scores. DEHP metabolites (MEHP, MEHHP, MECPP, MEOHP) were converted to molar concentrations and summed for analysis. Effect modification was examined within models stratified by child sex. Non-linear effects were examined within models using prenatal metabolite quartiles as predictors. Results were presented as estimated coefficients and corresponding 95% confidence intervals. Results were not corrected for multiple testing, and the combined effect of multiple exposures was not assessed.
	Metric 5B:	Sensitivity	Low	The analytic sample size for MCOP was less than optimal for analyses of prenatal (n=72 out of n=209 participants with other phthalate metabolite measures) and age 3 (n=113 out of n=166 participants with other phthalate metabolite measures) analyses given the number of covariates as well as within the sex-stratified analyses of age 11 motor function outcomes.

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Domain	Metric	Rating	Comments
Additional Comments:	This prospective analysis of maternal prenatal and child age 3, 5 and 7 postnatal phthalate exposures with motor skills at age 11 as assessed by the short form of the BOT-2 were selected from participants in an ongoing longitudinal birth cohort study of 727 mothers and newborns conducted by the Columbia Center for Children's Environmental Health (CCCEH). The original CCCEH cohort was restricted to nonsmoking African American or Dominican women ages 18-35 years residing in northern Manhattan or the South Bronx in New York City for at least 1 year before pregnancy and who delivered between 1999 and 2006. The sample size for MCOP, a DiNP metabolite (n=72 out of n=209 participants with other phthalate metabolite measures) for maternal prenatal exposures with age 11 motor skills was less than optimal. There is uncertainty with the utilization of the short-form for BOT-2, with reported inconsistent findings regarding its validity within the literature, the lack of data in terms of clinical validation of developmental coordination disorder, and the lack of the ability to examine several BOT-2 subset outcome fine details in terms of fine motor precision, integration, manual dexterity, etc. There is additional uncertainty regarding the use of a single spot urine for analysis of phthalate exposures at each time point. Among girls, prenatal MnBP (b = -2.09; 95%CI: [-3.43, -0.75]), MBzP(b = -1.14; [95%CI:-2.13, -0.14]), and MiBP (b = -1.36; 95%CI: [-2.51, -0.21] were associated with lower total BOT-2 composite score. MnBP (b= –1.43; 95% CI: [–2.44, –0.42]) was associated with lower fine motor scores and MiBP (b = –0.56; 95% CI: [-1.12, –0.01]) was associated with lower gross motor scores. Among boys, prenatal MBzP (b = –0.79; 95% CI: [–1.40, 0.19]) was associated with lower fine motor composite score. Regarding postnatal exposure time points, among boys, age 3 (b = –1.30; 95% CI: [–2.34, -0.26]) and age 7 (b = –0.96; 95% CI: [– 1.79, -0.13]) sum DEHP metabolites were associated with lower fine motor composite scores, while age 7 (b = -1.30; 95% CI: [-2.56, -0.03]) sum DEHP metabolites was also associated with lower total composite scores. Additionally among boys, age 3 MCOP was associated with lower total composite scores (b = -3.08; 95% CI: [-5.35, -0.80]), fine motor scores (b=-1.64; 95% CI: [-3.16, -0.12]), and gross motor scores (b = -1.44; 95% CI: [-2.60, -0.28]. No statistically significant associations between postnatal exposures and outcomes were observed among girls.	

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Domain 2: Exposure Characterization				

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Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Age 11 motor function in terms of total, fine and gross motor composite point scores was assessed using the short form of the Bruininks-Oseretsky Test of Motor Proficiency, 2nd edition (BOT-2). The BOT-2 is a widely used individually administered test that measures a wide range of motor skills in children and young adults, and was standardized on a U.S. nationally representative sample of $>$ 1500 individuals 4–21 years of age. The short form of the BOT-2 was utilized, with good to excellent reliability in terms of test-retest and interrater reliability reported. There is uncertainty in the lack of clinical developmental coordination disorder diagnoses to validate below average BOT-2 scores, as well as the lack of refinement in motor skills outcomes able to be assessed due to the use of the short form of the BOT-2.
	Metric 3B:	Selective Reporting	Medium	There were no concerns for selective reporting.
Domain 4: Potential Confounding / Variability Control				

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Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Multivariate generalized linear models analyzed the association between prenatal, child age 3, child age 5, and child age 7 urinary phthalate metabolite concentrations and age 11 BOT-2 total motor composite, fine motor composite, and gross motor composite scores. DEHP metabolites (MEHP, MEHHP, MECPP, MEOHP) were converted to molar concentrations and summed for analysis. Effect modification was examined within models stratified by child sex. Non-linear effects were examined within models using prenatal metabolite quartiles as predictors. Results were presented as estimated coefficients and corresponding 95% confidence intervals. Results were not corrected for multiple testing, and the combined effect of multiple exposures was not assessed.
	Metric 5B:	Sensitivity	Low	The analytic sample size for MCOP was less than optimal for analyses of prenatal (n=72 out of n=209 participants with other phthalate metabolite measures) and age 3 (n=113 out of n=166 participants with other phthalate metabolite measures) analyses given the number of covariates as well as within the sex-stratified analyses of age 11 motor function outcomes.

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Domain	Metric	Rating	Comments
Additional Comments:	This prospective analysis of maternal prenatal and child age 3, 5 and 7 postnatal phthalate exposures with motor skills at age 11 as assessed by the short form of the BOT-2 were selected from participants in an ongoing longitudinal birth cohort study of 727 mothers and newborns conducted by the Columbia Center for Children's Environmental Health (CCCEH). The original CCCEH cohort was restricted to nonsmoking African American or Dominican women ages 18-35 years residing in northern Manhattan or the South Bronx in New York City for at least 1 year before pregnancy and who delivered between 1999 and 2006. The sample size for MCOP, a DiNP metabolite (n=72 out of n=209 participants with other phthalate metabolite measures) for maternal prenatal exposures with age 11 motor skills was less than optimal. There is uncertainty with the utilization of the short-form for BOT-2, with reported inconsistent findings regarding its validity within the literature, the lack of data in terms of clinical validation of developmental coordination disorder, and the lack of the ability to examine several BOT-2 subset outcome fine details in terms of fine motor precision, integration, manual dexterity, etc. There is additional uncertainty regarding the use of a single spot urine for analysis of phthalate exposures at each time point. Among girls, prenatal MnBP (b = -2.09; 95%CI: [-3.43, -0.75]), MBzP(b = -1.14; [95%CI:-2.13, -0.14]), and MiBP (b = -1.36; 95%CI: [-2.51, -0.21] were associated with lower total BOT-2 composite score. MnBP (b= –1.43; 95% CI: [–2.44, –0.42]) was associated with lower fine motor scores and MiBP (b = –0.56; 95% CI: [-1.12, –0.01]) was associated with lower gross motor scores. Among boys, prenatal MBzP (b = –0.79; 95% CI: [–1.40, 0.19]) was associated with lower fine motor composite score. Regarding postnatal exposure time points, among boys, age 3 (b = –1.30; 95% CI: [–2.34, -0.26]) and age 7 (b = –0.96; 95% CI: [– 1.79, -0.13]) sum DEHP metabolites were associated with lower fine motor composite scores, while age 7 (b = -1.30; 95% CI: [-2.56, -0.03]) sum DEHP metabolites was also associated with lower total composite scores. Additionally among boys, age 3 MCOP was associated with lower total composite scores (b = -3.08; 95% CI: [-5.35, -0.80]), fine motor scores (b=-1.64; 95% CI: [-3.16, -0.12]), and gross motor scores (b = -1.44; 95% CI: [-2.60, -0.28]. No statistically significant associations between postnatal exposures and outcomes were observed among girls.		

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Health Outcome(s) Assessed:	Lung/Respiratory- Lung function (FEV1), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	6813726

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Study participants were selected from the cohort Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) and were 319 infant mother pairs from the Salinas Valley of California. Mothers were recruited from prenatal clinics in 1999-2000. Women were eligible if they qualified for MediCal, at least 18 years of age, <20 weeks gestation, and were planning to deliver at the county hospital. The study originally included 531 infants, where 392 met inclusion criteria, but was brought down to 319 complete cases including covariate data. Mothers were interviewed during pregnancy, at delivery, and when children were 6 months, 1 year, 2 years, 3.5 years, 5 years, and 7 years old. Characteristics of participants included versus excluded from the current study are shown in Table 1. Missing data was noted for 212 pairs; mothers in these pairs tended to be younger and to have lived in the US for a less time. Participant loss is unlikely to be related to exposure.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Urine MCNP, MCOP, MBzP, MiBP, MBP, MEHP, MEHHP, MEOHP, and MECCP samples were collected from mothers at two time points during pregnancy (mean, SD: 14.0, 5.0 and 26.9, 2.5 weeks gestation). Samples were measured using solid-phase extraction coupled with HPLC-ESI-MS/MS. Concentrations were corrected for urinary dilution using specific gravity measurements; specific gravity was imputed for 77 women missing measurements using urinary creatinine concentrations. LODs ranged from 0.2 ng/mL to 2.3 ng/mL; specific values for each phthalate metabolite were not provided. MCNP concentrations were 95 and 96.7% > LOD (early and late pregnancy), MCOP concentrations were 96.5% and 96.4% > LOD (early and late pregnancy), MBP concentrations were 98.4% and 100% > LOD (early and late pregnancy), MiBP concentrations were 92.4% and 95.7% > LOD (early and late pregnancy), and MBzP concentrations were 97.8% and 98.7% >LOD (early and late pregnancy). DEHP metabolites (MEHP, MEHHP, MEOHP, MECCP); summed DEHP metabolite concentrations were 87.7% and 91.8% > LOD (early and late pregnancy). Values below the LOD were assigned the instrumental reading values or were assigned a value below the LOD randomly selected from the log-normal distribution using maximum likelihood estimation. For each participant, the log 2 average of the two samples was used as the exposure variable in analysis. The exposure was measured in a relevant time window.
Domain 3: Outcome Assessment				

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Health Outcome(s) Assessed:	Lung/Respiratory- Lung function (FEV1), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
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Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Lung function at age 7, probable asthma at age 7: Trained research assistants conducted lung function tests using spirometers and conducted 8 expiratory maneuvers, measuring FEV1, which were reviewed and verified by two pediatric spirometer physician specialists. Probable asthma was defined based on a combination of maternal report and clinical data (probable asthma defined as taking asthma medication or having any current respiratory symptom, doctor diagnosis of asthma, or positive bronchodilator test. Respiratory symptoms were not further defined.
	Metric 3B:	Selective Reporting	Medium	No concerns for selective reporting.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Covariates included maternal age, parity, poverty at baseline, and family history of asthma. Information on covariates was collected from questionnaires provided to mothers during pregnancy. No discussion of strategy for identifying key confounders. No discussion of child's sex as a potential confounder; however, exposure measured prenatally is unlikely to be correlated with child's sex.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Log2 averages of urinary measures were used in all analyses. Analyses were focused on examining outcomes in relation to chemical mixtures, including phthalates, phenols, and parabens. Bayesian Profile Regression (BPR) was used to group participants into clusters based on biomarker concentration patterns and chi square test was used to determine if clusters differed significantly in outcome frequency. Logistic and linear regressions for outcomes were also conducted with cluster assignment as categorical predictors. Bayesian Kernel Machine Regression (BKMR) was used to assess outcomes as functions of urinary phthalates and other chemicals adjusting for confounders. Conducted sensitivity analyses using BKMR component wise variable selection. Sensitivity analyses showed several association changes with no consistencies.
	Metric 5B:	Sensitivity	Medium	Appropriate sample size. Exposure distribution means and standard deviations shown in figure but not quantitatively noted in the main study. Analysis was focused on determining associations between chemical mixtures and outcomes; individual results for specific phthalate metabolites not available in this study.

Additional Comments: Overall rating of medium for this longitudinal cohort with minimal limitations. Authors reported missing data for 212 individuals but participant loss is unlikely to be related to exposure. Analytic methods were appropriate but were focused on examining chemical mixtures rather than individual phthalates / phthalate metabolites. Limitations are unlikely to affect the validity of the results. In addition to relevant phthalates, paper includes MCPP and states that MCPP is "a metabolite of several high molecular weight phthalates and a minor metabolite of dibutyl phthalate."

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	Metric 1A:	Participant Selection	Medium	Study participants were selected from the cohort Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) and were 319 infant mother pairs from the Salinas Valley of California. Mothers were recruited from prenatal clinics in 1999-2000. Women were eligible if they qualified for MediCal, at least 18 years of age, <20 weeks gestation, and were planning to deliver at the county hospital. The study originally included 531 infants, where 392 met inclusion criteria, but was brought down to 319 complete cases including covariate data. Mothers were interviewed during pregnancy, at delivery, and when children were 6 months, 1 year, 2 years, 3.5 years, 5 years, and 7 years old. Characteristics of participants included versus excluded from the current study are shown in Table 1. Missing data was noted for 212 pairs; mothers in these pairs tended to be younger and to have lived in the US for a less time. Participant loss is unlikely to be related to exposure.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Urine MCNP, MCOP, MBzP, MiBP, MBP, MEHP, MEHHP, MEOHP, and MECCP samples were collected from mothers at two time points during pregnancy (mean, SD: 14.0, 5.0 and 26.9, 2.5 weeks gestation). Samples were measured using solid-phase extraction coupled with HPLC-ESI-MS/MS. Concentrations were corrected for urinary dilution using specific gravity measurements; specific gravity was imputed for 77 women missing measurements using urinary creatinine concentrations. LODs ranged from 0.2 ng/mL to 2.3 ng/mL; specific values for each phthalate metabolite were not provided. MCNP concentrations were 95 and 96.7% > LOD (early and late pregnancy), MCOP concentrations were 96.5% and 96.4% > LOD (early and late pregnancy), MBP concentrations were 98.4% and 100% > LOD (early and late pregnancy), MiBP concentrations were 92.4% and 95.7% > LOD (early and late pregnancy), and MBzP concentrations were 97.8% and 98.7% >LOD (early and late pregnancy). DEHP metabolites (MEHP, MEHHP, MEOHP, MECCP); summed DEHP metabolite concentrations were 87.7% and 91.8% > LOD (early and late pregnancy). Values below the LOD were assigned the instrumental reading values or were assigned a value below the LOD randomly selected from the log-normal distribution using maximum likelihood estimation. For each participant, the log 2 average of the two samples was used as the exposure variable in analysis. The exposure was measured in a relevant time window.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Low	Aeroallergy at age 7: Aeroallergies were defined based on maternal report of a diagnosis of hay fever/rhinitis, runny or itchy eyes apart from colds, or sneezing/runny nose apart from colds in the last year. No information on the validity of the questionnaire used to assess aeroallergy was provided.
	Metric 3B:	Selective Reporting	Medium	No concerns for selective reporting.

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Study Citation:	Berger, K., Coker, E., Rauch, S., Eskenazi, B., Balmes, J., Kogut, K., Holland, N., Calafat, A. M., Harley, K. (2020). Prenatal phthalate, paraben, and phenol exposure and childhood allergic and respiratory outcomes: Evaluating exposure to chemical mixtures. Science of the Total Environment 725:138418.
Health Outcome(s) Assessed:	Lung/Respiratory- Aeroallergies, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	6813726

Domain	Metric	Rating	Comments
Domain 4: Potential Confounding / Variability Control			
	Metric 4A: Potential Confounding	Medium	Covariates included maternal age, parity, poverty at baseline, and family history of asthma. Information on covariates was collected from questionnaires provided to mothers during pregnancy. No discussion of strategy for identifying key confounders. No discussion of child's sex as a potential confounder; however, exposure measured prenatally is unlikely to be correlated with child's sex.
Domain 5: Analysis			
	Metric 5A: Analysis	Medium	Log2 averages of urinary measures were used in all analyses. Analyses were focused on examining outcomes in relation to chemical mixtures, including phthalates, phenols, and parabens. Bayesian Profile Regression (BPR) was used to group participants into clusters based on biomarker concentration patterns and chi square test was used to determine if clusters differed significantly in outcome frequency. Logistic and linear regressions for outcomes were also conducted with cluster assignment as categorical predictors. Bayesian Kernel Machine Regression (BKMR) was used to assess outcomes as functions of urinary phthalates and other chemicals adjusting for confounders. Conducted sensitivity analyses using BKMR component wise variable selection. Sensitivity analyses showed several association changes with no consistencies.
	Metric 5B: Sensitivity	Medium	Appropriate sample size. Exposure distribution means and standard deviations shown in figure but not quantitatively noted in the main study. Analysis was focused on determining associations between chemical mixtures and outcomes; individual results for specific phthalate metabolites not available in this study.

Additional Comments: Overall rating of medium for this longitudinal cohort with minimal limitations. Authors reported missing data for 212 individuals but participant loss is unlikely to be related to exposure. Analytic methods were appropriate but were focused on examining chemical mixtures rather than individual phthalates / phthalate metabolites. Limitations are unlikely to affect the validity of the results. In addition to relevant phthalates, paper includes MCPP and states that MCPP is "a metabolite of several high molecular weight phthalates and a minor metabolite of dibutyl phthalate."

Overall Quality Determination — Medium

Study Citation:	Berger, K., Eskenazi, B., Balmes, J., Kogut, K., Holland, N., Calafat, A. M., Harley, K. G. (2019). Prenatal high molecular weight phthalates and bisphenol A, and childhood respiratory and allergic outcomes. Pediatric Allergy and Immunology 30(1):36-46.
Health Outcome(s) Assessed:	Lung/Respiratory- spirometry measures [forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC, forced expiratory flow from 25-75% of FVC (FEF25-75%)], Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5041286

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Participants in this study were recruited as part of the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) cohort, which has followed children living in the area from birth until the age of 16. Eligible individuals included women attending first prenatal care visits at local clinics between 1999 and 2000. Inclusion criteria were speaking English or Spanish, being <= 20 weeks pregnant, being 18 years or older, qualifying for MediCal, and planning to deliver at the county hospital. 601 women were enrolled, and 531 were followed until live birth. Of these individuals, 517 children had at least one prenatal high molecular weight phthalate or BPA measurement. The authors reported the number of children missing prenatal samples for various metabolites and children missing data on the outcomes of interest. In total, 392 children had data on prenatal biomarkers and at least one relevant outcome. The authors provided sufficient details about their methods of participant selection, although there is no comparison of included children and those excluded due to missing data. There are minimal concerns of selection bias
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Spot urine samples were obtained from mothers at two interviews during pregnancy, at an average of 13 and 26 weeks' gestation. Samples were collected in BPA- and phthalate-free polypropylene cups and stored in glass vials at -80C until shipment to CDC for analysis. Solid phase extraction coupled with isotope dilution high-performance liquid chromatography-tandem mass spectrometry was used to quantify concentrations of relevant phthalate metabolites using previously published methods. QA/QC methods are not described. Limits of detection ranged from 0.2-0.5 ng/mL, and values below the LOD were assigned the instrument-reading values if they were available or were given an imputed value below the LOD selected at random from the log-normal distribution using maximum likelihood estimation. Authors also utilized a handheld refractometer to measure urinary specific gravity. 81 urine samples missing specific gravity measurements had specific gravity imputed based on urinary creatinine. These allowed for the correction of samples by urinary dilution. These tools are an appropriate analytical method for quantifying phthalate metabolite concentrations, and the samples represent an etiologically relevant time period. Authors reported the percent of samples detected above the LOD, and the lowest detection was for MCPP, being detected in 90.3% of samples. Exposure misclassification is expected to be minimal.
Domain 3: Outcome Assessment				

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Study Citation:	Berger, K., Eskenazi, B., Balmes, J., Kogut, K., Holland, N., Calafat, A. M., Harley, K. G. (2019). Prenatal high molecular weight phthalates and bisphenol A, and childhood respiratory and allergic outcomes. Pediatric Allergy and Immunology 30(1):36-46.
Health Outcome(s) Assessed:	Lung/Respiratory- spirometry measures [forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC, forced expiratory flow from 25-75% of FVC (FEF25-75%)], Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5041286

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	High	For lung function measurements, children were examined with spirometers at age 7. Each child completed up to eight expiratory maneuvers, which were verified by two physicians with experience in pediatric spirometry and the best verified maneuver was used for analysis. Physicians utilized three identical EasyOne spirometers which were calibrated daily. Measurements included forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC, and forced expiratory flow from 25-75% of FVC. For children whose mothers reported respiratory symptoms at age 7, they were offered a bronchodilator test and repeated spirometry 20 minutes after inhaling albuterol (n = 54). For cytokine outcomes, Th1 and Th2 cells were detected in unfrozen pediatric blood using flow cytometry using previously published methods. Blood samples were collected at ages 2, 5, and 7. Cell counts were divided by the total number of CD4+ cells to calculate Th1% and Th2%, and the Th1:Th2 ratio was defined as Th1% divided by Th2%.Use of daily calibrated spirometers and repeat measures lend confidence to appropriate classifications of the lung function measurements. Administration by trained physicians is also a strength, and it is unlikely that they would have been aware of children's exposure status. Similarly, cytokine-producing cells were detected using appropriate methods at multiple time points. Any outcome misclassification is unlikely to be differential by exposure status and is not a major concern.
	Metric 3B:	Selective Reporting	Medium	The results reported by the authors align with the analyses described within the methods section of the paper.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Authors considered a number of variables identified a priori via directed acyclic graphs in demographically adjusted models. These variables included maternal age at birth, parity, household income as a proportion of poverty at baseline, and family history of asthma. Authors also created fully adjusted models which controlled for chemical co-exposures such as metabolites of low molecular weight phthalates and phenols that were measured in urine samples. Bayesian model averaging was used to identify the most important variables for inclusion, and authors kept the three most influential variables with the highest posterior inclusion probabilities for each outcome. The authors utilized appropriate techniques for classifying potential confounders, and they had a clear strategy to identify variables for inclusion in the models. Residual confounding is of minimal concern.
Domain 5: Analysis				

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Study Citation:	Berger, K., Eskenazi, B., Balmes, J., Kogut, K., Holland, N., Calafat, A. M., Harley, K. G. (2019). Prenatal high molecular weight phthalates and bisphenol A, and childhood respiratory and allergic outcomes. Pediatric Allergy and Immunology 30(1):36-46.
Health Outcome(s) Assessed:	Lung/Respiratory- spirometry measures [forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC, forced expiratory flow from 25-75% of FVC (FEF25-75%)], Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5041286

Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	High	Descriptive information about outcome and exposure are reported. Urinary metabolite concentrations were averaged over pregnancy, and specific-gravity adjusted values were used for analysis. These concentrations were log2-transformed. Measurements from the first and second collection were used in sensitivity analyses. Lung function measurements were analyzed as continuous variables. FEV1 and FVC were not transformed and other lung function measurements were assessed as continuous log10-transformed variables. Lung function outcomes were analyzed using linear regression of generalized estimating equations. Longitudinal associations of cytokine variables were evaluated using generalized estimating equations with Gaussian specification and an exchangeable correlation structure. These analyses considered interaction terms with child age. All analyses included crude models, models adjusted for demographic factors, and fully adjusted models that accounted for both demographic factors and chemical co-exposures. Generalized additive models with three degrees of freedom were used to test for linearity of relationships.Quantitative results were presented for each analysis with the estimate and and 95% confidence intervals. The number of samples below LOD was reported. Methods for handling missing data and data <LOD are described. No major deficiencies in analytical methods are noted.
	Metric 5B:	Sensitivity	Medium	The range of exposure levels is reported and there is adequate variability to evaluate the authors' hypothesis. The children exposed prenatally were sensitive to the development of relevant outcomes in childhood, and outcome ascertainment was performed at an appropriate time. Sample size is adequate. Correlation between phthalate biomarkers may reduce sensitivity to detect the effects of individual chemicals, but adjustment for co-exposures in the models mitigates this concern.

Additional Comments: This study examined associations between in utero urinary phthalate exposure and respiratory and allergic outcomes in children as part of the CHAMACOS mother-child cohort study. The study utilized high-quality exposure assessment and outcome methods. Analytical methods and examination of potential confounding variables were strengths. There is minimal concern of bias.

Overall Quality Determination Medium

Study Citation:	Berger, K., Eskenazi, B., Balmes, J., Kogut, K., Holland, N., Calafat, A. M., Harley, K. G. (2019). Prenatal high molecular weight phthalates and bisphenol A, and childhood respiratory and allergic outcomes. Pediatric Allergy and Immunology 30(1):36-46.
Health Outcome(s) Assessed:	Lung/Respiratory- Probable asthma, aeroallergies, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5041286

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Participants in this study were recruited as part of the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) cohort, which has followed children living in the area from birth until the age of 16. Eligible individuals included women attending first prenatal care visits at local clinics between 1999 and 2000. Inclusion criteria were speaking English or Spanish, being <= 20 weeks pregnant, being 18 years or older, qualifying for MediCal, and planning to deliver at the county hospital. 601 women were enrolled, and 531 were followed until live birth. Of these individuals, 517 children had at least one prenatal high molecular weight phthalate or BPA measurement. The authors reported the number of children missing prenatal samples for various metabolites and children missing data on the outcomes of interest. In total, 392 children had data on prenatal biomarkers and at least one relevant outcome. The authors provided sufficient details about their methods of participant selection, although there is no comparison of included children and those excluded due to missing data. There are minimal concerns of selection bias.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Spot urine samples were obtained from mothers at two interviews during pregnancy, at an average of 13 and 26 weeks' gestation. Samples were collected in BPA- and phthalate-free polypropylene cups and stored in glass vials at -80C until shipment to CDC for analysis. Solid phase extraction coupled with isotope dilution high-performance liquid chromatography-tandem mass spectrometry was used to quantify concentrations of relevant phthalate metabolites using previously published methods. QA/QC methods are not described. Limits of detection ranged from 0.2-0.5 ng/mL, and values below the LOD were assigned the instrument-reading values if they were available or were given an imputed value below the LOD selected at random from the log-normal distribution using maximum likelihood estimation. Authors also utilized a handheld refractometer to measure urinary specific gravity. 81 urine samples missing specific gravity measurements had specific gravity imputed based on urinary creatinine. These allowed for the correction of samples by urinary dilution. These tools are an appropriate analytical method for quantifying phthalate metabolite concentrations, and the samples represent an etiologically relevant time period. Authors reported the percent of samples detected above the LOD, and the lowest detection was for MCPP, being detected in 90.3% of samples. Exposure misclassification is expected to be minimal.
Domain 3: Outcome Assessment				

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Study Citation:	Berger, K., Eskenazi, B., Balmes, J., Kogut, K., Holland, N., Calafat, A. M., Harley, K. G. (2019). Prenatal high molecular weight phthalates and bisphenol A, and childhood respiratory and allergic outcomes. Pediatric Allergy and Immunology 30(1):36-46.
Health Outcome(s) Assessed:	Lung/Respiratory- Probable asthma, aeroallergies, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5041286

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	All outcomes examined were determined in children at age 7. Children were classified as having ”probable asthma” if they were taking asthma medication or met two or more of the following criteria: current respiratory symptoms, a doctor’s diagnosis of asthma at any age (as reported by the mother), or a positive bronchodilator test during spirometry examinations. A child was considered to have respiratory symptoms based on mothers’ report using the International Study of Asthma and Allergies in Childhood questionnaire. Eczema was classified based on mothers reporting a doctor diagnosis of eczema or an allergic skin rash within the last year. Aeroallergies were defined by mothers’ report of ”runny or itchy eyes apart from colds,” ”sneezing or runny nose apart from colds,” or a doctor’s diagnosis of ”hay fever or allergic rhinitis” in the last year. Due to the self-reported nature of these outcomes, there is some concern for outcome misclassification. This concern is mitigated for the ”probable asthma” outcome by the use of multiple criteria to define cases. Outcome misclassification is a larger concern for eczema and aeroallergies, which rely solely on mothers’ reporting of a diagnosis or symptoms. Diagnoses were not confirmed by review of medical records or other methods. However, mothers’ reporting of outcomes is unlikely to be affected by knowledge of their children’s exposure status, particularly given the 7-year period between exposure measurement and outcome ascertainment. Thus, while outcome misclassification is a concern, it is not expected to be differential with respect to exposure level.
	Metric 3B:	Selective Reporting	Medium	The results reported by the authors align with the analyses described within the methods section of the paper.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Authors considered a number of variables identified a priori via directed acyclic graphs in demographically adjusted models. These variables included maternal age at birth, parity, household income as a proportion of poverty at baseline, and family history of asthma. Authors also created fully adjusted models which controlled for chemical co-exposures such as metabolites of low molecular weight phthalates and phenols that were measured in urine samples. Bayesian model averaging was used to identify the most important variables for inclusion, and authors kept the three most influential variables with the highest posterior inclusion probabilities for each outcome. The authors utilized appropriate techniques for classifying potential confounders, and they had a clear strategy to identify variables for inclusion in the models. Residual confounding is of minimal concern.
Domain 5: Analysis				

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Study Citation:	Berger, K., Eskenazi, B., Balmes, J., Kogut, K., Holland, N., Calafat, A. M., Harley, K. G. (2019). Prenatal high molecular weight phthalates and bisphenol A, and childhood respiratory and allergic outcomes. Pediatric Allergy and Immunology 30(1):36-46.
Health Outcome(s) Assessed:	Lung/Respiratory- Probable asthma, aeroallergies, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5041286

Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	High	Descriptive information about outcome and exposure are reported. Urinary metabolite concentrations were averaged over pregnancy, and specific-gravity adjusted values were used for analysis. These concentrations were log2-transformed. Measurements from the first and second collection were used in sensitivity analyses. Logistic regression analyses were used to examine probable asthma, aeroallergies and eczema as binary variables. Analyses included crude models, models adjusted for demographic factors, and fully adjusted models that accounted for both demographic factors and chemical co-exposures. Generalized additive models with three degrees of freedom were used to test for linearity of relationships.Quantitative results were presented for each analysis with the estimate and and 95% confidence intervals. The number of samples below LOD was reported. Methods for handling missing data and data <LOD are described. No major deficiencies in analytical methods are noted.
	Metric 5B:	Sensitivity	Medium	The range of exposure levels is reported and there is adequate variability to evaluate the authors' hypothesis. Sample size is adequate. The children exposed prenatally were sensitive to the development of relevant outcomes in childhood, and outcome ascertainment was performed at an appropriate time. However, authors note that the study focuses on atopic illnesses, but their definition of "probable asthma" does not distinguish between atopic and non-atopic cases. This may reduce sensitivity to detect differentiated effects by etiology. Additionally, correlation between phthalate biomarkers may reduce sensitivity to detect the effects of individual chemicals, but adjustment for co-exposures in the models mitigates this concern.

Additional Comments: This study examined associations between in utero urinary phthalate exposure and respiratory and allergic outcomes in children as part of the CHAMACOS mother-child cohort study. The study utilized high-quality exposure assessment methods. Strengths included appropriate a priori confounder considerations and analytical methods. There is some concern of outcome misclassification due to self-reported measures of probable asthma, eczema, and aeroallergies. The study is also somewhat limited in its sensitivity to detect differentiated effects by asthma etiology. Overall, however, there is minimal concern of bias.

Overall Quality Determination Medium

Study Citation:	Berger, K., Eskenazi, B., Kogut, K., Parra, K., Lustig, R. H., Greenspan, L. C., Holland, N., Calafat, A. M., Ye, X., Harley, K. G. (2018). Association of Prenatal Urinary Concentrations of Phthalates and Bisphenol A and Pubertal Timing in Boys and Girls. Environmental Health Perspectives 126(9):97004.
Health Outcome(s) Assessed:	Reproductive/Developmental- Timing of puberty (thelarche), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4829221

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This longitudinal cohort study examines prenatal urinary phthalate levels and the association with timing of puberty (measured via thelarche, menarche, pubarche, and gonadarche) in 338 mother-child pairs from the Center for Health Assessment of Mothers and Children of Salinas (CHAMACOS) study in Salinas Valley, CA. Pregnant women (<20 weeks' gestation) were recruited from prenatal care clinics serving the Salinas Valley's farmworker population from 1999-2000. Women were eligible if they spoke English or Spanish, were eligible for low-income health insurance (medicaid), and were >=18 years old. 601 pregnant women were recruited, and 537 remained in the study through live birth. Mother-child pairs were included if they had at least one in utero urinary phthalate measure and one pubertal timing assessment (n = 338; 159 boys and 179 girls). It appears that cohort recruitment followed appropriate protocols, but nearly half of the original study population was lost to follow-up. A comparison of the analytical sample and the eligible population is not provided, making it difficult to assess the potential for selection bias. However, the available data has no indications that loss to follow-up was related to exposure.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Urinary phthalates were measured via solid-phase extraction coupled with isotope dilution high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry (HPLC-ES-MS/MS). Sample storage and transportation are adequately described. Samples were corrected for specific gravity (specific gravity measures imputed for those with missing data). Mothers provided two urine samples throughout pregnancy (sample timing means: 14.0 and 26.9 gestational weeks), which represents the etiologically relevant time-period. The average interval between sampling was 90 days. Limit of detection (0.2 ng/mL for MCNP, MCOP, MEHHP, MEOHP, MECPP; 0.3 ng/mL for MBzP; 0.5 ng/mL for MEHP) and %<LOD (<5% for MCNP, MCOP, MEHHP, MEOHP, MECPP, MBzP; 10.1% for MEHP) are reported. There is minor concern for exposure misclassification due to the short half-life of phthalate chemicals, however, there was evidence that daily measures remain fairly consistent over time.
Domain 3: Outcome Assessment				

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Study Citation:	Berger, K., Eskenazi, B., Kogut, K., Parra, K., Lustig, R. H., Greenspan, L. C., Holland, N., Calafat, A. M., Ye, X., Harley, K. G. (2018). Association of Prenatal Urinary Concentrations of Phthalates and Bisphenol A and Pubertal Timing in Boys and Girls. Environmental Health Perspectives 126(9):97004.
Health Outcome(s) Assessed:	Reproductive/Developmental- Timing of puberty (thelarche), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4829221

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Low	Six research assistants trained and supervised by pediatric endocrinologists assessed thelarche using the clinical Tanner staging. Thelarche was assessed every 9 months from 9 through 13 years. Mothers were asked to report Tanner stage information for girls starting at 7 years of age. Breast development was assessed via palpation. Inter-rater reliability Kappas for breast development was 0.70. Research assistants also determined the Tanner stage (e.g., Stage 1 or 2), which agreed with the endocrinologist ratings 90% of the time.Concern for misclassification due to limited ability to detect breast tissue vs. adipose tissue and the high proportion of overweight/obese girls in the sample. However, the associations were close to the null, minimizing concern that the effect was substantially biased. Additionally, puberty measures did not take place until age 9, and 39% of the study population had onset of thelarche before this age.
	Metric 3B:	Selective Reporting	Medium	Results for all anticipated analyses are reported.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Low	Concern for residual confounding due to a suspected but unknown confounder related to obesity that was not controlled for. Obesity was suspected to be on the causal pathway and not adjusted for but stratified for in sensitivity analyses and also considered for in mediation analyses. Results indicated that there may be some residual confounding by some factor related to obesity, but not obesity itself.Confounders were selected a priori and via directed acyclic graph. Maternal education, maternal years in US, family income, diet quality during pregnancy, and maternal prepregnancy BMI were included as covariates. Males and females were assessed separately. Information on these factors was collected at maternal interviews during study activity (twice during pregnancy, at child puberty measures) via structured questionnaire. Information on maternal race/ethnicity and maternal age at menarche also collected. Child height and weight (measured via stadiometer and scale) were used to calculate BMI and classify children into weight classes per CDC guidelines.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Parametric accelerated failure time (AFT) models used to assess timing of puberty and prenatal phthalate levels. Two-parameter Weibull distribution was assumed. Both interval and left censoring was assessed to account for those with pubertal onset before the follow-up period. Phthalate metabolites were log2 transformed for continuous analyses due to skew. Time ratios from AFT models were multiplied by the median age when children reached the pubertal milestone (calculated via unadjusted AFT model) to generate a mean shift in months per doubling of phthalate metabolite. LOD and % <LOD are reported. Samples below the LOD were assigned the instrumental reading value or were imputed via maximum likelihood estimation. Effect estimates with 95% confidence intervals are reported.Sensitivity analyses examined the role of overweight/obesity via inclusion of additional confounders and stratification via Paramed models.

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Health Outcome(s) Assessed:	Reproductive/Developmental- Timing of puberty (thelarche), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4829221

Domain	Metric	Rating	Comments
	Metric 5B: Sensitivity	Medium	Adequate sample size (n=338) and exposure distribution to detect an effect. Exposure measured at sensitive time period. Some concern with outcome measure and detection of early onset puberty, however this was addressed in the Outcome domain.

Additional Comments: This longitudinal cohort Center for Health Assessment of Mothers and Children of Salinas (CHAMACOS) examined prenatal urinary phthalate levels and the association with timing of puberty milestones (thelarche, menarche, pubarche, gonadarche) in children (n=338). Mild concern for bias due to residual confounding and some outcome misclassification due to puberty onset prior to follow-up period, however, these concerns do not threaten the validity of the study conclusions. The study reported that MBzP and DEHP were associated with later thelarche in girls.

Overall Quality Determination Low

Study Citation:	Berger, K., Eskenazi, B., Kogut, K., Parra, K., Lustig, R. H., Greenspan, L. C., Holland, N., Calafat, A. M., Ye, X., Harley, K. G. (2018). Association of Prenatal Urinary Concentrations of Phthalates and Bisphenol A and Pubertal Timing in Boys and Girls. Environmental Health Perspectives 126(9):97004.
Health Outcome(s) Assessed:	Reproductive/Developmental- Timing of puberty (pubarche, menarche, gonadarche), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4829221

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This longitudinal cohort study examines prenatal urinary phthalate metabolite levels and the association with timing of puberty (measured via thelarche, menarche, pubarche, and gonadarche) in 338 mother-child pairs from the Center for Health Assessment of Mothers and Children of Salinas (CHAMACOS) study in Salinas Valley, CA. Pregnant women (<20 weeks gestation) were recruited from prenatal care clinics serving the Salinas Valley's farmworker population from 1999-2000. Women were eligible if they spoke English or Spanish, were eligible for low-income health insurance (medicaid), and were >=18 years old. 601 pregnant women were recruited, and 537 remained in the study through live birth. Mother-child pairs were included if they had at least one in utero urinary phthalate measure and one pubertal timing assessment (n = 338; 159 boys and 179 girls). It appears that cohort recruitment followed appropriate protocols, but nearly half of the original study population was lost to follow-up. A comparison of the analytical sample and the eligible population is not provided, making it difficult to assess the potential for selection bias. However, the available data has no indications that loss to follow-up was related to exposure.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Urinary phthalate metabolites were measured via solid-phase extraction coupled with isotope dilution high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry (HPLC-ES-MS/MS). Sample storage and transportation were adequately described. Samples were corrected for specific gravity (specific gravity measures imputed for those with missing data). Mothers provided two urine samples throughout pregnancy (sample timing means: 14.0 and 26.9 gestational weeks), which represents the etiologically relevant time-period. The average interval between sampling was 90 days. Limit of detection (0.2 ng/mL for MCNP, MCOP, MEHHP, MEOHP, MECPP; 0.3 ng/mL for MBzP; 0.5 ng/mL for MEHP) and %<LOD (<5% for MCNP, MCOP, MEHHP, MEOHP, MECPP, MBzP; 10.1% for MEHP) are reported. There is minor concern for exposure misclassification due to the short half-life of phthalate chemicals, however, there was evidence that daily measures remain fairly consistent over time.
Domain 3: Outcome Assessment				

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Study Citation:	Berger, K., Eskenazi, B., Kogut, K., Parra, K., Lustig, R. H., Greenspan, L. C., Holland, N., Calafat, A. M., Ye, X., Harley, K. G. (2018). Association of Prenatal Urinary Concentrations of Phthalates and Bisphenol A and Pubertal Timing in Boys and Girls. Environmental Health Perspectives 126(9):97004.
Health Outcome(s) Assessed:	Reproductive/Developmental- Timing of puberty (pubarche, menarche, gonadarche), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4829221

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Six research assistants trained and supervised by pediatric endocrinologists assessed pubertal milestones using the clinical Tanner staging. Milestones were assessed every 9 months from 9 through 13 years. Additionally, mothers reported on Tanner stages in girls beginning at age 7. Pubic hair development was assessed via visual inspection, menarche status was assessed via questioning at visits, and boys' genital development was measured visually, although testicular volume was measured via orchidometer beads. Inter-rater reliability Kappas was 0.79 for pubic hair development (girls), 0.86 for pubic hair development (boys), and 0.75 for gential development (boys). Research assistants determined the Tanner stage (e.g., Stage 1 or 2), which agreed with the endocrinologist ratings 92% (girls - pubic hair development, boys - genital development) and 100% (boys - pubic hair development) of the time. Pubertal development was determined to be Stage 2 for pubarche or gonadarche. Minor concern for misclassification because puberty measures did not take place until age 9, and portions of the study population had onset of pubarche (girls only - 20%) before this age.
	Metric 3B:	Selective Reporting	Medium	Results for all anticipated analyses are reported.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Low	Concern for residual confounding due to a suspected but unknown confounder related to obesity that was not controlled for. Obesity was suspected to be on the causal pathway and not adjusted for but stratified for in sensitivity analyses and also considered for in mediation analyses. Results indicated that there may be some residual confounding by some factor related to obesity, but not obesity itself.Confounders were selected a priori and via directed acyclic graph. Maternal education, maternal years in US, family income, diet quality during pregnancy, and maternal prepregnancy BMI were included as covariates. Males and females were assessed separately. Information on these factors was collected at maternal interviews during study activity (twice during pregnancy, at child puberty measures) via structured questionnaire. Information on maternal race/ethnicity and maternal age at menarche also collected. Child height and weight (measured via stadiometer and scale) were used to calculate BMI and classify children into weight classes per CDC guidelines.
Domain 5: Analysis				

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Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4829221

Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Medium	Parametric accelerated failure time (AFT) models used to assess timing of puberty and prenatal phthalate levels. Two-parameter Weibull distribution was assumed. Both interval and left censoring was assessed to account for those with pubertal onset before the follow-up period. Phthalate metabolites were log2 transformed for continuous analyses due to skew. Time ratios from AFT models were multiplied by the median age when children reached the pubertal milestone (calculated via unadjusted AFT model) to generate a mean shift in months per doubling of phthalate metabolite. LOD and % <LOD are reported. The samples below the LOD were assigned the instrumental reading value or were imputed via maximum likelihood estimation. Effect estimates and 95% confidence intervals are reported.Sensitivity analyses examined the role of overweight/obesity via inclusion of additional confounders and stratification via Paramed models.
	Metric 5B:	Sensitivity	High	Adequate sample size (n=338) and exposure distribution to detect an effect. Exposure measured at sensitive time period. Some concern with outcome measure and detection of early onset puberty, however this was addressed in the Outcome domain.

Additional Comments: This longitudinal cohort Center for Health Assessment of Mothers and Children of Salinas (CHAMACOS) examined prenatal urinary phthalate levels and the association with timing of puberty milestones (thelarche, menarche, pubarche, gonadarche) in children (n=338). Mild concern for bias due to residual confounding and some outcome misclassification due to puberty onset prior to follow-up period, however, these concerns do not threaten the validity of the study conclusions. The study reported significant associations between all phthalate metabolites and earlier gondarche and pubarche in boys, as well as an association between DEHP and later menarche in girls.

Overall Quality Determination Medium

Study Citation:	Chin, H. B., Jukic, A. M., Wilcox, A. J., Weinberg, C. R., Ferguson, K. K., Calafat, A. M., Mcconnaughey, D. R., Baird, D. D. (2019). Association of urinary concentrations of phthalate metabolites and bisphenol A with early pregnancy endpoints. Environmental Research 168:254-260.
Health Outcome(s) Assessed:	Reproductive/Developmental- Early pregnancy outcome measures: time from ovulation to implantation, pattern of human chorionic gonadotropin (hCG) hormone rise (an early indicator of pregnancy), and type of ovarian corpus luteum "rescue" (timing and pattern of ovarian progesterone rise, necessary for maintaining an early pregnancy), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5043528

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This study used data from the North Carolina Early Pregnancy study (EPS), a prospective cohort study conducted in 1982-1986. The EPS enrolled 221 healthy women with no known fertility problems from the time they discontinued birth control and followed them for up to 6 months for the occurrence of a clinical pregnancy. Eligible women for this study included those who became pregnant and whose pregnancy lasted at least 6 weeks; women with early pregnancy losses were excluded because of distinct irregular hormone patterns in those conceptions. Of 151 clinical pregnancies, this study excluded one woman with missing phthalate measures, four who had been exposed to diethylstilbestrol (also associated with irregular hormone patterns in early pregnancy), and 10 with no day of ovulation or implantation identified (n=136). There was a minor discrepancy in the N shown in supplemental data and the manuscript. Ultimately, analysis included up to 137 women with a median age of 29 years, 66% of whom had a prior pregnancy. 95% of participants were white. Exclusions were appropriately justified and there was no evidence of any selection bias.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	High	Phthalate metabolite concentrations during the conception cycle were measured in a pool of three spot urine samples collected from each participant. Nine metabolites from six parent phthalates were analyzed. In addition to individual metabolites, the molar sum of four DEHP metabolites was analyzed. Participants collected daily morning spot urine samples in polypropylene jars without preservatives that were stored in their freezers for up to 2 weeks before collection by study staff. The three samples pooled for analysis were collected during the interval between the day after the end of menses and the day before implantation to estimate habitual exposure during the window prior to pregnancy establishment. Samples used were preferentially those collected on Mondays (the day participants were asked to collect a larger volume); if three adequate Monday samples were not available, a sample from a nearby day was used. Phthalate metabolites were measured at the CDC laboratories using high performance liquid chromatography-isotope dilution tandem mass spectrometry; methodological references were cited. All measures were standardized using creatinine concentrations. Important strengths include that no concentrations were below detection limits, and the use of three spot urine samples to characterize exposure during the relatively short conception cycle period.
Domain 3: Outcome Assessment				

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Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5043528

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Early pregnancy outcomes were characterized using measures of reproductive hormone metabolites in daily urine samples using radioimmunoassay methods. Major metabolites of estrogen (estrone 3-glucuronide (E1G)) and progesterone (pregnanediol 3-glucuronide (PdG) were measured, along with human chorionic gonadotropin (hCG) hormone. References were cited for the radioimmunoassay methods and markers used. These measures were used to define the three outcomes analyzed: pattern of early human chorionic gonadotropin (hCG) hormone, time from ovulation to implantation, and type of ovarian corpus luteum "rescue". Definitions used for each outcome measure were adequately characterized and references were cited to support their utility. hCG rise was used as an indicator of clinical pregnancy (3 days $\geq$ 0.02h ng/mL) and to estimate day of implantation ($\geq$0.015 ng/mL). The rate of hCG rise was characterized using repeated continuous measures of this hormone on the day of implantation and the following 6 days. Day of ovulation was identified by a rapid decline in the ratio of estrogen to progesterone metabolites, which has been validated against ultrasounds and luteinizing hormone measures. Time from ovulation to implantation was categorized in three groups ranging from n=34 to 52. Corpus luteum "rescue", or sustained progesterone production by the ovary prior to implantation, is critical for maintaining an early pregnancy. By design, only a subsample of pregnancies had progesterone metabolites measured outside of an ovulatory window. Type of rescue was characterized in this subset (n=74 women, 54%) with luteal (menstrual cycle) progesterone measures, with day of rescue defined as the first 2-day sequence in which progesterone metabolites were at least 31% higher than the preimplantation value. Type of rescue was characterized as early (within 2 days after implantation, n=42), late (3 to 6 days after implantation, n=16) and rescue with no rise during the first week of hCG rise (n=16). Early rise is hypothesized to be optimal. While there is limited data on the validity of outcome measures, and characteristics of the subset with and without corpus luteum rescue information were not compared, there was no evidence of important error or bias. However, numbers were limited for the analysis of corpus luteum rescue.
	Metric 3B:	Selective Reporting	Medium	Results were presented or described for all primary and secondary analyses included as aims.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Low	Covariates were identified a priori based on participant characteristics associated with exposure and outcomes, excluding potential mediators. Maternal age, smoking status, and body mass index (BMI) were considered as covariates but were ultimately excluded as the authors stated they did not appreciably change effect estimates. Criteria for determining what constituted an appreciable change were not specified. In addition, the authors did not discuss potential confounding by other variables such as participant education level, or co-exposure to other phthalates and BPA, some of which were significantly associated with outcomes. However, correlations among phthalates and BPA were not shown, and there was no evidence of residual confounding bias.

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Health Outcome(s) Assessed:	Reproductive/Developmental- Early pregnancy outcome measures: time from ovulation to implantation, pattern of human chorionic gonadotropin (hCG) hormone rise (an early indicator of pregnancy), and type of ovarian corpus luteum "rescue" (timing and pattern of ovarian progesterone rise, necessary for maintaining an early pregnancy), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5043528

Domain	Metric		Rating	Comments
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Descriptive data were presented for the analysis sample as a whole. Associations with the outcome variable time from ovulation to implantation, which was categorized as 6-8 (n=34), 9 (n=52) and 10-12 days (n=50), was analyzed using polytomous logistic regression. Phthalates exposure variables were natural log transformed. Associations with hCG rise, a continuous variable characterized by repeated measures, were analyzed using linear mixed models with biomarker exposure variables dichotomized at the median. Associations with type of corpus luteum rescue, which was also categorical, were analyzed using polytomous logistic regression models and natural log transformed exposure variables. Sensitivity analyses to evaluate robustness, effect modification (e.g., by smoking status) or linearity of dose-response were not discussed, but there was no evidence of important error or bias.
	Metric 5B:	Sensitivity	Low	There was variability in creatinine-adjusted phthalate metabolites. However, sensitivity may be limited by sample size, which ranged from 74 to 137, depending on the outcome.

Additional Comments: This prospective study used data from 137 participants in the North Carolina Early Pregnancy Study (1982-1986) to analyze the association between conception cycle urinary phthalates and three early pregnancy outcomes. Exposure was characterized using samples measures obtained in a pool of three spot urine samples. Early pregnancy outcomes, characterized using changes in three reproductive hormones, included time from ovulation to implantation, pattern of hCB rise (an indicator of pregnancy), and type of corpus luteum "rescue" (an indicator of ovarian progesterone production prior to implantation, necessary for sustaining and early pregnancy). The pattern of associations suggested some protective and other adverse associations between these early pregnancy outcomes and varied phthalate metabolites; associations for MBzP and sumDEHP reached statistical significance. Strengths include the prospective design, the use of multiple urine samples to characterize exposure, and the availability of detailed hormone measures to characterize very early pregnancy outcomes. Limitations include relatively small sample size and the potential for residual confounding.

Overall Quality Determination — Medium

Study Citation:	Heggeseth, B. C., Holland, N., Eskenazi, B., Kogut, K., Harley, K. G. (2019). Heterogeneity in childhood body mass trajectories in relation to prenatal phthalate exposure. Environmental Research 175:22-33.
Health Outcome(s) Assessed:	Reproductive/Developmental- Body mass index (BMI), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5514974

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Participants in this study were members of the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) cohort study, a prospective birth cohort of pregnant women in California's Salinas Valley in 1999 and 2000. The study location was stated to be an agricultural area with a large Latino population and high rates of obesity. Eligibility criteria included being 18 years of age or older, speaking English or Spanish, being eligible for low-income health insurance (Medicaid), being less than 20 weeks gestation, receiving prenatal care at partnering community clinics that served the farmworker populations, and planning to deliver at county hospital. The number of participants recruited was n=601, and n=536 women remained enrolled at delivery. Follow-up visits were performed on mothers and children from infancy through adolescence. Only n=435 had recorded prenatal phthalate measurements, and the analysis was focused on n=335 children who had height and weight measurements at 4 or more visits. Attrition is reported at various instances due to whether or not mother/child pairs could attend follow-up visits. The number of participants fell to as low as n=265 at 9.75 years follow-up but stayed within the range of 265-322. Some years of follow-up had more participants than prior years, indicating that many children did not fall out of the study but rather were unable to make certain study visits. There is no evidence that this attrition or loss to follow-up is related to exposure status and outcome. The study states that the sample used in analysis is not different from the larger cohort in terms of various demographic characteristics, except that in this sample there was a slightly higher percentage of mothers who exclusively breastfed for longer than 6 months (48% vs. 40%). Generally, there is limited risk of selection bias due to the reporting of eligibility criteria and recruitment and provision of participation rates.
Domain 2: Exposure Characterization				

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Health Outcome(s) Assessed:	Reproductive/Developmental- Body mass index (BMI), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5514974

Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Medium	Exposure to phthalates was measured via urinary metabolites, all of which are valid biomarkers of exposure for their respective parent compounds. Urine samples were collected from the mothers at the time of two pregnancy interviews - mean 14 (SD=4.8) and mean 26.9 (SD=2.5) weeks of gestation. The storage and transportation of samples is well-described. Quantification was performed using solid-phase extraction coupled with isotope dilution high performance liquid chromatography-electrospray ionization-tandem mass spectrometry. Limits of detection are stated to be between 0.2 to 0.6 ng/mL, and concentrations below the limit of detection were assigned an imputed value less than the LOD randomly selected from the log-normal distribution using maximum likelihood estimates. Specific percentages above the LOD are not specified, but ranges presented indicate that all metabolites were detected in more than 75% of samples. Urinary samples were corrected for creatinine. Temporality is established as the outcome is in children at various ages, thus outcome assessment proceeds exposure assessment. However, due to the short-lived nature of phthalates in the human body, it is uncertain how well these spot measurements reflect exposure relevant to the outcome of child BMI.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	High	The primary outcome of this study was childhood BMI at ages between 2 and 14 years old. Child height was measured in triplicate to nearest 0.1 cm using a stadiometer. For weight, at ages 2-7 children were weighed using the Tanita Mother-Baby Scale with shoes and coats removed. At ages 9-14, children were weighted standing barefoot with coats removed on a Tanita bioimpedance scale. Clothing weights were estimated as 0.5 kg for ages 9-12.75 and 1 kg at age 14. BMI was calculated as weight/height^2 (kg/m^2). BMI z-scores were also computed using CDC growth charts. The outcome is well-standardized and reported. Although it is not specified whether or not those conducting the outcome assessment were aware of participants' exposure status, this is not expected to greatly affect estimates given the use of standardized instruments.
	Metric 3B:	Selective Reporting	Medium	All analyses specified in the methods are reported sufficiently in the results. Thus, there are no concerns.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Considered covariates included pre-pregnancy BMI, smoking status during pregnancy, gestational weight gain, diet quality index during pregnancy, number of years living in the United States, age, marital status, and education. Results were also stratified based on sex. Potential covariates were identified based on a previous study of the same cohort. It is unclear why no child-specific covariates were chosen other than sex, and these may account for some residual confounding. However, the most relevant potential covariates (age, height, weight) are considered as part of the characterization of the outcome and in the analysis. The distribution of potential confounders was also not presented by exposure and outcome.

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Health Outcome(s) Assessed:	Reproductive/Developmental- Body mass index (BMI), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
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Domain	Metric		Rating	Comments
Domain 5: Analysis				
	Metric 5A:	Analysis	High	Growth mixture models were used to categorize four subgroups of the data with similar BMI and BMI z-score trajectories, based on longitudinal data from multiple study visits. The number of subgroups for the model was chosen Bayesian Information Criteria, and the potential for nonlinear trajectories was accounted for using piecewise quadratic B-splines. Functional principal component analysis was also conducted to identify the functional structures that explained the most variability in BMI trajectories across time. Phthalate exposure was categorized as the average of the two samples taken during pregnancy, and concentrations were examined continuously and log2-transformed.To assess the variability in the association between phthalates and BMI at various ages, generalized additive models were conducted, and inputs are well-reported. Phthalates and other covariates were then added to the growth mixture models to attempt to explain variation in BMI trajectory group membership. Finally, the principal component analysis scores were used regressed on phthalate concentrations, fitting separate models for each principal component, for both individual phthalates and all phthalates together. Generally analyses methods are well-reported and justified, with effect estimates and errors when appropriate.
	Metric 5B:	Sensitivity	Medium	No concerns for sensitivity. The sample size is likely large enough to detect an effect (n=335), and exposure ranges are wide enough to provide some contrast.

Additional Comments: This prospective birth cohort study used data from the CHAMACOS cohort to assess the association between prenatal urinary phthalate measurements and BMI trajectories throughout childhood. Generally, there is a low risk of bias, as the outcome and analysis are robust and aim to assess longitudinal outcomes rather than outcomes at a set point in time. The use of a multitude of models is useful for the purposes of risk evaluation and data interpretation. MCOP and DEHP metabolites were found to be an explanatory variable for variation in BMI trajectories among girls.

Overall Quality Determination Medium

Study Citation:	Hyland, C., Mora, A. M., Kogut, K., Calafat, A. M., Harley, K., Deardorff, J., Holland, N., Eskenazi, B., Sagiv, S. K. (2019). Prenatal exposure to phthalates and neurodevelopment in the CHAMACOS cohort.
Health Outcome(s) Assessed:	Neurological/Behavioral- Executive Function, Social Cognition, Cognition/Intelligence, Attention and Behavior., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	6815846

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	Hyland et al 2019 HEROID 6815846 analyzed the relationship between prenatal phthalates exposure and neurodevelopment using data from Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), a birth cohort of Mexican-American children. The cohort recruited Spanish- or English-speaking pregnant women <20 weeks' gestation who qualified for low-income health insurance and planned to deliver at the county hospital in 1999-2000. Participation rates were not provided. Of 601 women who initially enrolled, 527 (88%) remained in the study and delivered a live born singleton. This study included children with prenatal phthalates measures and at least one neurodevelopmental assessment through age 16y, comprising 334 unique participants (56% of the initial cohort). Analysis sample sizes varied by type of neurodevelopmental assessment and the number of repeated assessments at each age, with Ns ranging from 300 to 322. Characteristics of children with at least one neurodevelopmental assessment were largely similar to the sample of all live-born singletons. However, the analysis sample included a larger proportion of households above the poverty line (30.1 vs 18.0%) and children who had been breastfed for >6 months (49.4 vs 38.9%). Phthalate concentrations in the analysis vs. larger sample were not compared. While the analysis sample differed in some ways from the larger cohort there was no evidence of selectivity, i.e. that initial participation or loss to follow-up was associated with prenatal phthalates or with neurodevelopmental outcomes.
Domain 2: Exposure Characterization			

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Study Citation:	Hyland, C., Mora, A. M., Kogut, K., Calafat, A. M., Harley, K., Deardorff, J., Holland, N., Eskenazi, B., Sagiv, S. K. (2019). Prenatal exposure to phthalates and neurodevelopment in the CHAMACOS cohort.
Health Outcome(s) Assessed:	Neurological/Behavioral- Executive Function, Social Cognition, Cognition/Intelligence, Attention and Behavior., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	6815846

Domain	Metric	Rating	Comments
	Metric 2A: Exposure Measurement	Medium	Phthalates exposure was measured in two maternal spot urine samples collected at median times of 13- and 26-weeks' gestation, and the mean of two measures used in analysis. Eleven phthalate metabolites were measured in each sample at the CDC using HPLC-tandem mass spectrometry, applying quality control methods. Concentrations were adjusted for urine dilution using specific gravity. Given the short half-life of phthalates, within-person variability is typically high, risking non-differential misclassification. The availability of two urine samples was a strength of the exposure assessment: analyses used the mean of concentrations in both samples. Nonetheless, the low intra-class correlation coefficients (from 0.11 to 0.33 for repeat measures) indicate that misclassification of habitual exposure remains a concern. Another strength was the high proportion of samples with concentrations above LOD (range 88.3% to 100%). Values below LOD were imputed using instrumental reading values, or maximum likelihood predictions if there was no instrumental reading. Variables reflect exposure during the prenatal period, a critical time for neurodevelopment that preceded outcome assessment. However, measures of early childhood exposure, another critical period for brain development, were not available. Associations with individual metabolites were analyzed, though the primary exposure variables were the molar sum of DEHP metabolites, the sum of high molecular weight (MBzP, MCPP, MCOP, and MCNP) and low molecular weight (MEP, MBP, and MiBP) metabolites.

Domain 3: Outcome Assessment

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Study Citation:	Hyland, C., Mora, A. M., Kogut, K., Calafat, A. M., Harley, K., Deardorff, J., Holland, N., Eskenazi, B., Sagiv, S. K. (2019). Prenatal exposure to phthalates and neurodevelopment in the CHAMACOS cohort.
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Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	6815846

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	The study analyzed a diverse array of age-appropriate, standardized, established neurodevelopmental assessments spanning four broad areas, collected at ages 7, 9, 10.5, 12, 14 and 16 years. Tests were administered by appropriately supervised bilingual and bicultural psychometricians in the child's dominant language, in quiet rooms free from distractions, with additional assessments by parents, teachers and child self-report. (1) Executive function assessments included: (i) the Behavior Rating Inventory of Executive Function (parents multiple ages, teachers 7y), (ii) the NEPSY tower at 9y; (iii) the computerized Wisconsin Card Sort Task-64 (9 and 12y). (2) Cognition was assessed using the Weschler Intelligence Scale for Children (WISC-IV) at ages 7 and 10.5y. (3) Social Cognition was assessed using the Evaluacion Neuropsicologica del Nino at 9y, the NEPSY-II Affect Recognition Subtest at 12y, and the Social Responsiveness Scale (SRS-2) at 14y. (4) Attention and Behavior were assessed using the Behavior Assessment System for Children (BASC-2) by parents (multiple ages) and teachers (7y), and by the children using the BASC-2 Self-Report of Personality at ages 10.5 and 14y. Conners' Attention Deficit Hyperactivity Disorder DSM-IV Scale parent versions were completed by parents (multiple ages) and teachers (7y). Conners Continuous Performance Test version 5 (CPT II), a computerized test, was completed by children at 9 and 12 years of age. Multiple subscales were analyzed for each domain (e.g. verbal, perceptual, processing speed, working memory, and full-scale IQ). Strengths include the availability of repeated measures, the use of widely accepted methods, the broad array of domains assessed, and the use of trained, bilingual evaluators. Limitations include the varying number and timing of assessments for each participant. In addition, the authors did not report evaluating consistency across evaluators or the validity of assessments within this study population. However, there was no evidence of important error or bias.
	Metric 3B:	Selective Reporting	Medium	The authors reported findings for their main hypotheses. Associations using GEE to simultaneously model repeated measures of each outcome were presented consistently for their three primary exposure variables: the sum of low-molecular weight (LMW), the sum of high molecular weight (HMW) and the sum of DEHP phthalates. Sex differences were evaluated for these exposure variables. In addition, extensive supplemental material included associations between individual phthalate metabolites; sex differences were not discussed. Age-specific associations were not shown. The authors reported that they analyzed associations with each outcome measured at specific individual time points to assess whether the pattern of associations varied over time. These results were not shown or described in detail, but such analyses were not a primary aim.

Domain 4: Potential Confounding / Variability Control

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Study Citation:	Hyland, C., Mora, A. M., Kogut, K., Calafat, A. M., Harley, K., Deardorff, J., Holland, N., Eskenazi, B., Sagiv, S. K. (2019). Prenatal exposure to phthalates and neurodevelopment in the CHAMACOS cohort.
Health Outcome(s) Assessed:	Neurological/Behavioral- Executive Function, Social Cognition, Cognition/Intelligence, Attention and Behavior., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	6815846

Domain	Metric	Rating	Comments
	Metric 4A: Potential Confounding	Medium	The authors used a directed acyclic graph to select confounders. Covariates included maternal age, education, country of birth, and depression at time of assessment; child sex, age at assessment and language; HOME score evaluating the quality of the home environment; and household income at the time of each assessment. Analyses of computer-based tests also adjusted for child video game use. Sensitivity analyses examined the effect of additionally adjusting for breastfeeding duration, maternal vocabulary, and several neurotoxicants (polybrominated diphenyl ether flame retardants, organophosphate pesticide metabolites, organochlorine compounds, manganese). Though maternal smoking was not included, few mothers (n=13) smoked during pregnancy. The potential confounding influence of prenatal growth was addressed in sensitivity analyses that found no meaningful difference after excluding preterm or low birth weight infants. Cumulative effects of multiple related phthalates was addressed in part by analyzing the sum of HMW and LMW phthalates. However, potential confounding by phthalate co-exposures was not otherwise discussed. Correlations ranged from 0.11 to 0.70 between individual metabolites from differing parent phthalates. Confounding adjustments were appropriate. However, residual confounding (e.g. child schooling, marital status and potential neurotoxicant co-exposures such as Pb, illicit drug use, phthalate co-exposures) cannot be ruled out.

Domain 5: Analysis

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Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Medium	Descriptive data were provided for participant characteristics, phthalate distributions and test scores. Statistical analysis methods were appropriate. The primary analyses used generalized estimating equations to analyze associations between log2 transformed prenatal phthalates, adjusted for dilution using specific gravity, and repeated measures of each neurodevelopmental outcome. Results were shown as adjusted beta coefficients with 95% confidence intervals; the number of children and number of observations were presented for each model. A small number of missing covariates were imputed using data from the nearest available visit. One potential concern is that the authors did not address multiple comparisons, but all analyses were hypothesis driven. Though methods were appropriate, it is a limitation that some potentially relevant analyses were not presented, despite including 38 supplemental tables. First, sex differences were not examined for analyses of individual phthalate metabolites. This omission may be important given that the authors found important sex differences in associations between child cognition and the sums of DEHP and HMW phthalates. There was a pattern of negative associations in boys while some associations were positive among girls. Sex differences were significant for perceptual reasoning, processing speed, and working memory subscales, but not for verbal comprehension. Second, the authors used continuous exposure variables in all analyses of individual phthalates. However, there was evidence of non-linearity as well as sex differences in associations between HMW phthalate tertiles and behavioral outcomes (e.g. teacher reported ADHD outcomes, parent reported hyperactivity). Third, the authors did not report examining interactions or stratifying to evaluate whether any associations changed with increasing age. These limitations may affect the extent to which findings for individual metabolites are consistent with the more detailed analyses conducted for DEHP, LMW and HMW phthalates, which were the primary exposure variables.
	Metric 5B:	Sensitivity	Medium	Analytic sample sizes typically included more than 300 children, with repeated observations for some outcomes exceeding 1,000. There was variability in specific gravity-adjusted metabolite concentrations. Although statistical power may have been limited for conducting some stratified analyses, there is no evidence for concern with sensitivity.

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Health Outcome(s) Assessed:	Neurological/Behavioral- Executive Function, Social Cognition, Cognition/Intelligence, Attention and Behavior., Non-cancer
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Domain	Metric	Rating	Comments
Additional Comments:	This cohort study analyzed associations between prenatal phthalates and neurodevelopment in 334 of the 527 live singletons in CHAMACOS, a birth cohort of low-income Mexican-American children in Salinas, California. Phthalate exposures were estimated as the mean of two maternal spot urines collected during pregnancy. Executive function, cognition, social cognition, and attention/behavior were assessed in visits at ages 7, 9, 10.5, 12, 14 and 16 years using established instruments. The number and timing of assessments available varied for each participant. Generalized estimating equations were used to analyze repeated measures of developmental outcomes collected at different ages. The longitudinal design, long follow-up, use of two measures to estimate exposure, high detection rates for phthalate metabolites, and extensive neurodevelopmental testing are strengths of this study. However, the utility of this study for evaluating effects of individual phthalate metabolites is limited by the fact that potential sex differences and non-linear associations were not presented for these measures. Analyses of the primary exposure variables, the sums of DEHP, LMW and HMW metabolites, suggested that prenatal DEHP and HMW phthalates were associated with lower IQ scores in boys and higher scores in girls. However, associations between IQ scores and numerous individual metabolites, which were shown only for combined sexes, were largely null. Similarly, analyses using exposure tertiles suggested potential non-linearities and sex differences in relationships with some behavioral outcomes. For example, there was a non-linear association between HMW phthalates and increased teacher-reported DSM-IV inattention scores in boys which was inverted in girls (interaction p=0.08, S9). While this study had important strengths, the extent to which the limited analyses conducted for individual metabolites may have affected results obtained for those measures.		

Overall Quality Determination Medium

Study Citation:	James-Todd, T. M., Chiu, Y. H., Messerlian, C., Mínguez-Alarcón, L., Ford, J. B., Keller, M., Petrozza, J., Williams, P. L., Ye, X., Calafat, A. M., Hauser, R., Team, E.S. (2018). Trimester-specific phthalate concentrations and glucose levels among women from a fertility clinic. Environmental Health 17(1):55.
Health Outcome(s) Assessed:	Nutritional/Metabolic- pregnancy glucose levels, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4728454

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This study is a sub-analysis within the Environment and Reproductive Health (EARTH) study, an ongoing prospective study that recruited participants seeking infertility evaluation or treatment from a since Massachusetts hospital fertility center. In the larger study, 60% of eligible women (aged 18-46 at enrollment) agreed to participate. For the current study, women were included if they had a singleton or twin pregnancy between 2005 and 2015, provided at least one urine sample during 1st and/or 2nd trimester for phthalates measurement, and had electronic medical record data on the glucose challenge test (GCT); women with a history of diabetes were excluded (n=1). 166 women who did not meet inclusion criteria were excluded and had similar baseline characteristics as those included in the analysis (n=245).
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	High	Spot urine samples were collected in each trimester using sterile polypropylene cups; only samples collected prior to or at the time of the GCT test were included in the analysis. Solid phase extraction coupled with high performance liquid chromatography-isotope dilution tandem mass spectrometry with standard QA/QC procedures was used to analyze the samples for phthalate metabolites at the CDC lab in Atlanta. Values below the limit of detection (LOD) were substituted with LOD/square root of 2, and samples were corrected for urinary specific gravity to adjust for dilution. Gold standard methodology was used to measure the metabolites, and storage information is detailed. The use of multiple measures of urinary metabolites limits concerns for exposure misclassification.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	High	Trained study staff ascertained outcome data by abstracting clinic information from the patient's electronic medical record. All women receiving obstetric care at the study hospital underwent gestational diabetes mellitus (GDM) screening with a non-fasting, 50-g GCT at 24-28 weeks of gestation (median: 27 weeks). In accordance with standard criteria, women with blood glucose levels at least 140 mg/dL after GCT were considered to have impaired glucose tolerance (IGT).
	Metric 3B:	Selective Reporting	Medium	Results from primary and secondary analyses described in the methods section were reported in the results section and in related tables/figures.
Domain 4: Potential Confounding / Variability Control				

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Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
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Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	High	Confounding was evaluated using directed acyclic graphs based on prior knowledge of potential confounding variables, which included: 1) age at GCT, pre-pregnancy overweight or obese, total physical activity, race/ethnicity, family history of diabetes, infertility diagnosis, and number of fetuses in the pregnancy. Effect modification by age at rapid fertility decline, BMI, and infertility treatment modes was assessed using cross-product terms in the multivariable models. Data on all previously mentioned variables were collected by trained study personnel from the patients' electronic medical records.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Demographic data were analyzed descriptively. Continuous variables were log-transformed to improve normality for analysis. Phthalate data were analyzed in quartiles for the 1st and 2nd trimesters separately to assess potentially critical windows of exposure with respect to glucose tolerance. Pregnancy glucose was modeled as a continuous outcome variable using multivariable linear models. Several sensitivity analyses were conducted: 1) excluding 14 women without prospectively collected urine samples, 2) excluding 85 women with only one urine sample collected, 3) among the 159 women with prospectively collected urine samples in both the 1st and 2nd trimesters, associations between trimester-specific phthalates and glucose levels, and associations between phthalates and GCT dichotomized at 140, indicating impaired glucose tolerance, 4) restricting the analysis to singleton births only, 5) excluding those taking metformin (n=8), 6) excluding those with PCOS (n=21), 7) examining the effect of year of urine sample collection on phthalate levels, and 8) examining the effect of diet among a subgroup of women who had completed a validates 131-item food frequency questionnaire. LOD and % below LOD were presented for all phthalate metabolites. Tests of trend were conducted across phthalate quartiles. Estimates and 95% confidence intervals (CIs), as well as results from unadjusted and adjusted models, were presented in tables.
	Metric 5B:	Sensitivity	Medium	The study population (n=245) was relatively small given this is a sub-analysis of the larger cohort. However, the availability of multiple urine samples for a large proportion of participants and the detection of the outcome in 45 participants allowed for a very in-depth analysis of the available data. Every phthalate metabolite was detected in at least 90% of the study population, and covariate and outcome data were collected from medical records. The timing of exposure assessment was appropriate in assessing associations with the pregnancy-specific outcome.

Additional Comments: This prospective study is a sub-analysis of the EARTH study that assessed associations between phthalate metabolites measured in pregnant women during the 1st and 2nd trimesters and pregnancy glucose measured at 24-28 weeks gestation. The study utilized gold standard exposure measurement, collected covariate and outcome data from medical records, and measured exposure prior to outcome ascertainment (for all but 8 participants, whose exposure and outcome were measured simultaneously). Detailed and thoughtful statistical analyses were used to summarize the data. The study found that women in the highest quartile of 2nd trimester MiBP concentrations had lower glucose levels during the 2nd trimester.

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Health Outcome(s) Assessed:	Nutritional/Metabolic- pregnancy glucose levels, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4728454

Domain	Metric	Rating	Comments
Overall Quality Determination		**High**	

Study Citation:	Li, N., Papandonatos, G. D., Calafat, A. M., Yolton, K., Lanphear, B. P., Chen, A., Braun, J. M. (2019). Identifying periods of susceptibility to the impact of phthalates on children's cognitive abilities. Environmental Research 172:604-614.
Health Outcome(s) Assessed:	Neurological/Behavioral- Full-scale IQ at age 5 years (Wechsler Preschool and Primary Scale of Intelligence-III [WPPSI-III]) and full scale IQ at age 8 years (Wechsler Intelligence Scale for Children-IV [WISC-IV])), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5053633

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	This prospective cohort study on phthalates exposure and child cognition used data from 253 mother-child pairs in the Cincinnati Health Outcomes and Measures of the Environment (HOME) Study (Cincinnati, Ohio). Pregnant women (~ 16 weeks' gestation) who lived in housing built prior to 1978 were recruited in 2003-2006. 401 of 1263 (31.7%) eligible women enrolled and remained in the study through delivery; 398 had live singleton births. This study included 253 (64% of eligible participants retained through delivery) mother-child pairs with at least one gestational and one childhood measurement of urinary phthalate metabolites, complete covariates, and at least one measure of cognitive abilities obtained at age 5 (n=202) or 8 (n=220) years. Effective sample size varied by availability of phthalate measures. Although there was substantial attrition, there is no evidence that inclusion in the analysis was associated with both phthalate exposures and cognitive outcomes.
Domain 2: Exposure Characterization			

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Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
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Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Medium	Phthalates were measured in repeated spot urine samples, an appropriate medium, including prenatal measures in maternal urine and child samples collected concurrent with outcome measures. Materna urine samples were collected at 16 and 26 weeks of gestation); samples in children were collected annually from ages 1 to 5 years, and again at age 8. Phthalates were measured using an automated isotope dilution HPLC-MS method with calibration standards and quality controls. Published data indicate this method performed well (e.g., MCOP and MCNP accuracy was within 1.5 ng/mL, Silva et al 2007, HEROID 807138). The number of urine samples with measured phthalates from each wave ranged from a minimum of 166 (66%) to a maximum of 251 (99%). Measures included four DEHP metabolites (MEHP, MEHHP, MEOHP, MECPP), DiNP metabolite MCOP, DiDP metabolite MCNP, DBP metabolite MnBP (a small % may also reflect BBP exposure), DiDP metabolite MiBP, and BBP metabolite MBzP. The molar sum of DEHP metabolites was analyzed. MCOP and MCNP were not measured in maternal urine, as the analytic method including those biomarkers was not yet developed at the time of those analyses. MnBP, MiBP, and MEHP in urine samples collected at ages 1–3 years were excluded from analysis because of contamination from diaper inserts. Dilution was addressed by adjusting for urinary creatinine. LODs ranged from ~0.1 to ~1 ng/mL; values below LOD were imputed as LOD divided by the square root of 2. Some details on the distributions of phthalates were shown in a supplement not available at the time of this evaluation; distributions provided elsewhere indicate that proportions below LOD were largely <5% and consistently <25% (Watkins et al. 2015, HEROID 2347098; Schoaff et al 2015, HEROID 3230353). The availability of repeated exposure measures for phthalates was an important strength. However, it is a potential limitation that exposure during critical time windows for brain development may be represented by measures in a single spot sample, or that measures of key phthalates may have been unavailable for that period.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	High	Cognitive outcomes were assessed at aged 5 and 8 years by three trained examiners by means of two very widely used instruments (Wechsler Preschool and Primary Scale of Intelligence-III [WPPSI-III], Wechsler Intelligence Scale for Children-IV [WISC-IV]). A single expert performed quality checks and recertified examiners every 6 months. Full scale IQ scores were normalized based on US population reference data; SD scores were analyzed. Associations with indices for specific domains (e.g., verbal IQ, performance IQ, working memory) were also analyzed for phthalate metabolites that were inversely associated with full scale IQ (results described as similar to full scale IQ, included in supplement not available at the time of this assessment).
	Metric 3B:	Selective Reporting	Medium	There was no evidence of selective reporting. Results for all analyses were shown or described in the manuscript or supplementary materials.
Domain 4: Potential Confounding / Variability Control				

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Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
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Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	Medium	Confounders were identified using directed acyclic graphs. Models adjusted for maternal age, education, marital status, IQ, serum cotinine in pregnancy and pre-pregnancy BMI along with household income, child race, child sex, and HOME scores for the caregiving environment. Urinary creatinine was included as a covariate to account for dilution. Sensitivity analyses confirmed that there was little impact of adjusting for test examiner or for maternal pregnancy-induced hypertension, which was excluded as a potential intermediate. The confounders included were strongly associated with IQ scores. Co-exposure to correlated phthalates was addressed by analyzing associations with a weighted phthalate index (weighted quantile sum regression) in one analysis. Though it cannot be ruled out, there was no evidence of residual confounding (e.g., childhood environmental tobacco exposure, diet, psychosocial stress, other neurotoxic exposures such as Pb).
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Statistical analyses used a multiple informant method to investigate associations between log transformed repeated urinary phthalate measures and repeated full scale IQ measures obtained at ages 5 and 8 years. The method used generalized estimating equations to jointly estimate the exposure-outcome association including each exposure measurement period and cognitive outcomes at both ages. Associations between age 8 phthalates and age 5 IQ were excluded (potential reverse causality). Phthalate x visit interaction terms were included to assess the heterogeneity of associations by timing of exposure measurement ($p<0.20$); the authors documented when findings indicated heterogeneity for any one period. Both unadjusted and adjusted effect estimates were presented. Sex differences were evaluated in sensitivity analyses using visit x phthalate x sex interaction terms; p-values but not sex-stratified associations were shown. It is a potential limitation that several sensitivity analyses were conducted only for the subset of phthalate metabolites with at least one significant inversely association in the linear models. However, these sensitivity analyses did not provide evidence of non-linear dose-response using cubic splines and reported similar associations with specific cognitive domains as those presented for full scale IQ.
	Metric 5B:	Sensitivity	Medium	The range of and variability in exposure and outcome measures was large. However, the sample size was modest (N up to 218 across exposure waves). In addition, the descriptive data showed that IQ scores were strongly associated with each of the potential confounders ($p<0.01$ for 9 variables). It is possible that strong confounding reduced effective statistical power, including the ability to detect interactions. However, there is no evidence of insufficient sensitivity.

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Domain	Metric	Rating	Comments
Additional Comments:	This study used data from 253 children in the Cincinnati HOME cohort to analyze associations between multiple phthalate metabolites and child cognition measured at ages 5 and 8 years. Child IQ was measured by means of the widely used Wechsler tests. Phthalate metabolites were measured in both maternal urine at 16- and 26-weeks' gestation, and in child spot urine samples collected annually from ages 1 to 5, and again at age 8. Prenatal measures were not available for MCOP and MCNP as the methods used did not include those metabolites at that time. The pattern of associations varied by metabolite: adjusted associations reached significance for several measures obtained in urine samples collected at ages 3y and 4y. These included significant negative associations between full scale IQ and age 3y samples for the sum of DEHP metabolites and MBzP, along with MCPP and MEP, with null associations for exposure measured at age 4y. The negative association with MBzP was also significant at age 8y, and marginally non-significant associations with MBzP in early gestation and at age 5y. There were significant positive associations with MnBP and MiBP measured at age 4y; phthalates measures at age 3 years were not available for MnBP and MiBP. Strengths include the longitudinal design, repeated measures of exposures as well as outcomes, and quality control of the cognitive assessments. Potential limitations include that the sample size may have limited statistical power, particularly to detect interactions, and that critical time windows for exposure effects on brain development may be represented by a single spot sample.		

Overall Quality Determination Medium

Study Citation:	Li, N., Papandonatos, G. D., Calafat, A. M., Yolton, K., Lanphear, B. P., Chen, A., Braun, J. M. (2020). Gestational and childhood exposure to phthalates and child behavior. Environment International 144:106036.
Health Outcome(s) Assessed:	Neurological/Behavioral- Child behavior, as reported by parents or caregivers using the Behavioral Assessment System for Children-2 (BASC-2) (internalizing problems, externalizing problems, Behavioral Symptoms Index [BSI]) and nine clinical subscales., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	9419532

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	Li et al 2020 HEROID 9419532 analyzed the relationship between child behavior and phthalates exposure – including DiDP/DiNP metabolites – using data from the longitudinal Health Outcomes and Measures of the Environment (HOME) cohort. The HOME study recruited pregnant women in greater Cincinnati, Ohio between 2003 and 2006, and conducted follow-ups through age 8 years. Eligibility criteria for pregnant women included age >= 18 years, being within 16 +/- 3 weeks of gestation, living in a home built before 1978, and not taking medications for thyroid disorders. Of 1263 eligible women, 468 (37%) participated, and 389 had live singleton births. This study included 314 (80.7% of live singleton births; 171 girls, 143 boys) mother-child pairs with at least one urinary phthalate measure in pregnancy or childhood, at least one child behavior assessment, and complete covariate data. Children excluded from the analysis had slightly younger and slightly more educated mothers, with a slightly higher prevalence of smoking during pregnancy. However, there was no evidence of selection bias (i.e. that selection was associated with phthalates exposure and child behavior outcomes).
Domain 2: Exposure Characterization			

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Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
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Domain	Metric	Rating	Comments
	Metric 2A: Exposure Measurement	High	Phthalates were measured in urine samples collected from mothers during gestation (~weeks 16 and 26) and from children annually from ages 1 to 5 and at age 8 years. Given their short half-lives and typical high variability in exposure, availability of repeated measures of urinary phthalates was an important strength. Measures in both mothers and children included four DEHP metabolites [mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), and mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP], and one metabolite each of DBP [mono-n-butyl phthalate (MnBP)], BBP metabolite [monobenzyl phthalate (MBzP)], and DiBP [mono-isobutyl phthalate (MiBP)]. Childhood measures included the DiDP metabolite mono-carboxynonyl phthalate (MCNP) and the DiNP metabolite monocarboxyoctyl phthalate (MCOP). While repeated measures were a strength, it was a minor limitation that maternal concentrations of these metabolites were not measured, as the methods to do so had not been developed. Another minor limitation was that MEHP, MnBP and MiBP were not quantified in samples from ages 1-3 years due to contamination in diaper inserts used to collect samples. DEHP exposure was analyzed as the molar sum of three metabolites MEOHP, MECPP and MECPP, excluding MEHP as this metabolite was not available at all ages. Methods established by the CDC (high performance liquid chromatography-mass spectrometry with standards and quality controls) were used to measure phthalate metabolites. Fewer than 3% of samples were below LOD (0.1 to 1 ng/mL); these values were imputed LOD divided by the square root of 2. Creatinine was used to account for dilution. 64.7% of children had 6-8 repeated urinary phthalate measures; 7.3% had 2-3 measurements. The use of measurement error models to estimate exposure was an additional strength. Exposure measurement error was addressed using subject-specific repeated measures in regression calibration models that estimated adjusted creatinine-standardized log-10 transformed phthalate concentrations at each age. Model specifications incorporated repeated measures of exposure as time-varying variables to evaluate periods of susceptibility. Sample size and percentile distribution of corrected and uncorrected phthalates were presented for each age. To reduce risk of reverse causation, longitudinal exposure-outcome associations analyzed exposure estimates through the time of assessment of each outcome measure.

Domain 3: Outcome Assessment

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Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Child behavior outcomes at ages 2, 3, 4, 5 and 8 years were evaluated based on parent or caregiver ratings on the Behavioral Assessment System for Children-2 (BASC-2), a validated and reliable tool. An assessment of validity within the study population was not mentioned. However, intraclass correlation coefficients ranging from 0.52 to 0.68 across repeated assessments was indicative of stability. The study analyzed three behavior problem composite scales (internalizing problems, externalizing problems, and Behavioral Symptoms Index [BSI]) and nine clinical subscales (anxiety, depression, somatization, aggression, conduct problems, hyperactivity, attention problems, atypicality, and withdrawal). Standardized T-scores were analyzed. The stability of outcome measures facilitated the analysis of repeated measures of most outcomes, which increased effective power and precision. Conduct problems were only assessed at age 8 years. Teacher ratings were not available.
	Metric 3B:	Selective Reporting	Medium	Results were presented or described for all analyses discussed in the methods.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Covariates were selected using previous literature and directed acyclic graphs; causal intermediate or colliders were excluded. Covariates included maternal age, pre-pregnancy BMI, cotinine levels in pregnancy, maternal depression, alcohol use in pregnancy, maternal education, marital status, child sex, race/ethnicity, and age at outcome assessment. Effects of additionally adjusting for co-exposure to BPA and triclosan, child blood lead, household income, pregnancy induced hypertension, parity, caregiving environment, and maternal ADHD were examined. Mothers with diabetes were not eligible for the cohort. Co-exposure to phthalates was addressed using a weighted quantile sum mixture variable, as well as in models that mutually adjusted for gestational and childhood metabolite concentrations. The study was unable to evaluate the potential influence of gestational concentrations of MCOP and MCNP on results. However, for several other phthalates, childhood concentrations were more strongly associated with some – though not all – outcomes than were gestational levels. There was no evidence to suggest important residual confounding bias in this study.
Domain 5: Analysis				

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Study Citation:	Li, N., Papandonatos, G. D., Calafat, A. M., Yolton, K., Lanphear, B. P., Chen, A., Braun, J. M. (2020). Gestational and childhood exposure to phthalates and child behavior. Environment International 144:106036.
Health Outcome(s) Assessed:	Neurological/Behavioral- Child behavior, as reported by parents or caregivers using the Behavioral Assessment System for Children-2 (BASC-2) (internalizing problems, externalizing problems, Behavioral Symptoms Index [BSI]) and nine clinical subscales., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	9419532

Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Medium	Descriptive data included detailed exposure distributions, along with outcome means presented overall as well as stratified by levels of multiple covariates. Random intercept linear mixed models were used to analyze associations between time-varying repeated measures of phthalate metabolites and repeated behavioral outcomes. Results were presented as adjusted mean differences in scores per interquartile increase in each metabolite. Phthalate metabolites were log-10 transformed, creatinine adjusted, and measurement error corrected using regression calibration. Calibration approaches used repeated measures of exposure and accounted for time trends in exposure patterns. Effect modification by child sex was examined. The authors also used general estimating equations to examine whether associations between phthalates and outcomes varied by age at exposure or outcome assessment; heterogeneity p-values were not significant. Sensitivity analyses to evaluate robustness included adjustments for additional covariates as noted earlier. The authors did not discuss evaluating non-linearity in dose-response, but there was no evidence of non-linear patterns of association.
	Metric 5B:	Sensitivity	Medium	There was no evidence of inadequate sensitivity. There was variability in phthalate exposures at all ages. The time-varying sample size of up to 314 mother-child pairs was moderate, with statistical power increased by repeated measures of exposure and outcome.

Additional Comments: This study used data from 314 children (171 girls, 143 boys) in the longitudinal Health Outcomes and Measures of the Environment (HOME) cohort in greater Cincinnati, Ohio to analyze associations between urinary phthalate metabolites and parent/caregiver ratings of child behavior in multiple assessments through age 8 years. Outcomes were measured using the Behavioral Assessment System for Children-2 (BASC-2). Phthalate metabolites were measured in maternal urine at gestational weeks 16 and 26, and in annual child urine samples from ages 1 to 5 years, and at age 8 years. Availability of metabolite measures varied due to changes in laboratory methods (no gestational MCNP and MCOP), and phthalate contamination of diaper inserts used to collect samples at ages 1-3 years (no MEHP, MnBP, MiBP at those ages). Repeated phthalate metabolite measures were used to address measurement error due to within-person variability and the short half-lives of phthalate metabolites, using regression calibration to estimate adjusted or predicted exposure concentrations. Childhood but not gestational measures of several phthalates were associated with behavioral outcomes. Notably, urinary MCOP and MCNP were associated with significantly higher composite Behavioral Symptoms Index (BSI) scores, with somewhat stronger associations in boys. MCNP was also associated with higher externalizing problems composite scores overall and in boys, and both MCNP and MCOP were associated with significantly higher somatization subscale scores. Gestational measures of MCNP and MCOP were not available in this study, since methods to assay these metabolites were not available when maternal samples were analyzed.

Overall Quality Determination — Medium

Study Citation:	Mustieles, V., Mínguez-Alarcón, L., Christou, G., Ford, J. B., Dimitriadis, I., Hauser, R., Souter, I., Messerlian, C. (2019). Placental weight in relation to maternal and paternal preconception and prenatal urinary phthalate metabolite concentrations among subfertile couples. Environmental Research 169:272-279.
Health Outcome(s) Assessed:	Reproductive/Developmental- Placental weight, birth weight to placental weight ratio, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5742214

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This study on phthalates and placental weight in sub-fertile couples included participants in the Environment and Reproductive Health (EARTH) Study, a prospective preconception cohort of couples recruited from a fertility center in Massachusetts. Participation rates were not discussed. The sample was predominantly Caucasian (95% of mothers) and highly educated (45% of mothers with graduate degrees). Women aged 18-46 and men aged 18-55 were eligible. The analysis sample included data from participants who used their own gametes, had singleton infants born between 2005 and 2016, had an available placenta at delivery, and phthalates quantified in at least one pre-conception urine sample. The authors stated that characteristics of parents in the analysis sample (N=132 mothers, N=68 fathers) did not differ substantially from the full cohort (N=364 mothers, N=195 fathers, Messerlian et al 2017 HEROID 3972328). Although proportions of preterm and low birth weight infants were elevated in the subsample, the main findings relating phthalates with birth weight were consistent with the full sample. While sample size was small, there was no evidence of selection bias.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Both preconception and prenatal phthalate exposures were estimated. Preconception phthalate exposures were quantified using the mean of available preconception spot urine samples for both men and women; prenatal exposure was estimated using the mean of up to three spot urine samples (one per trimester) for women. Specific gravity was used to adjust for dilution; the mean of log-transformed specific-gravity adjusted samples was used. Preconception samples were collected at enrollment from both men and women, with up to two additional samples per fertility treatment cycle for women and one per cycle for men. Phthalate metabolites were measured at the CDC laboratories using HPLC-MS with quality control procedures. Concentrations below detection limits (which ranged from 0.1 to 1.2 across metabolites) were assigned the LOD divided by the square root of 2. For all metabolites except MEHP and MBzP, the proportion of samples with detectable levels of metabolites ranged from 80% to 100%. Detection rates for MBzP were 87% to 93% except for 70% in maternal preconception samples. While other DEHP metabolites had detection rates of 81% to 99%, MEHP detection rates ranged from 47% (maternal preconception samples) to 69% (paternal preconception samples). The availability of a mean of 2.5, 4 and 2.5 urine samples for paternal, maternal preconception and maternal prenatal urine samples was an important strength. However, only one sample was available for 24%, 20% and 13% of paternal and maternal preconception and maternal prenatal urine samples, respectively.
Domain 3: Outcome Assessment				

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Study Citation:	Mustieles, V., Mínguez-Alarcón, L., Christou, G., Ford, J. B., Dimitriadis, I., Hauser, R., Souter, I., Messerlian, C. (2019). Placental weight in relation to maternal and paternal preconception and prenatal urinary phthalate metabolite concentrations among subfertile couples. Environmental Research 169:272-279.
Health Outcome(s) Assessed:	Reproductive/Developmental- Placental weight, birth weight to placental weight ratio, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5742214

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Placental weight (umbilical cord and fetal membranes removed) was measured by nurses immediately after delivery, and birth weight was abstracted from hospital records. The birth weight to placental weight ratio (BW:PW) was calculated. Placental weight and its ratio to birth weight are used as indicators of placental functioning.
	Metric 3B:	Selective Reporting	Medium	There was no indication of selective reporting.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Confounders were identified using directed acyclic graphs. Maternal exposure models adjusted for maternal age, maternal BMI, maternal education, maternal smoking status, and infant sex. Paternal preconception samples were additionally adjusted for paternal age and BMI and paternal smoking. The authors did not adjust for mode of conception based on the absence of association with placental weight or BW:PW in a different study population. Gestational age, which was correlated with some phthalate metabolites, birth weight and placental weight, was not discussed as a confounder; gestational age may have been considered as a potential intermediate. However, a sensitivity analysis excluded preterm births. Parity (88% of women were nulliparous) was not considered. Potential confounding by gestational age, mode of conception, parity, or other variables (e.g., any parental medical conditions, time to conception), was not explored but there is also no evidence of bias. Notably, for one phthalate (MEP), the authors found that mutually adjusting for maternal preconception and prenatal exposure was influential.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Multiple linear regression models were used to analyze associations between phthalate exposures and both placental weight and the BW:PW ratio. Separate models were run for each phthalate measure, including separate models for maternal and paternal pre-conception and prenatal measures. Adjusted and unadjusted models were shown; results did not meaningfully differ. Sample size varied considerably across these models based on maternal vs. paternal urine availability (N=68 vs. 123 or 131). The authors did not conduct sensitivity analyses examining linearity or excluding individuals with only one urine sample. A sensitivity analysis excluded preterm births; the potential influence of low birth weight was not discussed but was likely partially addressed by this analysis. A limitation of the study is that the potential influence of sample size differences is unknown, as the authors did not discuss whether associations with maternal exposures conducted in larger samples yielded similar results if repeated within the smaller subset that had paternal exposure data.

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Study Citation:	Mustieles, V., Mínguez-Alarcón, L., Christou, G., Ford, J. B., Dimitriadis, I., Hauser, R., Souter, I., Messerlian, C. (2019). Placental weight in relation to maternal and paternal preconception and prenatal urinary phthalate metabolite concentrations among subfertile couples. Environmental Research 169:272-279.
Health Outcome(s) Assessed:	Reproductive/Developmental- Placental weight, birth weight to placental weight ratio, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5742214

Domain	Metric	Rating	Comments
	Metric 5B: Sensitivity	Medium	Sample size was small, particularly for paternal exposure (N=68). Nonetheless, there is no evidence that this was a limitation, since statistically significant, or marginally significant associations with outcomes were observed for paternal measures of a number of other phthalate measures. Statistical power was optimized by using continuous variables. In addition, the range of and variability in exposure and outcome measures appeared to be adequate. For example, in paternal preconception samples, the SG-adjusted median (IQR) for MCOP was 35.0 (10.7 to 69.5) ng/mL, for MCNP 4.4 (2.9 to 7.8) ng/mL, and for MEHP 2.7 (1.3 to 6.2) ng/mL.

Additional Comments: This study used data from a small cohort of subfertile couples in the Environment and Reproductive Healthy (EARTH) study to analyze the association between paternal (N=68) and maternal (N=132) preconception urinary phthalates, as well as maternal prenatal (N=123) phthalates, and measures of placental weight. Several phthalate metabolites, including paternal ∑DEHP, were associated with decreased placental weight. Limitations including small sample size and the potential for residual confounding. However, exposure estimation was an important strength; for most participants, there were multiple urine samples collected throughout the preconception and prenatal periods, with measures from both parents. Detection rates were high for most phthalates, with the exception of one DEHP metabolite.

Overall Quality Determination Medium

Study Citation:	Nakiwala, D., Peyre, H., Heude, B., Bernard, J. Y., Béranger, R., Slama, R., Philippat, C. (2018). In-utero exposure to phenols and phthalates and the intelligence quotient of boys at 5 years. Environmental Health 17(1):11.
Health Outcome(s) Assessed:	Neurological/Behavioral- , Full-Scale iQ, Verbal IQ, Performance IQ, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4728401

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	In this cohort study mother-son pairs were selected from the French EDEN (Etude des Determinants pre et post natals du development et de la sante de l'Enfant) cohort which examined the relationship between DINP metabolite (Monocarboxy-isooctyl phthalate), DIDP metabolite (Monocarboxy-isononly phthalate), DBP metabolites (Mono-n-butyl phthalate (MBP); Mono(3-carboxypropyl) phthalate (MCPP)), DIBP metabolite (Mono-isobutyl phthalate (MiBP)), DEHP metabolites (Mono(2-ethyl-5-carboxypentyl) phthalate (MECPP);Mono(2-ethyl-5-hydroxyhexyl) phthalates (MEHHP); Mono(2-ethyl-5-hdroxyhexyl) phthalate (MEOHP); Mono(2-ethylhexyl phthalate) (MEHP), and BBP metabolite (Monobenzyl phthalate (MBzP)) and Verbal and performance IQs of boys at 5-6 years old. Pregnant women (before the end of the 28th gestational week) were recruited from February 2003 through January 2006 from the obstetric departments of Nancy and Poitiers university hospitals in France. A subset of participants (n=452) of male participants (n=998 originally recruited) were randomly chosen from the EDEN cohort for follow-up. IQ assessments were conducted on 452 boys at 5 years. Inclusion criteria for biomarker assessments was being a boy, having at least one urine sample available during pregnancy, and having data on growth during the pre and postnatal period (up to 3 years). Compared to mother-son pairs from EDEN not included in this analysis, pairs in this study were more likely to be from Poitiers, from households that earned >1500 euros/month, and less likely to smoke during pregnancy; all of these were considered as covariates.
Domain 2: Exposure Characterization			

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Study Citation:	Nakiwala, D., Peyre, H., Heude, B., Bernard, J. Y., Béranger, R., Slama, R., Philippat, C. (2018). In-utero exposure to phenols and phthalates and the intelligence quotient of boys at 5 years. Environmental Health 17(1):11.
Health Outcome(s) Assessed:	Neurological/Behavioral- , Full-Scale iQ, Verbal IQ, Performance IQ, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4728401

Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Medium	Maternal urine samples were taken during pregnancy between 22 and 29 gestational weeks and phthalates were extracted using solid phase extraction-high performance liquid chromatography-tandem mass spectrometry. Sample transportation and storage are not described. Concentrations were standardized for collection conditions such as hour of sampling, gestational age at collects, duration of storage at room temperature before freezing, day of sampling, year of biomarker assessments and creatinine levels. For concentrations below the LOD the instrumental reading values were used. All samples were collected under similar conditions and were used in all of the analyses. LOD values were 0.5 ug/L for MEHP, 0.3 ug/L for MbzP, and 0.2 ug/L for MBP, MiBP, MECPP, MEHHP, MEOHP, MCPP, MCOP, and MCNP. The percentage of values below the LOD were 0% for MBP, MiBP, MECPP, MEHHP, MEOHP, MBzP, MCOP, and MCPP and 1% for MCNP and 3% for MEHP. This study used one single urine measurement to assess exposure, which could lead to exposure misclassification due to the short half-life of phthalate metabolites in the human body. The exposure window was developmental, while outcomes were only measured at 5 years of age - it is unclear whether this is appropriate consideration of temporality, as phthalate metabolites may exhibit adverse neurological effects when exposure is post-natal; it is unclear whether maternal exposure to phthalates is representative of a child's exposure. However, there is no explicit evidence of bias or that the chosen exposure window is not related to the outcome.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	High	Full-scale IQ, Performance IQ, and Verbal IQ were assessed at an average of 5.7 years of age using the French version of the Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III). The scale was calibrated in a sample of 999 children representative of French children between ages 2.5 and 7.25 years. The IQ assessments were conducted by trained psychologists using 7 core subtests (information, vocabulary, word reasoning, block design, matrix reasoning, picture concepts, and coding) to compute verbal and performance IQ scores. There are no concerns for bias in the outcome assessment.
	Metric 3B:	Selective Reporting	Medium	Analyses described in the methods were reported in the results.
Domain 4: Potential Confounding / Variability Control				

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Study Citation:	Nakiwala, D., Peyre, H., Heude, B., Bernard, J. Y., Béranger, R., Slama, R., Philippat, C. (2018). In-utero exposure to phenols and phthalates and the intelligence quotient of boys at 5 years. Environmental Health 17(1):11.
Health Outcome(s) Assessed:	Neurological/Behavioral- , Full-Scale iQ, Verbal IQ, Performance IQ, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4728401

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	Medium	Considered confounders included center of recruitment, parity, maternal age, maternal BMI, parental education level, breastfeeding duration, monthly household include, smoking during pregnancy, maternal psychological difficulty during pregnancy, child cognitive stimulation, and child age at assessment. Confounders were identified a priori via literature review. Child cognitive stimulation was assessed using the Home Observation for the Measurement of the Environmental Scale questionnaire (HOME) at 5 years. Maternal psychological difficulties score during pregnancy was calculated as combined scores from the Center for Epidemiologic Studies Depression Scale Revised (CESD) and the State-Trait Anxiety Inventory (STAI). The study does not state where other covariate information came from, but it was likely pulled from questionnaires or interviews administered by research staff.
Domain 5: Analysis				
	Metric 5A:	Analysis	High	Structural Equation Models (SEMs) were used to study the associations between the urinary biomarker concentrations and Verbal or Performance IQ scores. Authors reported standardized association estimates as change in SD of IQ scores associated with a 1-SD increase in the ln-transformed biomarker concentrations. P-values were presented along with corrections for multiple testing using the false discovery method. Additional analyses were run stratified by center due to exposure levels and IQ scores differing across recruitment centers. In addition to the SEM, linear regression models were run using the manual IQ scores. Sensitivity analyses were also performed that used full-scale IQ. Statistical methods are well-reported and take into account model assumptions.
	Metric 5B:	Sensitivity	Medium	Sample size is large (n=452 boys) and exposure range is adequate (MCOP median = 4.0 ug/L [5th 1.1, 95th 19]) (MCNP median = 1.3 ug/L[5th 0.4, 95th 9.7]) (MBP median = 44.6 ug/L [5th 11.6, 95th 444]) (MiBP median = 38.8 ug/L [5th 11.8, 95th 168]) (MECPP median = 39.2 ug/L [5th 12.5, 95th 176]) (MEHHP median = 29 ug/L [5th 6.9, 95th 106]) (MEOHP median = 23.3 ug/L [5th 5.8, 95th 87]) (MEHP median = 7.6 ug/L [5th 1.5, 95th 37]) (MBzP median = 18.9 ug/L [5th 4.7, 95th 114]) (MCPP median = 2.0ug/L [5th 0.8, 95th 9.4]). It is unclear if a single spot urine adequately represents the intensity, duration and potential peak exposures responsible for the initiation of the outcome of interest.

Additional Comments: This cohort study assessed the relationship between full-scale IQ, verbal IQ, and performance IQ in 5-year-old boys and DINP, DIDP, DBP, BBP, DEHP, and DIBP metabolite concentrations. Generally, there are minimal concerns for bias - concerns exist for exposure assessment due to the use of a single spot urine sample during pregnancy to explain neurological outcomes at 5 years of age. However, other aspects of the study are well described and there is no direct evidence that the exposure assessment is biased. No statistically significant results were reported for any relevant phthalates.

Overall Quality Determination — Medium

Study Citation:	Parada, H., Gammon, M. D., Chen, J., Calafat, A. M., Neugut, A. I., Santella, R. M., Wolff, M. S., Teitelbaum, S. L. (2018). Urinary Phthalate Metabolite Concentrations and Breast Cancer Incidence and Survival following Breast Cancer: The Long Island Breast Cancer Study Project. Environmental Health Perspectives 126(4):047013.
Health Outcome(s) Assessed:	Mortality- Breast cancer mortality, Cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4728408

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Participants in this study were women who were recruited into the Long Island Breast Cancer Study Project (LIBCSP), which was initially a case-control study then continued as a prospective cohort study. The prospective cohort analysis solely focused on cases. Cases were adult women with a first diagnosis with in situ or invasive breast cancer from August 1, 1996 to July 31, 1997 via a rapid reporting system used by the LIBCSP. Controls were recruited from the same two Long Island counties as LIBCSP, and were frequency matched to the expected distribution of women with breast cancer in 5-year age groups from 1996 to 1997. Controls 65 years of age and older were identified form the Health Care Finance Administration rosters, and all other controls were identified via random digit dialing in eight waves.82% (n=1,508) of eligible cases completed the main questionnaire, while 63% (n=1,556) of controls completed the main questionnaire. LIBSCP participants ranged from 20-98 years of age and were 93% white and 67% postmenopausal. Among all included women, random sampling was performed twice (once in 2007 and once in 2010) to identify women with available urine samples for analysis. Not all urine samples were analyzed for phthalates due to limited resources, so women whose urine was not selected were excluded from further analysis. 400 cases and 400 controls were selected for urine analysis in 2007, and 493 cases and 250 controls were selected in 2010. Further exclusions were made for women with missing creatinine (n=224), women with dilute urine defined as creatinine $<$ 10 mg/dL (n=10), and one woman with insufficient urine volume. The final sample consisted of 710 women with in situ (n=112) or invasive breast cancer (n=598) and 598 women without breast cancer. Since MCNP and MCOP were only measured in 2010, the final sample for those phthalates consisted of 320 cases and 205 controls.Overall there is limited risk of bias in participant selection. Controls and cases were pulled from the same representative population and matched based on age. There is no evidence to suggest that any random sampling done or exclusions would be differential based off of exposure status. The study does not report the total number of eligible participants, but this is also unlikely to be differential or have a significant impact on results.
Domain 2: Exposure Characterization				

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Study Citation:	Parada, H., Gammon, M. D., Chen, J., Calafat, A. M., Neugut, A. I., Santella, R. M., Wolff, M. S., Teitelbaum, S. L. (2018). Urinary Phthalate Metabolite Concentrations and Breast Cancer Incidence and Survival following Breast Cancer: The Long Island Breast Cancer Study Project. Environmental Health Perspectives 126(4):047013.
Health Outcome(s) Assessed:	Mortality- Breast cancer mortality, Cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4728408

Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Medium	Exposure to phthalates was measured via urinary concentrations of relevant metabolites. Urine samples were collected between 1996-1997 and were actually analyzed for MCNP and MCOP in 2010. Sample transportation and storage are sufficiently described. MCNP and MCOP were measured using online solid-phase extraction followed by high-performance liquid chromatography-electrospray ionization-isotope-dilution tandem mass-spectrometry. The limit of detection is specified to be 0.2 ug/L for both metabolites, and only 0.4% of samples were below the limit of detection for MCNP and MCOP was detected in all samples (Table S1). There is concern regarding temporality given the short-lived nature of phthalates and the chronic nature of the primary outcome, breast cancer. Samples were taken on average 3 months after diagnosis, and thus proceed outcome assessment. For mortality-related outcomes, there is limited concern because exposure precedes the outcome of mortality. All metabolites were specific to the parent compound.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	The primary outcome in this study was breast cancer incidence. Cases were recruited from a rapid reporting system created for Long Island Breast Cancer Study Project (LIBCSP). Diagnosis of breast cancer was confirmed by each patient's physician and medical record review. However, the article does not specify whether they confirmed controls did not have breast cancer, and it is possible that controls may have the disease without being aware. However, this is generally difficult to account for and not expected to have an outsized impact on effect estimates. Outcome assessment occurred before the exposure assessment, limiting the concern that outcome ascertainment was informed by exposure status.Secondary outcomes of the study were all-cause mortality and breast cancer mortality. Vital status was determined among cases from 1996-1997 until December 31, 2014. ICD-9/10 codes 174.9 and C-50.9 on death certificates were used to identify deaths associated with breast cancer. There are no concerns regarding the accuracy of the mortality assessment.
	Metric 3B:	Selective Reporting	Medium	The primary and secondary analyses are well described and extensively reported in the results.
Domain 4: Potential Confounding / Variability Control				

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Study Citation:	Parada, H., Gammon, M. D., Chen, J., Calafat, A. M., Neugut, A. I., Santella, R. M., Wolff, M. S., Teitelbaum, S. L. (2018). Urinary Phthalate Metabolite Concentrations and Breast Cancer Incidence and Survival following Breast Cancer: The Long Island Breast Cancer Study Project. Environmental Health Perspectives 126(4):047013.
Health Outcome(s) Assessed:	Mortality- Breast cancer mortality, Cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4728408

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	High	Considered covariates included age, income, education, reproductive factors, menopausal status, oophorectomies/hysterectomies, other surgical information, pregnancy status, lactation status, hormone replacement therapy use, parity and lactation history, age at first birth, family history of breast cancer, exogenous hormone use, age at menarche, BMI, alcohol intake, and estrogen receptor status. Analyses in cases only also used chemotherapy as a covariate. Potential covariates were identified based on a literature review. Associations between covariates and both exposure and outcome are reported separately (Table S3 and Table 1). All potential confounders were identified through questionnaire and medical record review. In analysis, only covariates significantly associated with phthalate metabolite concentrations in controls were used in statistical models.
Domain 5: Analysis				
	Metric 5A:	Analysis	High	Associations between breast cancer incidence and phthalates were measured using multivariable unconditional logistic regression. Odds ratios and 95% CIs are reported. Analyses were done on quintiles of creatine-corrected concentrations of both metabolites, and continuous natural log-transformed concentrations of both metabolites. Secondary analyses were also performed on tertiles to assess effect modification by BMI. Associations between mortality outcomes and phthalates were assessed via multivariable Cox regression models and reported hazard ratios and 95% CIs. Quintiles of creatinine-corrected phthalate metabolites were used. Assumptions were evaluated using Kaplan-Meier survival curves and log[-log(survival)] plots to assess the proportional hazards assumption, alongside assessing Schoenfeld residuals. No violations of the proportional hazards assumption were reported. In analyses of breast cancer mortality, non-breast cancer deaths were censored at the time of death. Sensitivity analyses were also conducted assessing effect modification by BMI and estrogen receptor status.
	Metric 5B:	Sensitivity	Medium	Generally, sensitivity was high due to large sample sizes (n=525 in the case-control analysis and n=320 in the mortality analysis) and exposure ranges wide enough to provide sufficient contrast between high and low exposures. However, there is some concern about sensitivity due to the exposure assessment occurring after the outcome assessment for a short-lived compound, and the lack of confirmation that controls were cancer-free.

Additional Comments: This study was a case-control analysis with a mortality follow-up component among women in the Long Island Breast Cancer Study Project. The mortality analysis was generally well-conducted and described with minimal concerns for bias. The largest concerns are the short-term nature of phthalate metabolite measurements in urine, but there is no evidence to suggest that any misclassification would be differential by outcome status. The primary outcomes were breast cancer mortality and all-cause mortality, and no significant results were reported.

Overall Quality Determination Medium

Study Citation:	Parada, H., Gammon, M. D., Chen, J., Calafat, A. M., Neugut, A. I., Santella, R. M., Wolff, M. S., Teitelbaum, S. L. (2018). Urinary Phthalate Metabolite Concentrations and Breast Cancer Incidence and Survival following Breast Cancer: The Long Island Breast Cancer Study Project. Environmental Health Perspectives 126(4):047013.
Health Outcome(s) Assessed:	Reproductive/Developmental- Breast cancer, Cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4728408

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Participants in this study were women who were recruited into the Long Island Breast Cancer Study Project (LIBCSP), which was initially a case-control study then continued as a prospective cohort study. The prospective cohort analysis solely focused on cases. Cases were adult women with a first diagnosis with in situ or invasive breast cancer from August 1, 1996 to July 31, 1997 via a rapid reporting system used by the LIBCSP. Controls were recruited from the same two Long Island counties as LIBCSP, and were frequency matched to the expected distribution of women with breast cancer in 5-year age groups from 1996 to 1997. Controls 65 years of age and older were identified form the Health Care Finance Administration rosters, and all other controls were identified via random digit dialing in eight waves.82% (n=1,508) of eligible cases completed the main questionnaire, while 63% (n=1,556) of controls completed the main questionnaire. LIBSCP participants ranged from 20-98 years of age and were 93% white and 67% postmenopausal. Among all included women, random sampling was performed twice (once in 2007 and once in 2010) to identify women with available urine samples for analysis. Not all urine samples were analyzed for phthalates due to limited resources, so women whose urine was not selected were excluded from further analysis. 400 cases and 400 controls were selected for urine analysis in 2007, and 493 cases and 250 controls were selected in 2010. Further exclusions were made for women with missing creatinine (n=224), women with dilute urine defined as creatinine $<$ 10 mg/dL (n=10), and one woman with insufficient urine volume. The final sample consisted of 710 women with in situ (n=112) or invasive breast cancer (n=598) and 598 women without breast cancer. Since MCNP and MCOP were only measured in 2010, the final sample for those phthalates consisted of 320 cases and 205 controls.Overall there is limited risk of bias in participant selection. Controls and cases were pulled from the same representative population and matched based on age. There is no evidence to suggest that any random sampling done or exclusions would be differential based off of exposure status. The study does not report the total number of eligible participants, but this is also unlikely to be differential or have a significant impact on results.
Domain 2: Exposure Characterization				

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Study Citation:	Parada, H., Gammon, M. D., Chen, J., Calafat, A. M., Neugut, A. I., Santella, R. M., Wolff, M. S., Teitelbaum, S. L. (2018). Urinary Phthalate Metabolite Concentrations and Breast Cancer Incidence and Survival following Breast Cancer: The Long Island Breast Cancer Study Project. Environmental Health Perspectives 126(4):047013.
Health Outcome(s) Assessed:	Reproductive/Developmental- Breast cancer, Cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4728408

Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Low	Exposure to DiDP was measured via urinary concentrations of the metabolite MCNP, while exposure to DiNP was measured via urinary concentrations of MCOP. Urine samples were collected between 1996-1997 and were actually analyzed for MCNP and MCOP in 2010. Sample transportation and storage are sufficiently described. MCNP and MCOP were measured using online solid-phase extraction followed by high-performance liquid chromatography-electrospray ionization-isotope-dilution tandem mass-spectrometry. The limit of detection is specified to be 0.2 ug/L for both metabolites, and only 0.4% of samples were below the limit of detection for MCNP and MCOP was detected in all samples (Table S1). There is concern regarding temporality given the short-lived nature of phthalates and the chronic nature of the primary outcome, breast cancer. Samples were taken on average 3 months after diagnosis, and thus proceed outcome assessment. The study cites several additional papers as evidence that single measurements of phthalates are somewhat reproducible over several days and month, but regardless there is uncertainty especially if womens' diets and consumption patterns changed after diagnosis. Concentrations of phthalates were creatinine-adjusted.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	The primary outcome in this study was breast cancer incidence. Cases were recruited from a rapid reporting system created for Long Island Breast Cancer Study Project (LIBCSP). Diagnosis of breast cancer was confirmed by each patient's physician and medical record review. However, the article does not specify whether they confirmed controls did not have breast cancer, and it is possible that controls may have the disease without being aware. However, this is generally difficult to account for and not expected to have an outsized impact on effect estimates. Outcome assessment occurred before the exposure assessment, limiting the concern that outcome ascertainment was informed by exposure status.Secondary outcomes of the study were all-cause mortality and breast cancer mortality. Vital status was determined among cases from 1996-1997 until December 31, 2014. ICD-9/10 codes 174.9 and C-50.9 on death certificates were used to identify deaths associated with breast cancer. There are no concerns regarding the accuracy of the mortality assessment.
	Metric 3B:	Selective Reporting	Medium	The primary and secondary analyses are well described and extensively reported in the results.
Domain 4: Potential Confounding / Variability Control				

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Study Citation:	Parada, H., Gammon, M. D., Chen, J., Calafat, A. M., Neugut, A. I., Santella, R. M., Wolff, M. S., Teitelbaum, S. L. (2018). Urinary Phthalate Metabolite Concentrations and Breast Cancer Incidence and Survival following Breast Cancer: The Long Island Breast Cancer Study Project. Environmental Health Perspectives 126(4):047013.
Health Outcome(s) Assessed:	Reproductive/Developmental- Breast cancer, Cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4728408

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	High	Considered covariates included age, income, education, reproductive factors, menopausal status, oophorectomies/hysterectomies, other surgical information, pregnancy status, lactation status, hormone replacement therapy use, parity and lactation history, age at first birth, family history of breast cancer, exogenous hormone use, age at menarche, BMI, alcohol intake, and estrogen receptor status. Analyses in cases only also used chemotherapy as a covariate. Potential covariates were identified based on a literature review. Associations between covariates and both exposure and outcome are reported separately (Table S3 and Table 1). All confounders were identified through questionnaire and medical record review. In analysis, only covariates significantly associated with phthalate metabolite concentrations in controls were used in statistical models.
Domain 5: Analysis				
	Metric 5A:	Analysis	High	Associations between breast cancer incidence and DiDP/DiNP were measured using multivariable unconditional logistic regression. Odds ratios and 95% CIs are reported. Analyses were done on quintiles of creatine-corrected concentrations of both metabolites, and continuous natural log-transformed concentrations of both metabolites. Secondary analyses were also performed on tertiles to assess effect modification by BMI. Associations between mortality outcomes and DiDP/DiNP were assessed via multivariable Cox regression models and reported hazard ratios and 95% CIs. Quintiles of creatinine-corrected phthalate metabolites were used. Assumptions were evaluated using Kaplan-Meier survival curves and log[-log(survival)] plots to assess the proportional hazards assumption, alongside assessing Schoenfeld residuals. No violations of the proportional hazards assumption were reported. In analyses of breast cancer mortality, non-breast cancer deaths were censored at the time of death. Sensitivity analyses were also conducted assessing effect modification by BMI and estrogen receptor status.
	Metric 5B:	Sensitivity	Medium	Generally, sensitivity was high due to large sample sizes (n=525 in the case-control analysis and n=320 in the mortality analysis) and exposure ranges wide enough to provide sufficient contrast between high and low exposures. However, there is some concern about sensitivity due to the exposure assessment occurring after the outcome assessment for a short-lived compound, and the lack of confirmation that controls were cancer-free.

Additional Comments: This study was a case-control analysis with a mortality follow-up component among women in the Long Island Breast Cancer Study Project. The breast cancer analysis was generally well-reported but concerns exist for exposure misclassification. The study uses a spot urine sample collected three months after breast cancer diagnosis, which may introduce bias given the short half-life of phthalate metabolites and the potential for recall bias/change in diet or consumption patterns post breast cancer diagnosis. Inverse associations were observed for breast cancer and MiBP, MCOP, and MECCP.

Overall Quality Determination — Medium

Study Citation:	Philippat, C., Heude, B., Botton, J., Alfaidy, N., Calafat, A. M., Slama, R., Group, E.M. (2019). Prenatal Exposure to Select Phthalates and Phenols and Associations with Fetal and Placental Weight among Male Births in the EDEN Cohort (France). Environmental Health Perspectives 127(1):17002.
Health Outcome(s) Assessed:	Reproductive/Developmental- Placental-to-birth weight ratio (PFR), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5041225

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	The study population was a subgroup from the Etude des Déterminants pré et postnatals du développement et de la santé de l'Enfant (EDEN) mother-child cohort that consist of pregnant women recruited from 2003 to 2006.. Exclusion criteria for the entire cohort included multiple pregnancies, known diabetes prior to pregnancy, French illiteracy, or having a move-out plan in the next 3 years. In total, 473 mother-son pairs were included in the analysis. Additional criteria for the current study were male birth and available data on both birth weight and placental weight. Participation rate from the whole cohort was not reported, but number of male births that were excluded (n=525) was provided. Comparison of characteristics between included and excluded subjects were reported in Table 1. The authors reported that high frequency of missing placental weight in Nancy (43%) hospital compared with Poitiers (7%) might lead to selection bias; this potential bias was addressed via inverse probably weighting. While some information on participation was not available, the information provided does not raise major concerns regarding selection bias.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Phthalate biomarkers were assessed in urine samples. First morning urine samples were collected from participants between 23 and 29 gestational weeks, which represents an appropriate exposure window. Most women collected urine samples at home, while spot samples were collected at the hospital from 66 (14%) women. The LOD and detection frequency were reported for each phthalate metabolite. Values below the LOD were replaced with the instrumental reading, unless the reading was 0 in which case the value was replaced with the lowest reading divided by the square root of two. LODs were: MCOP 0.2 ug/L, MCNP 0.2 ug/L, MBP 0.2 ug/L, MiBP 0.2 ug/L, MBzP 0.3 ug/L, MEHP 0.5 ug/L, MEHHP 0.2 ug/L, MEOHP 0.2 ug/L, MECCP 0.2 ug/L. The percent of samples above the LOD was 100% for all metabolites except for MEHP (98% $>$ LOD) and MCNP (99% $>$ LOD). The samples were assessed by a CDC lab and the process is blinded. Further analytic details including instrumentation (on-line solid phase extraction coupled with isotope dilution-high performance liquid chromatography-tandem mass spectrometry) were reported in Silva et al. 2007 (HERO ID 807138). Exposures were standardized for creatinine. Factors potentially contributing to exposure misclassification include the collection of only one sample per pregnant women and variation in sample collection methods (i.e., home collection of first morning urine vs. spot sample collection in clinic). However, there is no evidence to suggest that such misclassification would be differential by outcome status.
Domain 3: Outcome Assessment				

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Health Outcome(s) Assessed:	Reproductive/Developmental- Placental-to-birth weight ratio (PFR), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5041225

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	The outcomes of interest were placental weight, birth weight, and placental-to-birth weight ratio (PFR). Placental and infant birth weight were obtained from hospital maternity records. Although validation process was not provided with some uncertainty, medical records obtained from the hospital is unlikely to introduce serious misclassification.
	Metric 3B:	Selective Reporting	Medium	The primary and secondary/sensitivity analyses in the method sections were described in details. Results were reported for all primary analyses. There is minimal concern of selective reporting.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Confounders were selected a priori. Those variables were "likely to be common causes of both the exposures and the outcomes without being likely consequences thereof and factors that were possible predictors of the outcomes only". Confounders included in models were: gestational duration, maternal pre-pregnancy weight and height, maternal active and passive smoking, maternal education, parity, and recruitment center. Elastic net regression models also included all other measured exposures (phthalates and phenols) , while unpenalized linear regression models included all other exposures retained in elastic net models. The distribution of potential confounders by exposure or outcome levels were not provided. The missing rate of confounders are low because analysis was restricted to participants having non-missing values.
Domain 5: Analysis				
	Metric 5A:	Analysis	High	The authors used adjusted Elastic Net penalized regression models (ENET) to select biomarkers (phthalates and phenols) associated with placental weight, birth weight, and placental to birth weight ratio (PFR). Unpenalized effect estimates were obtained by fitting linear regression models adjusted for the ENET-selected biomarkers and potential confounders. The statistical methods were described in detail, and also reported imputations for missing biomarkers. Concentrations below LOD were replaced by instrumental reading values. Method to replace instrument reading of 0 was provided. Sensitivity analyses included estimation of recruitment center-specific effects, single-pollutant models, and evaluation the extent to which results were driven by extreme values from inverse probability weighting.
	Metric 5B:	Sensitivity	Medium	The population size (n=473) is large in this study. The outcomes were measured at birth so the timing of assessment is not a concern. Phthalate metabolite detection rates were high (>=98% for all relevant metabolites) and exposure ranges likely provide sufficient contrast. Median (5th-95th percentiles) were: MCOP 3.86 (1.17, 17.4) ug/L, MCNP 1.26 (0.49, 10.2) ug/L, MBP 43.4 (11.7, 454) ug/L, MiBP 39.4 (11.8, 170) ug/L), MBzP 18.2 (4.47, 100) ug/L, MEHP 7.40 (1.30, 33.7) ug/L, MEHHP 27.7 (6.41, 98.5) ug/L, MEOHP 22.9 (5.28, 81.6) ug/L, MECPP 38.9 (12.0, 156) ug/L.

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Health Outcome(s) Assessed:	Reproductive/Developmental- Placental-to-birth weight ratio (PFR), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5041225

Domain	Metric	Rating	Comments
Additional Comments:	This birth cohort study evaluated associations between phthalate metabolites and a set of outcomes measured at birth (birth weight, placental weight, placental-to-birth weight ratio). MCNP and MCOP were both associated with lower placental-to-birth weight ratio; MCNP was additionally associated with lower placental weight. Minor concerns include potential exposure misclassification due measurement of metabolites in a single urine sample per participant and variability in urine sample collection methods.		

Overall Quality Determination Medium

Study Citation:	Reeves, K. W., Santana, M. D., Manson, J. E., Hankinson, S. E., Zoeller, R. T., Bigelow, C., Sturgeon, S. R., Spiegelman, D., Tinker, L., Luo, J., Chen, B., Meliker, J., Bonner, M. R., Cote, M. L., Cheng, T. D., Calafat, A. M. (2019). Urinary phthalate biomarker concentrations and postmenopausal breast cancer risk. Journal of the National Cancer Institute 111(10):1059-1067.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Breast cancer, Cancer; Reproductive/Developmental- Breast cancer, Cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5043615

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Participants in this Women's Health Initiative (WHI) nested case-control study were recruited from 40 clinical centers throughout the country between October 1, 1993, and December 21, 1998. This study included 419 cases and 838 controls. All participants were between 50 and 79 years of age at enrollment and had no prior cancer history (other than nonmelanoma skin cancer). Incident breast cancer cases were diagnosed through the end of follow-up in 2013. Cases were included if they had at least two urine samples available for phthalate measurement (from both the year 1 and year 3 follow-up visits) and were diagnosed after the year 3 visit. Two control subjects were individually matched to each case. Controls were not diagnosed with breast cancer, and were matched on enrollment date, length of follow-up, age at enrollment, and WHI study arm (clinical trials vs. observational study). If there were more than 2 eligible controls, two were randomly selected. Characteristics of included participants vs. the parent cohort were not described. There was no evidence to suggest concerns of bias based on participant selection, and inclusion and exclusion criteria were clearly outlined. The comparison group was adequately selected and methods for inclusion were provided.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	All participants in this study had provided at least two urine samples, collected at the year one and year three clinic visits, prior to breast cancer diagnosis among cases. Additional urine samples were collected at year 1 among participants in the WHI clinical trial arm: 168 cases (40.1%) and 336 controls (40.1%) had three urine samples available. First morning void samples were collected by participants at home and processed within 30 minutes of arrival at the clinic. The urine samples were analyzed for phthalate metabolite concentrations by solid phase extraction and high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry with quality controls. The DiNP metabolite monocarboxyoctyl phthalate (MCOP) was among those measured. Coefficients of variation for these metabolites was < or = 6.3%. The limit of detection for phthalate metabolites was not reported, but the authors highlighted that <1% of observations were below the LOD. For values below LOD, the authors imputed the value as the LOD divided by the square root of two. Samples were standardized for dilution using creatinine. The availability of multiple samples and prospective designs are important strengths. However, given the long latency for developing breast cancer, it cannot be ascertained to what extent the timing of urine sample collection reflects the most relevant exposure. In addition, the low intra-class correlations (ICC) for repeated measures of phthalate metabolites (mean ICC = 0.07 for MCOP) indicate that additional samples would have been optimal to characterize participants' exposure.

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Study Citation:	Reeves, K. W., Santana, M. D., Manson, J. E., Hankinson, S. E., Zoeller, R. T., Bigelow, C., Sturgeon, S. R., Spiegelman, D., Tinker, L., Luo, J., Chen, B., Meliker, J., Bonner, M. R., Cote, M. L., Cheng, T. D., Calafat, A. M. (2019). Urinary phthalate biomarker concentrations and postmenopausal breast cancer risk. Journal of the National Cancer Institute 111(10):1059-1067.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Breast cancer, Cancer; Reproductive/Developmental- Breast cancer, Cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5043615

Domain	Metric		Rating	Comments
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	High	This study analyzed incident primary invasive breast cancers among postmenopausal women. Breast cancer diagnoses were self-reported annually, and all included cases were subsequently adjudicated by trained physicians who reviewed medical records and pathology data. All eligible cases that occurred after year three clinic visits and during WHI follow-up through 2013 were included. Breast cancers were further characterized by estrogen receptor/progesterone receptor (ER/PR) status, and by time windows for diagnosis after the year 3 clinic visit. There are minimal concerns for error in case ascertainment. However, issues such as stage at diagnosis and breast cancer screening among controls were not discussed.
	Metric 3B:	Selective Reporting	Medium	There were no major concerns of selective reporting in this study. All results for primary and secondary analyses were presented or described, though few sensitivity analyses were shown in detail.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Potential confounders were selected a priori. The authors examined numerous variables as potential confounders in their analysis including: race/region; education level; neighborhood socioeconomic status; body mass index; physical activity; smoking status; alcohol use; Health Eating Index score; total dietary energy intake; hormone therapy (HT) use at enrollment; age at menarche; parity; age at first birth; breastfeeding history; age at menopause; Gail breast cancer risk score; diabetes; high cholesterol; hypertension; membership in the observational study and specific clinical trials. Adjusted models included all variables with a p-value less than 0.25 in a multivariable model that included all candidate covariates. Final models included age, race/region, neighborhood SES index, BMI, alcohol use, smoking status, Gail score, HT use, HT trial assignment, dietary modification trial assignment, and calcium and vitamin D trial assignment. Although the authors acknowledged that variables such as BMI and weight gain are potential intermediates, they did not discuss excluding intermediates. However, the authors presented both adjusted and unadjusted results, as well as models stratified by BMI. The similarity of unadjusted and adjusted results did not suggest bias due to including potential intermediates. While confounding was based on statistical significance, important variables were included in the final model, and there is no evidence of bias.
Domain 5: Analysis				

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Study Citation:	Reeves, K. W., Santana, M. D., Manson, J. E., Hankinson, S. E., Zoeller, R. T., Bigelow, C., Sturgeon, S. R., Spiegelman, D., Tinker, L., Luo, J., Chen, B., Meliker, J., Bonner, M. R., Cote, M. L., Cheng, T. D., Calafat, A. M. (2019). Urinary phthalate biomarker concentrations and postmenopausal breast cancer risk. Journal of the National Cancer Institute 111(10):1059-1067.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Breast cancer, Cancer; Reproductive/Developmental- Breast cancer, Cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5043615

Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Medium	Descriptive data for cases and controls were shown. These data included creatinine-corrected but not raw phthalate distributions, Phthalate distributions Odds ratios and their associated 95% confidence intervals were calculated using conditional logistic regression models. Unadjusted and adjusted results were presented. Phthalate concentrations were natural log-transformed to improve normality; exposure variables were creatinine corrected (method not specified). Analyses were shown using both transformed continuous exposure variables and quartiles. Numbers of cases and controls in each category were shown in analyses using quartiles. Results stratified by ER/PR status, obesity, and select periods of time to diagnosis (<3 years, <5 years of urine sample collection) were shown. Analysis limiting the sample to participants with lengthier duration of follow-up were not discussed. Sensitivity analyses included excluding women using hormone therapy at baseline, correcting for variability in phthalates using intra-class correlations, or using individual vs averaged phthalate measures. It was unclear whether missing data was an issue. Results stratified by other potentially relevant variables such as study arm or baseline health status were not mentioned. No important deficiencies in the analysis were noted.
	Metric 5B:	Sensitivity	Medium	The range of exposure levels reported within the study provide adequate variability for evaluation; few samples had concentrations of phthalates below detection. Two to three measures of phthalates were available for each participant. However, intra-class correlations were 0.07 for MCOP and 0.01 for MCNP, indicating that there was very high within-person variability. The extent to which the available measures may misclassify habitual exposure, and perhaps reduce ability to detect associations, cannot be ascertained.

Additional Comments: This nested case-control study of the WHI prospective cohort included 419 incident invasive breast cancer cases and 838 controls density matched on age, enrollment date, study arm, and length of follow-up. Participants were postmenopausal at enrollment. Subjects were recruited in 1993 to 1998 and followed through 2013. Exposure assessment included measures of urinary phthalate metabolites in 2-3 spot urine samples measured over three years following recruitment. Strengths included the prospective design, the availability of repeated urine samples to estimate exposure, and analyses stratified by estrogen and progesterone receptor status. Limitations included very low ICCs for repeated measures of phthalate metabolites (<0.08 for metabolites of interest), indicating high within-person variability. It cannot be ascertained to what extent available measures reflected habitual exposure. It is also uncertain whether the postmenopausal exposure estimates reflect the relevant timeframe for breast cancer etiology. Despite some limitations, the study had important strengths, and no major concerns were noted.

Overall Quality Determination — Medium

Study Citation:	Santana, Díaz, M. V., Hankinson, S. E., Bigelow, C., Sturgeon, , S. R., Zoeller, R. T., Tinker, L., Manson, E., J.A., Calafat, A. M., Meliker, , J. R., Reeves, K. W. (2019). Urinary concentrations of phthalate biomarkers and weight change among postmenopausal women: a prospective cohort study. Environmental Health 18(1):20.
Health Outcome(s) Assessed:	Nutritional/Metabolic- Overweight and obesity, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5613207

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This study performed cross-sectional and longitudinal analyses of postmenopausal women enrolled in the nested case-control Women's Health Initiative (WHI) study. Enrollment for the WHI was described briefly, and 50-79 year old women were enrolled from October 1, 1993 until December 21, 1998 at locations in Alabama, Pennsylvania, and Arizona. The WHI focused on individuals with breast cancer and had matched controls. Cases were comprised of women diagnosed with invasive breast carcinoma which occurred after a three-year follow-up through 2013. Controls were matched on numerous variables including enrollment date, length of follow-up, age at enrollment, and WHI study arm. Controls were matched to cases 2:1. The cross-sectional analysis included 337 cases and 660 controls with complete data available, while the longitudinal analysis only included the 660 controls from the parent study. The authors indicated that weight gain is common after breast cancer treatment, which is why the longitudinal analysis was restricted. The authors provided sufficient information about participant selection, contributing to minimal concerns of selection bias. The methods for determining the control group were also adequate, strengthened by the matching procedures.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	All participants provided first morning void urine samples at baseline, and the WHI used a standard collection, processing, and storage protocol. The samples were collected at home and processed upon arrival at the clinics. Phthalate metabolite concentrations were quantified via on-line solid phase extraction coupled to high performance liquid chromatography-electrospray ionization-isotope dilution tandem mass spectrometry after enzymatic hydrolysis of the metabolites. While the authors do not provide exact numbers for the LOD, they do link to the methods used for quantification and detail that the LODs were in the low ng/mL range. The LOD for creatinine was reported as 10 mg/mL. The methods utilized are appropriate for determining phthalate concentrations, and the samples represent the etiologically relevant time period. Concerns were raised about exposure misclassification because two clinics used urine collection containers that were not confirmed to be phthalate free. These concerns are lowered somewhat because the authors measured metabolite concentrations instead of parent phthalates, which should not reflect potential contamination. This contributes to more confidence in an adequate rating for this metric.
Domain 3: Outcome Assessment				

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Study Citation:	Santana, Díaz, M. V., Hankinson, S. E., Bigelow, C., Sturgeon, , S. R., Zoeller, R. T., Tinker, L., Manson, E., J.A., Calafat, A. M., Meliker, , J. R., Reeves, K. W. (2019). Urinary concentrations of phthalate biomarkers and weight change among postmenopausal women: a prospective cohort study. Environmental Health 18(1):20.
Health Outcome(s) Assessed:	Nutritional/Metabolic- Overweight and obesity, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5613207

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	The authors report that measurements of height and weight were collected three times: at baseline, year 3, and year 6 clinic visits. These measurements were used to determine participants BMI as weight(kg)/height^2(m^2). Respondents were then grouped based on their BMI into underweight/normal weight (<25.0 kg/m^2), overweight (25.0-<30.0 kg/m^2), and obese (>/=30.0 kg/m^2). There is some uncertainty about misclassification because the authors did not report the tools used for height and weight, but in the discussion section the authors highlight the objectively measured data, reducing this concern. This metric is adequate because it is likely that the instruments were appropriate, but there is no discussion of validation.
	Metric 3B:	Selective Reporting	Medium	There were no major concerns of selective reporting in this reference, and results for the primary and secondary analyses outlined in the methods section are reported.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	The WHI collected extensive data on participants, and numerous variables were considered as confounders. These included age, race/ethnicity, education level, income, health insurance, smoking status, alcohol use, Healthy Eating Index-2005 score, dietary energy intake, total recreational physical activity, oral contraceptive use, any hormone therapy use, ever had diabetes, ever had cardiovascular disease, hypertension, and dyslipidemia. All models were adjusted for age and urinary creatinine concentration. Other covariates were included if they had a p-value of less than 0.25 in a univariable model in a preliminary multivariable model, and their significant was evaluated using backward selection and keeping those with a p-value less than 0.10. Covariates included in the final models include creatinine, age, ethnicity, alcohol use, physical activity, smoking status, health eating index, dietary energy intake, hormone replacement therapy use, education, income, and history of diabetes, hypertension, dyslipidemia, and cardiovascular disease. While numerous covariates were considered, inclusion in the model was based on statistical significance, contributing to an adequate rating. The authors also note in the discussion section that residual confounding may have impacted their results.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	All phthalate concentrations were natural log transformed for normality. Cross-sectional analyses included cases and controls, with phthalate concentrations grouped into quartiles. Linear regression and multinomial logistic regression analyses were conducted to examine relationships between the biomarkers and weight and BMI categories. All results were appropriately reported with effect estimates and corresponding confidence intervals. While there was not an optimal characterization of the outcome variable because specific tools were not mentioned, there was an adequate description of the exposure. LOD was not provided in the report, but specific methods were linked. Overall, the analyses performed were robust and appropriate.

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Study Citation:	Santana, Díaz, M. V., Hankinson, S. E., Bigelow, C., Sturgeon, , S. R., Zoeller, R. T., Tinker, L., Manson, E., J.A., Calafat, A. M., Meliker, , J. R., Reeves, K. W. (2019). Urinary concentrations of phthalate biomarkers and weight change among postmenopausal women: a prospective cohort study. Environmental Health 18(1):20.
Health Outcome(s) Assessed:	Nutritional/Metabolic- Overweight and obesity, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5613207

Domain	Metric	Rating	Comments
	Metric 5B: Sensitivity	Medium	Study sensitivity was sufficient due to a range of exposure levels, which provides enough variability to evaluate the primary hypotheses, and the study population was sensitive to the development of the outcomes of interest. Even though the longitudinal analysis only included controls, these contributing factors are still true. The cross-sectional analysis sample size (n=337 cases; n=660 controls) had adequate power, as well as the longitudinal analysis (n=660).

Additional Comments: This cross-sectional and longitudinal analysis of participants from a nested case-control included a moderate number of individuals, with a high-quality exposure assessment methodology. There were no major flaws noted in this study, other than a potential for residual confounding and possible Type 1 error resulting from numerous statistical analyses.

Overall Quality Determination Medium

Study Citation:	Shin, H. M., Schmidt, R. J., Tancredi, D., Barkoski, J., Ozonoff, S., Bennett, D. H., Hertz-Picciotto, I. (2018). Prenatal exposure to phthalates and autism spectrum disorder in the MARBLES study. Environmental Health 17(1):85.
Health Outcome(s) Assessed:	Neurological/Behavioral- Autism spectrum disorder (ASD), non-typical development (Non-TD), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5043457

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	High	This cohort study examined a subset of participants (186 mothers and their 201 children) from the MARBLES (Markers of Autism Risk in Babies – Learning Early Signs) cohort, which follows pregnant women at a high risk of delivering another child who will develop autism spectrum disorder (ASD). Recruitment for the larger cohort was conducted from 2006-2014 "mostly in Northern California" primarily from "lists of children receiving services for autism through the California Department of Developmental Services, as well as from other studies, by self- or provider referrals and obstetrics/gynecology clinics. Participation rates and inclusion/exclusion criteria were not provided for the overall cohort. For the subset of mothers and children included in the current study, participants were limited to mothers who provided first morning voids and/or 24 hour urine samples during pregnancy between 2007-2014 and had a child who completed the study at age 3 (flow chart available in Figure S1). 43 mothers were excluded due to miscarriage or loss to follow-up. While there was a moderate degree of loss to follow-up, the information provided does not suggest that this was jointly related to exposure and outcome.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	High	Valid exposure assessment methods were used. Phthalate metabolites were measured in multiple maternal urine samples during pregnancy. Mothers were asked to provide three first morning voids (FMVs) each one week apart, as well as one 24-hour urine sample each trimester (collected between January 2007-February 2014). When mothers provided 3+ urine specimens a trimester, authors kept the first FMV as an individual sample and pooled the extra urine samples. Samples were refrigerated or frozen and sent to the UC Davis lab for analyses. The LODs (% above the LOD) were 0.2 ug/L (100%) for MCNP, 0.3 ug/L (100%) for MCOP, and 0.9 ug/L (50%) for MiNP, 0.4 ug/L (99%) for MBP, 0.4 ug/L (82% for MHBP, 0.8 ug/L (98%) for MiBP, 0.4 ug/L (97%) for MHiBP, 0.3 ug/L (99%) for MBzP, 0.8 ug/L (83%) for MEHP, 0.4 ug/L (100%) for MEHHP, 0.2 ug/L (100%) for MEOHP, and 0.4 ug/L (100%) for MECPP. DEHP metabolites were summed (molar sum). The number of urine samples actually provided varied among participants; as such, weighted averages were estimated across mid-to-late pregnancy as well as for the 2nd and 3rd trimesters separately, with weights proportional to the number of individual and pooled samples. Some non-differential exposure misclassification may be present particularly among participants with fewer samples across pregnancy, but this is not a major concern. Concentrations were corrected for specific gravity.
Domain 3: Outcome Assessment				

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Study Citation:	Shin, H. M., Schmidt, R. J., Tancredi, D., Barkoski, J., Ozonoff, S., Bennett, D. H., Hertz-Picciotto, I. (2018). Prenatal exposure to phthalates and autism spectrum disorder in the MARBLES study. Environmental Health 17(1):85.
Health Outcome(s) Assessed:	Neurological/Behavioral- Autism spectrum disorder (ASD), non-typical development (Non-TD), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5043457

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	High	There is high confidence in the validity in the outcome definition. ASD was assessed in children by licensed clinical psychologists using the gold standard, the Autism Diagnostic Observation Schedules (ADOS). Children were also administered the Mullen Scales of Early Learning (MSEL). Scores from ADOS and MEL were used to categorize children into those with ASD outcomes, non-typical development outcomes, and typical development outcomes. The study does not state whether outcome assessors were aware of exposure status, but this seems unlikely given the exposure was measured in a biological matrix (urine).
	Metric 3B:	Selective Reporting	Medium	The authors described their primary and secondary analyses in the methods section and results were reported for all primary and secondary analyses.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	High	Confounders were identified using a directed acyclic graph as well as a literature review. Authors adjusted for "child's birth year (continuous), maternal pre-pregnancy body mass index (BMI; underweight/normal weight, overweight, obese), and home-ownership (owner, non-owner) as a proxy of socioeconomic status" in the final model. Additionally, authors ran sensitivity analyses to further adjust for "(1) interpregnancy interval (continuous), (2) gestational age at birth (continuous), (3) maternal age at delivery (continuous), and (4) child's race/ethnicity (white, Hispanic, other)." Child's sex and maternal prenatal vitamin use were conceptualized and evaluated as potential effect measure modifiers.
Domain 5: Analysis				
	Metric 5A:	Analysis	High	The analytic approach was appropriate. Authors used multinomial logistic regression models to estimate the association of pre-natal phthalate exposure in mid to late pregnancy and risk of ASD or non-TD in children (vs. TD). Authors conducted sensitivity analyses (located in the supplemental file) to exclude any outliers, twin values from the cohort, and additional adjustment factors to address robustness of the results. Additional analyses included stratification by prenatal vitamin use and child's sex, as well as examination of trimester-specific associations. Phthalate metabolite concentrations were natural log-transformed prior to averaging over pregnancy. No relevant phthalate values were below the LOD. Missing covariate data was minimal and well-documented.
	Metric 5B:	Sensitivity	Medium	The sample size was adequate but the number of participants with each outcome status was relatively small (n=46 ASD, n=53 non-TD, n=109 TD). Authors note that the varying results could be due to random error from the smaller amount of cases in the study. Concentrations of MCNP were relatively low (median = 2.6 ug/L, 5th percentile = 0.8 ug/L, 95th percentile = 22.9 ug/L) compared to MCOP (median = 12.6 ug/L, 5th percentile = 2.8 ug/L, 95th percentile = 144.7 ug/L) and other measured metabolites.

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Study Citation:	Shin, H. M., Schmidt, R. J., Tancredi, D., Barkoski, J., Ozonoff, S., Bennett, D. H., Hertz-Picciotto, I. (2018). Prenatal exposure to phthalates and autism spectrum disorder in the MARBLES study. Environmental Health 17(1):85.
Health Outcome(s) Assessed:	Neurological/Behavioral- Autism spectrum disorder (ASD), non-typical development (Non-TD), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5043457

Domain	Metric	Rating	Comments
Additional Comments:	Overall, this cohort of mother-child pairs from MARBLES provided detailed methodology using the gold standard regarding the exposure assessment and outcome ascertainment. Other than the limitation of a smaller number of cases (n = 46 children with autism spectrum disorder) in the cohort, the study is well-designed with appropriate selection, confounding adjustment, and analytic methods). Among mothers who did not take prenatal vitamins, prenatal MCOP exposure during mid to late pregnancy was associated with higher risk of non-typical development (vs. typical development) [MCOP RRR = 1.86 (95% CI: 1.01, 3.39)]. Among mothers who did take prenatal vitamins, prenatal MCOP exposure during mid-to-late pregnancy was associated with lower risk of autism spectrum disorder (versus typical development) [MCOP RRR = 0.49 (95% CI: 0.27, 0.88)].		

Overall Quality Determination High

Study Citation:	Soomro, M. H., Baiz, N., Philippat, C., Vernet, C., Siroux, V., Maesano, Nichole, C., Sanyal, S., Slama, R., Bornehag, C. G., Annesi-Maesano, I. (2018). Prenatal exposure to phthalates and the development of eczema phenotypes in male children: results from the EDEN mother-child cohort study. Environmental Health Perspectives 126(2):027002.
Health Outcome(s) Assessed:	Immune/Hematological- Eczema, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4728712

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	The sample in this study is a subgroup of the French EDEN (Etude des Déterminants pré et postnatals du développement de la santé de l'Enfant) prospective birth cohort study. The cohort recruitment process is further described in Heude et al. 2015 (HEROID: 3366583). At two university maternity clinics in Nancy and Poitiers, France, women were recruited before the 24th week of pregnancy from 2003-2006. Among 3,758 women approached, 2,002 (58%) agreed to participate in the study. Exclusion criteria included multiple pregnancy, known pre-pregnancy diabetes, French illiteracy, or planning to move out of the region within three years. In the cohort, male offspring were followed up to 5 years of age (n=998). The analysis in this study was conducted on all male offspring for whom maternal urine samples had been analyzed for metabolites in a prior study of the same cohort (n=604). The study compared males with and without phthalate measurements and found small but significant differences in a few variables (e.g., maternal age, gestational age, low birth weight and season of urine sample) that were evaluated as potential confounders. Generally, there is little concern for selection bias. There is no discussion of potential attrition.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Prenatal exposure to phthalates was characterized using measures in urine samples from mothers during pregnancy. Women provided a first urine sample at home before a hospital visit between the 24th and 28th gestational weeks. If women forgot, the sample was collected at the hospital visit. All parent compounds were measured via urinary metabolites with high specificity. Sample storage and transportation are sufficiently described. Quantification was performed using on-line solid phase extraction-high-performance liquid chromatography-electrospray ionization isotope dilution-tandem mass spectrometry. Creatinine was also measured to account for dilution and concentrations are reported corrected for creatinine. The study reports that >97% of samples and metabolites were above the limit of detection, and the limit of detection is also described for metabolites.The study reports that were no significant differences between samples collected at home compared to those collected at the hospital. The temporality of outcome-exposure is clear, as outcomes were measured after exposure assessment. While a single spot urine sample may not represent the etiologically relevant time period for eczema and IgE outcomes due to the short half-life of phthalates in the body, there is no specific evidence to suggest the exposure is not representative of typical phthalate measures among mothers or that the etiologically relevant time period was not captured.
Domain 3: Outcome Assessment				

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Study Citation:	Soomro, M. H., Baiz, N., Philippat, C., Vernet, C., Siroux, V., Maesano, Nichole, C., Sanyal, S., Slama, R., Bornehag, C. G., Annesi-Maesano, I. (2018). Prenatal exposure to phthalates and the development of eczema phenotypes in male children: results from the EDEN mother-child cohort study. Environmental Health Perspectives 126(2):027002.
Health Outcome(s) Assessed:	Immune/Hematological- Eczema, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4728712

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Eczema was assessed by a standardized and validated questionnaire from the International Study of Asthma and Allergies in Childhood, given to the parents at follow-up visits at child ages of 1,2,3,4, and 5 years by appointment. The timing of eczema incidence was further characterized based on reported diagnoses by a doctor in the past 12 months at each annual follow-up visit. Eczema was defined as ever eczema, eczema incidence in each year of age, early onset eczema (diagnosed in the first 2 years of life), and late onset eczema (24 to 60 months of age).
	Metric 3B:	Selective Reporting	Medium	No concerns reported. All analyses discussed in the methods are reported in the results.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Considered covariates included birth weight, gestational age, season of birth, parity, number of siblings, exclusive breast-feeding for >= 4 months, maternal age at delivery, pre-pregnancy BMI, maternal and paternal history of allergies, maternal and paternal educational level, household income, city of residence, mode of delivery, smoking during pregnancy, maternal alcohol use during pregnancy, maternal and paternal physician-diagnosed cases of asthma/rhinitis/eczema, food allergies, and recruitment center. Potential covariates were selected a priori from a literature review and evaluated using a directed acyclic graph (DAG). Measurement of these variables occurred via maternal or parental interview near recruitment or at yearly follow-up visits. No concerns are reported for bias due to confounding.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Multiple logistic regression analyses were performed to assess the association between phthalate metabolites and eczema outcomes. Adjusted and unadjusted associations were shown for ever-diagnoses of eczema. Concentrations of phthalates were log-transformed to account for non-normality. Adjusted odds ratios and 95% confidence intervals are reported. A Cox proportional hazards discrete time survival model was also applied to assess the association between phthalates and eczema occurrence in the first five years of life. There was no discussion of the proportional hazards assumption. Sensitivity analyses were performed, stratifying by atopic status determined by serum IgE levels. The authors also analyzed associations between phthalates and IgE-defined atopic status. Bonferroni corrections for multiple comparisons were applied. Descriptive information was provided for both exposure and outcome.
	Metric 5B:	Sensitivity	Medium	No significant concerns for sensitivity. The sample size of n=604 is likely sufficient to detect an effect. Exposure ranges are relatively small, but still wide enough to likely allow for some contrast.

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Study Citation:	Soomro, M. H., Baiz, N., Philippat, C., Vernet, C., Siroux, V., Maesano, Nichole, C., Sanyal, S., Slama, R., Bornehag, C. G., Annesi-Maesano, I. (2018). Prenatal exposure to phthalates and the development of eczema phenotypes in male children: results from the EDEN mother-child cohort study. Environmental Health Perspectives 126(2):027002.
Health Outcome(s) Assessed:	Immune/Hematological- Eczema, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4728712

Domain	Metric	Rating	Comments
Additional Comments:	This prospective birth cohort of the EDEN (Etude des Déterminants pré et postnatals du développement de la santé de l'Enfant) study measured maternal urinary phthalate metabolites and their association with eczema and serum IgE at ages 1-5 in boys. There are limited concerns for bias in this study, as all aspects appear well-conducted and well-reported. Significant positive associations were reported for prenatal MCOP and ever diagnosed eczema, eczema diagnosed at ages 4 and 5, as well as for early-onset and late-onset eczema. The magnitude of associations was stronger for late onset eczema. Significant positive associations were observed for MiBP and eczema at ages 3 and later, as well as for late-onset eczema. Similar findings were found in the sum of all DEHP metabolites in ages 3 and later, and for MBzP at age 5. In a subset of 293 boys who had IgE measured at age 5, about one third were characterized as having allergic eczema and two thirds nonallergic asthma. Associations between these metabolites and ever diagnosed eczema did not vary by atopic status.		

Overall Quality Determination Medium

Study Citation:	Soomro, M. H., Baiz, N., Philippat, C., Vernet, C., Siroux, V., Maesano, Nichole, C., Sanyal, S., Slama, R., Bornehag, C. G., Annesi-Maesano, I. (2018). Prenatal exposure to phthalates and the development of eczema phenotypes in male children: results from the EDEN mother-child cohort study. Environmental Health Perspectives 126(2):027002.
Health Outcome(s) Assessed:	Immune/Hematological- Atopic status (total serum IgE ≥60 IU/mL), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4728712

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	The sample in this study is a subgroup of the French EDEN (Etude des Déterminants pré et postnatals du développement de la santé de l'Enfant) prospective birth cohort study. The cohort recruitment process is further described in Heude et al. 2015 (HEROID: 3366583) At two university maternity clinics in Nancy and Poitiers, France, women were recruited before the 24th week of pregnancy from 2003-2006. Among 3,758 women approached, 2,002 (58%) agreed to participate in the study. Exclusion criteria included multiple pregnancy, known pre-pregnancy diabetes, French illiteracy, or planning to move out of the region within three years. In the cohort, male offspring were followed up to 5 years of age (n=998). The analysis in this study was conducted on all male offspring for whom maternal urine samples had been analyzed for metabolites in a prior study of the same cohort (n=604). The study compared males with and without phthalate measurements and found small but significant differences in a few variables (e.g., maternal age, gestational age, low birth weight and season of urine sample) that were evaluated as potential confounders. Generally, there is little concern for selection bias. There was no discussion of attrition. The final sample for analyses of serum IgE is only n=293. Details are not provided on why this number is smaller but may be related to the collection of blood samples only at 5 years of age.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Prenatal exposure to phthalates was characterized using measures in urine samples from mothers during pregnancy. Women provided a first urine sample at home before a hospital visit between the 24th and 28th gestational weeks. If women forgot, the sample was collected at the hospital visit. All parent compounds were measured via urinary metabolites with high specificity. Sample storage and transportation are sufficiently described. Quantification was performed using on-line solid phase extraction-high-performance liquid chromatography-electrospray ionization isotope dilution-tandem mass spectrometry. Creatinine was also measured to account for dilution and concentrations are reported corrected for creatinine. The study reports that >97% of samples and metabolites were above the limit of detection, and the limit of detection is also described for metabolites.The study reports that were no significant differences between samples collected at home compared to those collected at the hospital. The temporality of outcome-exposure is clear, as outcomes were measured after exposure assessment. While a single spot urine sample may not represent the etiologically relevant time period for eczema and IgE outcomes due to the short half-life of phthalates in the body, there is no specific evidence to suggest the exposure is not representative of typical phthalate measures among mothers or that the etiologically relevant time period was not captured.
Domain 3: Outcome Assessment				

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Study Citation:	Soomro, M. H., Baiz, N., Philippat, C., Vernet, C., Siroux, V., Maesano, Nichole, C., Sanyal, S., Slama, R., Bornehag, C. G., Annesi-Maesano, I. (2018). Prenatal exposure to phthalates and the development of eczema phenotypes in male children: results from the EDEN mother-child cohort study. Environmental Health Perspectives 126(2):027002.
Health Outcome(s) Assessed:	Immune/Hematological- Atopic status (total serum IgE ≥60 IU/mL), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4728712

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	The outcomes of interest were eczema and IgE status. Total IgE was measured in serum samples from boys at 5 years of age using the CAP assay (Pharmacia and Upjohn Diagnostics AB, Uppsala, Sweden), which is assumed to be a reasonable method of measuring IgE. The authors cited a previous EDEN study publication to justify using IgE ≥60 IU=mL to define sensitization (Baiz et al., 2016, PMID 27566456). Pediatric reference values are not well established. This cutoff characerized 60 of the 293 boys with serum IgE measures as atopic. While details on the assay and cutoff are limited, there is no evidence of bias. Elevated total IgE was also used to characterize eczema as sensitized vs. not sensitized. Eczema was assessed by parental report of doctor diagnoses in annual visits using a standardized and validated questionnaire from the International Study of Asthma and Allergies in Childhood.
	Metric 3B:	Selective Reporting	Low	All analyses discussed in the methods are reported in the results. As the analysis of elevated IgE alone was complementary to the analysis of eczema with vs without sensitization, the authors described where results were significant, but effect estimates were not provided.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Considered covariates included birth weight, gestational age, season of birth, parity, number of siblings, exclusive breast-feeding for >= 4 months, maternal age at delivery, pre-pregnancy BMI, maternal and paternal history of allergies, maternal and paternal educational level, household income, city of residence, mode of delivery, smoking during pregnancy, maternal alcohol use during pregnancy, maternal and paternal physician-diagnosed cases of asthma/rhinitis/eczema, food allergies, and recruitment center.Potential covariates were selected a priori from a literature review and evaluated using a directed acyclic graph (DAG). Measurement of these variables occurred via maternal or parental interview near recruitment or at yearly follow-up visits. No concerns are reported for bias due to confounding.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	The association between elevated serum IgE levels (≥60 IU/mL) and phthalate metabolites was analyzed using multiple logistic regression. Concentrations of phthalates were log-transformed. Associations between elevated IgE and phthalates are described as significant for phthalate metabolites where that was the case. However, descriptive information on exposure and outcome are provided, and associations with eczema stratified by total IgE status are shown. As this analysis was complementary to the analysis of eczema stratified by IgE status, few details were provided.

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Study Citation:	Soomro, M. H., Baiz, N., Philippat, C., Vernet, C., Siroux, V., Maesano, Nichole, C., Sanyal, S., Slama, R., Bornehag, C. G., Annesi-Maesano, I. (2018). Prenatal exposure to phthalates and the development of eczema phenotypes in male children: results from the EDEN mother-child cohort study. Environmental Health Perspectives 126(2):027002.
Health Outcome(s) Assessed:	Immune/Hematological- Atopic status (total serum IgE $\geq$60 IU/mL), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4728712

Domain	Metric	Rating	Comments
	Metric 5B: Sensitivity	Medium	No significant concerns for sensitivity. The sample size of n=604 is likely sufficient to detect an effect. Exposure ranges are relatively small, but still wide enough to likely allow for some contrast. MCOP (ug/L) median = 3.9 ug/L, (25th-75th percentiles: 2.4-6.5 ug/L. MCNP (ug/L) median = 1.2 ug/L (25th-75th percentiles: 0.8-2.2 ug/L.

Additional Comments: This prospective birth cohort of the EDEN (Etude des Déterminants pré et postnatals du développement de la santé de l'Enfant) study measured maternal urinary phthalate metabolites and their association with eczema diagnosed at ages 1-5 in boys, and with elevated serum IgE at age 5 years. IgE data was available for a subset of 293 boys (total n=604); IgE data were used principally to characterize boys as having atopic (sensitized) vs non-atopic eczema. About one third of the 293 boys were characterized as having elevated IgE based on a cutoff used in a previous EDEN study publication; pediatric reference values are not well established. There are limited concerns for bias in this study, as all aspects appear well-conducted and well-reported. Results for the main effect association between phthalates and elevated IgE were described only as not significant for all pthahlates. However, associations with atopic vs. non-atopic eczema were shown for all phthalate metabolites (supplemental material). There are potential concerns given the limited information on IgE measurement and the cutoff used to define atopy. However, there is no evidence of bias.

Overall Quality Determination — Medium

Study Citation:	Tanner, E. M., Hallerbäck, M. U., Wikström, S., Lindh, C., Kiviranta, H., Gennings, C., Bornehag, C. G. (2020). Early prenatal exposure to suspected endocrine disruptor mixtures is associated with lower IQ at age seven. Environment International 134:105185.
Health Outcome(s) Assessed:	Neurological/Behavioral- full scale IQ, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5933606

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	High	The association of prenatal urinary DiDP (MHiDP, MCNP), DiNP (MHiNP, MOiNP, MCiOP), DBP (MBP), BBP (MBzP), and DEHP (MEHP, MEHHP, MEOHP, MECPP) metabolites and child full scale IQ at age 7 was assessed in this cohort study of mother-child pairs (n = 718) from the Swedish Environmental Longitudinal Mother and Child, Asthma and Allergy (SELMA) study. 2300 pregnant women were recruited for the study from November 2007 - March 2010 in prenatal clinics in Varmland county during the first trimester. Families were invited to participate in child cognitive functioning studies consecutively based on child age. 943 were assessed, but full data were only available for 718 children. Inverse probability weights were used to incorporate baseline characteristics (child sex, maternal age, education, and smoking) with significant differences between the recruited population (n=943) and the study population. Concern for selection bias is minimal.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	MBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, MHiDP, MCNP, MHiNP, MOiNP, and MCiOP were assessed in first morning void urine samples from pregnant women during the first prenatal clinic visit (median = 10 weeks gestation). Samples were analyzed via LC-MS/MS and creatinine (measured enzymatically) was used to adjust for urine dilution. Limits of detection are reported (MBP: 0.100 ng/mL; MBzP: 0.04 ng/mL; MEHP: 0.100 ng/mL; MEHHP: 0.02 ng/mL; MEOHP: 0.03 ng/mL; MECPP: 0.02 ng/mL; MHiDP and MCNP: 0.031 ng/mL, MHiNP: 0.020 ng/mL, MOiNP: 0.010 ng/mL, MCiOP: 0.020 ng/mL) and 100% of metabolite samples were >LOD. DiNP was calculated as the molar sum of 3 metabolites (MHiNP, MOiNP, and MCiOP) and DEHP was calculated as the molar sum of 4 metabolites (MEHP, MEHHP, MEOHP, MECPP).Urinary measure during pregnancy is the etiologically window to measure exposure. However, the use of single measurements for chemicals with short half-lives to represent exposure during pregnancy may lead to misclassification. Impacts expected to be minor.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Trained psychologists evaluated full scale IQ in children at age 7 using the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV). Scores were indexed to have a mean of 100 and SD of 15. There is no discussion of validation in the study population, but the WISC-IV is a well-established tool to assess cognitive function.
	Metric 3B:	Selective Reporting	Medium	All anticipated results are reported from primary and secondary analyses.
Domain 4: Potential Confounding / Variability Control				

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Study Citation:	Tanner, E. M., Hallerbäck, M. U., Wikström, S., Lindh, C., Kiviranta, H., Gennings, C., Bornehag, C. G. (2020). Early prenatal exposure to suspected endocrine disruptor mixtures is associated with lower IQ at age seven. Environment International 134:105185.
Health Outcome(s) Assessed:	Neurological/Behavioral- full scale IQ, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5933606

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	Medium	Covariates were selected for inclusion through examination of the literature and bivariate associations with study data. Child sex and the maternal characteristics (parity, age, weight, education, IQ (RAVEN), and smoking) were included as confounders in final models. Maternal fish consumption and breast feeding were also considered as confounders. Additionally, child sex, maternal age, maternal education, maternal smoking, and prenatal creatinine-corrected MEP and MBzP, trans-nonachlor, and PCBs were included via inverse probability weights to adjust for potential selection bias. These variables were summarized in a directed acyclic graph. Analyses were also stratified by child sex. Information on potential confounders was collected from mothers during visits via questionnaire. Subsequent information was collected via follow-up questionnaires (i.e., information on breast feeding). Gestational age, birth weight, and maternal weight data were obtained from the Swedish Medical birth register.
Domain 5: Analysis				
	Metric 5A:	Analysis	High	Weighted quantile sum (WQS) regression was used to examine the association between exposure to mixtures of EDC chemicals (natural log-transformed), including the phthalate metabolites of interest, and child full scale IQ. For these regressions, a WQS index (of all chemicals) is included in a multivariable linear model to assess the effects on the outcome. Effect estimates and 95% CI are reported from WQS regression. Construction of the WQS used negative weights from 100 bootstrap samples for each chemical, anchored by an assumption that IQ would decrease with increasing exposure. Chemicals with weights >3.8% were considered chemicals of concern. Authors deemed this an explanatory approach.A repeated holdout validation was conducted to simulate a distribution of validated results from the underlying population. The resulting mean estimate is reported along with the range of values representing the uncertainty in a weight uncertainty plot.Additional sensitivity analyses were conducted with the population stratified by child sex, with the addition of covariates (maternal fish consumption, breastfeeding). The WQS regression was conducted with 40% of the data to assess the origin of differences between the explanatory approach and repeated holdout validation. Additional analyses were conducted without the highest weight chemical and with an assumption of a positive association between exposure and outcome (i.e., using positive weights instead of negative).Analyses were conducted on individuals with complete data; thus, treatment of missing values was not necessary.
	Metric 5B:	Sensitivity	Low	Study had adequate sample size (n = 718 mother-child pairs) and exposure distribution to detect an effect. Importantly, the study analyzes the effect of EDC mixtures on child cognitive functioning (IQ). As a result, single chemical effects cannot be gleaned from the findings.

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Study Citation:	Tanner, E. M., Hallerbäck, M. U., Wikström, S., Lindh, C., Kiviranta, H., Gennings, C., Bornehag, C. G. (2020). Early prenatal exposure to suspected endocrine disruptor mixtures is associated with lower IQ at age seven. Environment International 134:105185.
Health Outcome(s) Assessed:	Neurological/Behavioral- full scale IQ, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5933606

Domain	Metric	Rating	Comments
Additional Comments:	This cohort study examined mother-child pairs (n=718) from the SELMA study and the association between prenatal urinary phthalate exposure (MBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, MHiDP, MCNP, MHiNP, MOiNP, MCiOP) and child IQ at age 7. The study used a robust analysis and appropriate recruiting, outcome, and exposure assessment methods. However, the results are reported for mixtures of EDCs only, limiting the study's sensitivity to determine single-pollutant effects. DEHP (calculated as the molar sum of MEHP, MEHHP, MEOHP, and MECPP), DiNP (calculated as the molar sum of MHiNP, MOiNP, and MCiOP), MBP, MHiDP, and MCiNP were below the threshold of concern, however, in some analyses with positive weights, DiNP was above the threshold. MBzP was above the threshold of concern in the full sample explanatory approach (weight: 6%).		

Overall Quality Determination Medium

Study Citation:	Trasande, L., Liu, B., Bao, W. (2021). Phthalates and attributable mortality: A population-based longitudinal cohort study and cost analysis. Environmental Pollution 292:118021.
Health Outcome(s) Assessed:	Mortality- Cancer mortality, Cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	9495379

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Subjects in this study cohort were participants in NHANES surveys from 2001-2010. Phthalate metabolites were measured in about third of randomly selected NHANES participants in various waves. However, data on MCNP and MCOP were only available in NHANES years 2005-2006 to 2009-2010, so analyses of those metabolites were restricted to this sub-sample of the overall participants. NHANES is a well-studied and well-reported cross-sectional study representative of the United States, so there is minimal concern for selection bias in the use of NHANES data. To be included in this study, participants had to be adults aged 40 or older and have available urinary phthalate metabolite data. Participants were linked to publicly available mortality data, allowing for up to 10 years of follow-up. No information is provided on any participants whose vital status may not have been identified, and no other inclusion/exclusion criteria are specified. The final number of participants was n=3,310 for MCOP/MCNP, and 5,303 for all other phthalate metabolites. The study provides covariate data stratified by exposure status, but this information is only provided for groupings of other phthalates and DEHP.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Exposure to phthalates were measured through concentrations of appropriate urinary metabolites. At NHANES enrollment, spot urine samples were collected. phthalate metabolites were quantified using solid phase extraction coupled with reversed phase high performance liquid chromatography-electrospray ionization-tandem mass spectrometry. While characterization of habitual exposure is uncertain due to the short half-life of phthalate metabolites. which were characterized using a single spot urine sample, exposure is appropriately measured prior to incidence of the outcome. There is no evidence to suggest participants changed behaviors in ways associated with exposure to phthalates. Concentrations of phthalates were adjusted for dilution by adjusting for creatinine. A change in the urinary creatinine measurement method in 2007 was addressed by adding a categorical variable to adjust for NHANES wave. Values below detection limits were imputed as the LOD divided by the square root of 2. The LOD and number of samples below the LOD are not provided in the study, but are available in NHANES data (Source: https://www.cdc.gov/exposurereport/data_tables.html).
Domain 3: Outcome Assessment				

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Study Citation:	Trasande, L., Liu, B., Bao, W. (2021). Phthalates and attributable mortality: A population-based longitudinal cohort study and cost analysis. Environmental Pollution 292:118021.
Health Outcome(s) Assessed:	Mortality- Cancer mortality, Cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	9495379

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Outcome data was obtained through the NHANES Public-Use Linked Mortality File through 12/31/2015 which allows for the linkage of NHANES participants to the National Death Index with a probabilistic matching algorithm to determine mortality status. Specific causes of death were categorized according to ICD-10 codes. Cardiovascular (CVD) mortality was classified by NCHS as death from heart disease (codes I00–I09, I11, I13, and I20–I51) or cerebrovascular disease (codes I60–I69), and cancer mortality as death from malignant neoplasms (codes C00–C97).
	Metric 3B:	Selective Reporting	Medium	All analyses described in the methods are reported in results. Methods for MCNP and MCOP are described as a sensitivity analysis to evaluate the specificity of associations; data from NHANES 2005-2010 were analyzed in separate models from other phthalates. Associations between these variables and mortality outcomes are presented using sample weights in the main manuscript, and without sample weights in the supplemental material. Results of the weighted analysis were also presented in the supplementary material: there were very minor differences in a few hazard ratios suggesting analyses were repeated with an inadvertent small change, but no evidence for concern (e.g. HR for tertile 3 of MCNP and cancer mortality 0.63, 0.30-1.34 vs. 0.65, 0.31-1.36).
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Considered covariates included age, sex, race/ethnicity, urinary creatinine, education, family income, smoking status, alcohol drinking, physical activity, total energy intake, Healthy Eating Index-2010, survey year and BMI. Total energy intake and the Healthy Eating index measure of overall diet quality were computed using multi-pass 24-hour dietary recall interviews. There are no details on why these specific covariates were chosen. Co-exposure confounding by BPA was evaluated for other phthalate variables, but it was unclear whether this issue was examined for MCOP and MCNP.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	The association between phthalates with mortality was assessed using Cox proportional hazards regression models. Exposure to each metabolite was categorized using tertiles to examine non-linear dose-response, as well as using as natural log transformed continuous variables to address skewed distributions. Follow-up time was calculated as the difference between the NHANES examination date and the last known date alive or censored from the linked mortality data. Effect estimates are reported with 95% CIs. While the proportional hazards assumption is not tested there is no evidence that the assumption would not be met. For their primary analyses of other phthalate exposure variables, the authors reported conducting several sensitivity analyses, including using evaluating the likelihood of potential residual confounding, using unweighted data, and stratifying results by variables including age (< vs >=60 years), gender, obesity, race/ethnicity, and physical activity level. For MCNP/MCOP, only weighted and unweighted associations were shown.

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Study Citation:	Trasande, L., Liu, B., Bao, W. (2021). Phthalates and attributable mortality: A population-based longitudinal cohort study and cost analysis. Environmental Pollution 292:118021.
Health Outcome(s) Assessed:	Mortality- Cancer mortality, Cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	9495379

Domain	Metric	Rating	Comments
	Metric 5B: Sensitivity	Medium	The number of participants is likely sufficient to detect an effect (n=3,310 for MCNP/MCOP and n=5,303 for other phthalates). The distribution of MCNP and MCOP were not provided in the manuscript for adults aged >=40 years, but NHANES data indicates that all metabolites were detected in sufficient numbers and with sufficient ranges of exposure (Source: https://www.cdc.gov/exposurereport/data_tables.html).

Additional Comments: This cohort study used NHANES 2001 to 2010 data for adults aged 40+ years linked to mortality information to estimate the association between urinary concentrations of several phthalate metabolites and risk of death (all cause, CVD, and cancer). While measures of other phthalates were included for the entire period (n = up to 5,303), MCOP and MCNP data were only available for NHANES survey waves from 2005-06 to 2009-10 (n = 3,310). Participants were followed for vital status and cause of death through 2015. Exposure was characterized using a single spot urine sample, which may misclassify habitual exposure given the high variability and short half-lives of these metabolites. Significant associations between phthalate metabolites and mortality outcomes were reported for several phthalates, including MBzP, MEHHP, MEOHP, and MECCP. There was limited information and fewer analyses reported for the supplementary analyses of MCNP/MCOP in comparison to other phthalate exposure variables. There was no direct evidence of concern due to issues such as low sensitivity or bias. However, no significant associations were reported for MCOP or MCNP, for which the duration of follow-up was shorter and sample size smaller.

Overall Quality Determination Medium

Study Citation:	Zettergren, A., Andersson, N., Larsson, K., Kull, I., Melen, E., Georgelis, A., Berglund, M., Lindh, C., Bergstrom, A. (2021). Exposure to environmental phthalates during preschool age and obesity from childhood to young adulthood. Environmental Research 192:10249-10249.
Health Outcome(s) Assessed:	Nutritional/Metabolic- Obesity: overweight/obesity, body mass index (BMI), waist circumference (WC), body fat %, and trunk fat %., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	7978414

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Participants in this longitudinal study are a sub-sample of the Swedish birth cohort, BAMSE (Swedish abbreviation for Children, Allergy, Milieu, Stockholm, Epidemiology) which enrolled 4,089 participants born in Stockholm in 1994-1996. Follow-up occurred at 2 months, and at 1, 4, 8, 12, 16, and 24 years of age. This analysis includes a sub-sample of 100 participants selected for a time trend analysis of preschool phthalates exposure. Eligible BAMSE participants had questionnaires at baseline, 4 and 16 years, and urine samples at age 4y (n=720); selection for urine sampling at age 4 was based on allergy prevalence (n=933, 684 with symptoms). The sub-sample of 50 girls and 50 boys was selected to have an equal number of each sex with/without symptoms. The sample was similar to the parent cohort in terms of parental occupation, breastfeeding duration, and maternal smoking in pregnancy. Attrition was modest (n=100 at 4 and 16y, n=91 at 8y, n=71 at 24y). There was no evidence of biased selection (i.e., associated with both phthalates and obesity). The authors stated there was no significant difference in phthalate concentrations for participants with vs without allergy symptoms (data not shown). The authors did not discuss whether there was an association between allergy prevalence and obesity measures within the sub-sample, as observed in some childhood studies.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	DiNP metabolites mono(hydroxy-isononyl) phthalate (MHiNP), mono(oxo-isononyl) phthalate (MOiNP) and mono(carboxy-isooctyl) phthalate (MCiOP) were measured in a single urine sample collected at age 4 years. The molar sum of the three metabolites was used as a measure of DiNP; this measure was converted back to ng/ml multiplying by the average molar mass of each metabolite. Liquid chromatography tandem mass spectrometry (LC-MS/MS) was used to analyze the samples. The laboratory conducting analyses participates in a European QA/QC and is certified as qualified for analysis of these phthalate metabolites. The authors stated that 100% of samples were above detection limits. Specific gravity was used to correct for urine dilution. The authors acknowledged that due to high within-person variability and short half-lives, use of a single spot urine sample collected at random times of day may to some extent misclassify habitual DiNP exposure. However, there was no evidence of differential misclassification.
Domain 3: Outcome Assessment				

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Study Citation:	Zettergren, A., Andersson, N., Larsson, K., Kull, I., Melen, E., Georgelis, A., Berglund, M., Lindh, C., Bergstrom, A. (2021). Exposure to environmental phthalates during preschool age and obesity from childhood to young adulthood. Environmental Research 192:10249-10249.
Health Outcome(s) Assessed:	Nutritional/Metabolic- Obesity: overweight/obesity, body mass index (BMI), waist circumference (WC), body fat %, and trunk fat %., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	7978414

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Outcomes of overweight/obesity at ages 4-24 and body mass index (BMI), waist circumference (WC), body fat % and trunk fat % at age 24 years were assessed for analysis with age 4 urinary phthalate metabolite concentrations. Overweight/ obesity ages 4-24 based on BMI was assessed using repeated measures over time; at age 24 y additional measures were obtained. Height and weight measures were obtained at ages 4, 8, 16, and 24. The International Obesity Task Force (childhood) and WHO standards (age 24y) were used to classify participants as overweight and obese. Height was measured to the nearest 0.1 cm, and weight to the nearest 0.1 kg. At age 24y, waist circumference was measured (nearest 0.1cm) and body fat percentages (total and trunk fat) were estimated using bioelectrical impedance analysis (BIA, Tanita MC-708 MA P). The use of multiple. longitudinal BMI measures, and of more direct measures of body fat amounts and distribution at age 24y, are an important strength. However, BIA based estimates of body fat are not a gold standard; estimates are based on prediction equations that may have substantial error.
	Metric 3B:	Selective Reporting	Medium	The authors presented all analyses reported in the methods and results sections adequately.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Covariates were identified based on previous literature. Models exploring the association between phthalate metabolite levels at age 4 years with repeated measures of BMI category outcomes of overweight/obesity versus thin/normal were adjusted for gender, baseline parental socioeconomic status (SES) based on parental education and occupation, maternal smoking during pregnancy, exclusive breastfeeding duration, total energy intake at 8 years, participation in organized physical activity at 8, 16 and 24 years, puberty stage at 16 years, smoking at 16 and 24 years and urinary cotinine. Associations between urinary phthalate concentrations and BMI, WC, body fat % and trunk fat % at age 24 years were adjusted for gender, parental socioeconomic status, maternal smoking during pregnancy, duration of exclusive breastfeeding, physical activity and smoking at age 24 years and urinary cotinine. Information on potential confounders came from questionnaires completed by both parents and participants. Models did not adjust for allergy, which may be a downstream effect of obesity. The authors noted residual confounding by dietary factors at age 4 (the time of exposure assessment) as a limitation. Other potential sources of residual confounding include changes in SES over time and measures of diet quality at age 8y beyond energy intake (measured with error in food frequency questionnaires). Co-exposure confounding by other phthalates was not evaluated, however, the authors analyzed both individual DiNP metabolites and their sum.
Domain 5: Analysis				

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Study Citation:	Zettergren, A., Andersson, N., Larsson, K., Kull, I., Melen, E., Georgelis, A., Berglund, M., Lindh, C., Bergstrom, A. (2021). Exposure to environmental phthalates during preschool age and obesity from childhood to young adulthood. Environmental Research 192:10249-10249.
Health Outcome(s) Assessed:	Nutritional/Metabolic- Obesity: overweight/obesity, body mass index (BMI), waist circumference (WC), body fat %, and trunk fat %., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	7978414

Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Medium	Descriptive data on participant characteristics, outcome measures, and phthalates exposures were presented. Analysis methods were appropriate. Phthalate metabolite measures were log-transformed for analyses. Associations between phthalates exposures at age 4y and repeated measures of overweight/obesity status were analyzed using generalized estimating equations with a logit link. Exposure by age interaction terms were used to estimate age-specific associations. Associations between phthalates and measures of BMI, waist circumference, body fat percentage and trunk fat percentage at age 24 years were estimated using multiple linear regression. Effect estimates were reported as odds ratios or beta coefficients with 95% confidence intervals. Stratified analyses (e.g., by gender) were not discussed. The authors did not mention conducting sensitivity analyses to assess the robustness of findings. However, robustness was observed in terms of consistent associations for associations at multiple ages and multiple outcome measures.
	Metric 5B:	Sensitivity	Medium	There was substantial variability in both individual DiNP metabolites and their sum (DINP mean $\pm$ sd =34.5 $\pm$ 47.4 ng/mL). The prevalence of overweight was adequate for analysis: 20% at age 4y and 23.9% at age 24y. Statistical power was increased by the availability of repeated measures for some outcomes. However, the relatively small sample size (n=71 to 100) means that power was likely limited for stratified analyses.

Additional Comments: This longitudinal cohort study analyzed associations between phthalates exposure at age 4 and obesity measures through age 24y in a subset of 100 participants in the Swedish BAMSE cohort. Cohort members were born in 1994-1996. DiNP metabolites mono(hydroxy-isononyl) phthalate (MHiNP), mono(oxo-isononyl) phthalate (MOiNP), and mono(carboxy-isooctyl) phthalate (MCiOP), along with DEHP metabolites, were measured in urine samples at 4 years of age. Overweight status was measured at ages 4, 8, 12, 16, and 24 years. In addition, waist circumference, and BIA based body fat percentage and trunk fat percentage were analyzed at age 24y. The study found significant associations between increases in DiNP metabolites at age 4y and obesity measures obtained at ages 8 and above. The cross-sectional association between DiNP and obesity at age 4, as well as associations between DEHP metabolites and obesity at all ages, were null. The long follow-up and multiple obesity measures are strengths of this study. However, sample size was small. An additional potential limitation is residual confounding, in particular by dietary factors, which were not assessed at age 4y.

Overall Quality Determination Medium

Study Citation:	Zota, A. R., Geller, R. J., Calafat, A. M., Marfori, C. Q., Baccarelli, A. A., Moawad, G. N. (2019). Phthalates exposure and uterine fibroid burden among women undergoing surgical treatment for fibroids: a preliminary study. Fertility and Sterility 111(1):112-121.
Health Outcome(s) Assessed:	Reproductive/Developmental- fibroid size, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP); Mono-hydroxyisobutyl phthalate (MHiBP)
HERO ID:	5043589

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Key elements of study design were reported within this cross-sectional pilot study of a racially diverse population of premenopausal (n=57) women undergoing either hysterectomy or myomectomy for symptomatic uterine fibroids to examine the potential associations between urinary phthalate biomarkers and two measures of fibroid burden (uterine volume and fibroid size). Women within the Fibroids Observational Research on Genes and the Environment (FORGE) study presenting to the George Washington University (GWU) gynecology clinic for evaluation for symptomatic fibroid tumors and surgical management were recruited 2014-2017. Eligible women were nonpregnant, premenopausal, English speaking, older than 18 years of age, and intending to have their surgery at the GWU hospital. Women with small or large fibroids were oversampled to capture fibroid size variability. As larger fibroid size is associated with greater morbidity and participants were presenting to the clinic for fibroid surgical management, the representativeness of variability in fibroid size and potentially related exposures is uncertain. Recruitment was initially limited to non-Hispanic black or non-Hispanic white women, but later expanded to all racial/ethnic groups in 2017. Ninety percent (n=61) of the n=68 women initially approached consented to participate. Final analysis was limited to the women (n=57) with urinary phthalate metabolite data. Insufficient information regarding comparison of participants and non-participants with respect to demographic or other characteristics possibly related to exposure and outcome.
Domain 2: Exposure Characterization				

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Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Medium	Methods used to quantify exposure to 14 urinary phthalate metabolites were well defined. Spot urines were obtained from participants during clinic visits prior to surgery for 91% of participants. Urines were not collected on the day of surgery to ensure participant samples more closely represented usual dietary practices however urine was collected up to 2 months after surgery in 9% (n=5) of participants. Quantification of urinary phthalate metabolite biomarkers was performed by the Centers for Disease Control and Prevention (CDC) utilizing online-solid phase extraction-high performance liquid chromatography-isotope dilution tandem mass spectrometry. Limits of detection (LOD) and percent detected were reported. Percent detected for exposure metabolites ranged from 42 percent (MiNP) to 100 percent (MEP, MCNP, MECPP). Biomarker concentrations below the LOD were replaced with the LOD divided by the square root of 2 prior to specific gravity (SG) adjustment or calculation of phthalate biomarker summary measures. There was uncertainty regarding the potential for reverse causality within this cross-sectional study of women presenting with symptomatic fibroids who might be undergoing more medical treatments with potentially higher phthalate concentrations due to parenteral exposure from medical devices. Given the short half-life of phthalates, it is unclear if a single spot urine measure adequately represents the intensity, frequency and potential peak exposures responsible for initiation and development of outcomes of interest.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Low	Low/deficient for fibroid outcomes: Percent difference in largest fibroid size (cm), percent difference in uterine volume (cm^3), fibroid size >= median, and uterine volume >= median were the outcomes utilized within the final analyses for this study. Data regarding fibroid size was limited in many participants to one or two dimensions, and calculation of fibroid volume was lacking. Fibroid diagnosis and size data was collected from radiographic studies, electronic medical records and pathology reports. Fibroid size was reported in up to three dimensions with the largest recorded dimension utilized. Magnetic resonance imaging (MRI), the gold standard for fibroid detection and measurement, was available for 69 percent of patients who underwent myomectomy and 46 percent of those who had a hysterectomy. Data for fibroid size from those patients for whom MRI was unavailable within 12 months prior to surgery was obtained through ultrasound (n=19), operative (n=3) or surgical pathology (n=1) reports. Uterine size data was obtained through MRI within 12 months of surgery (n=35), ultrasound (n=20) and surgical pathology (n=1) reports. Uterine size was missing for n=1 participant (excluded from uterine volume analyses). Uterine volume was calculated using a referenced (Levens et al., 2009) equation. There was some uncertainty as MRI was more likely to have been utilized for fibroid size among patients undergoing myomectomy rather than hysterectomy, with the potentially less accurate methods utilized for many of those undergoing hysterectomies with potentially more complex medical histories and potentially higher medical procedural phthalate exposures.

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Health Outcome(s) Assessed:	Reproductive/Developmental- fibroid size, Non-cancer
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HERO ID:	5043589

Domain	Metric	Rating	Comments
	Metric 3B: Selective Reporting	Medium	There were no concerns for selective reporting.
Domain 4: Potential Confounding / Variability Control			
	Metric 4A: Potential Confounding	Medium	Final models for all analyses were adjusted for age, body mass index (BMI), and race/ethnicity. Potential confounders were assessed using prior knowledge on biological relevance and directed acyclic graphs. The variables considered as potential confounders included factors previously related to fibroid outcomes in this and other studies, as well as factors associated with phthalate exposures in this study. Data regarding potential confounding variables was obtained from patient medical records (race/ethnicity, age, parity, BMI, last menstrual period, insurance type, use of oral contraceptives or Lupron and medical history) and interviewer-administered surveys (smoking behavior and educational attainment). Time since diagnosis was obtained from medical record and cross-referenced with interview data. The distribution of potential confounders was presented across outcomes of interest, with amount of missing data noted. Data regarding time since diagnosis was missing for n=9 participants. There was uncertainty regarding potential for residual confounding due to a lack of consideration for non-oral hormonal contraceptive options and other estrogen-dependent gynecologic conditions, such as endometriosis and adenomyosis, potentially related to exposure in these participants.
Domain 5: Analysis			
	Metric 5A: Analysis	Medium	Multivariate linear regression was utilized to examine the associations between natural log-transformed phthalate biomarker concentrations and natural log-transformed fibroid size with the percent difference in fibroid size and uterine volume calculated for a doubling , with the 95 percent confidence intervals (CIs), of phthalate biomarker concentrations. Multivariate logistic regression was utilized to evaluate the association between phthalate biomarker concentrations and fibroid size and uterine volume (below and at or above the median) with the estimated odds ratios (OR) and 95 percent CIs presented. Sensitivity analyses excluded n=6 women with previous fibroid surgery and potential surgically-induced alteration of fibroid biology. Additional sensitivity analyses excluded n=5 women providing a urine sample up to two months after surgery to assess potential for exposure misclassification. Examination of model fit, heteroscedasticity, and influence, as well as potential for examination of potential heterogeneity of effect were not described.

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Study Citation:	Zota, A. R., Geller, R. J., Calafat, A. M., Marfori, C. Q., Baccarelli, A. A., Moawad, G. N. (2019). Phthalates exposure and uterine fibroid burden among women undergoing surgical treatment for fibroids: a preliminary study. Fertility and Sterility 111(1):112-121.
Health Outcome(s) Assessed:	Reproductive/Developmental- fibroid size, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP); Mono-hydroxyisobutyl phthalate (MHiBP)
HERO ID:	5043589

Domain	Metric	Rating	Comments
	Metric 5B: Sensitivity	Medium	The analytic sample size (n=57) was limited for multivariate analyses. There was uncertainty regarding the potential for reverse causality within this cross-sectional study of women presenting with symptomatic fibroids who might be undergoing more medical treatments with potentially higher phthalate concentrations due to parenteral exposure from medical devices. There was additional uncertainty due to the 9 percent (n=5) of participants providing urine up to 2 months after surgery. However, there were reportedly no meaningful changes in associations between phthalate biomarkers and fibroid outcomes in sensitivity analyses excluding women with prior fibroid surgery or women with urine samples collected after surgery. Additionally, MRI (gold standard) measurements of fibroid detection and measurement were utilized for the majority (69 percent) of participants undergoing myomectomy, but only 46 percent of those undergoing hysterectomy, with the potential for fibroid size being measured with less accuracy in women undergoing hysterectomies, although measurements of fibroid size were highly correlated in the subset of participants with both measures. Uncertainty remains regarding potential for residual confounding from unassessed hormonal contraception, treatments or gynecological conditions potentially related to exposure, as well as the use of a single spot urine for analysis of phthalate exposures in adequately representing the intensity, frequency and potential peak exposures responsible for initiation and development of outcomes of interest.

Additional Comments: This cross-sectional pilot study included a racially diverse population of premenopausal women within the Fibroids Observational Research on Genes and the Environment (FORGE) study presenting to a university gynecology clinic and undergoing either hysterectomy or myomectomy for symptomatic uterine fibroids to examine the potential associations between urinary phthalate biomarkers and two measures of fibroid burden (uterine volume and fibroid size). Gold standard (MRI) measurements of fibroid size were utilized for the majority of, but not all, participants and urine phthalates were quantified by CDC labs. The number of participants for study (n=57) was limited, a single spot urine, taken prior to surgery in most (91 percent) but not all participants, was utilized for phthalate exposure, and potential for residual confounding remains from unassessed hormonal contraception, treatments and gynecological conditions. Higher urinary concentrations of MHiBP, MCOP, MCNP, MEHP, MEHHP, MEOHP, MECPP, the sum of DEHP metabolites and the sum of anti-androgenic metabolites (MnBP, MHBP, MiBP, MHiBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, MCOP, MEP) were significantly associated with adjusted odds of greater uterine volume. MCNP was the only phthalate biomarker marginally significantly associated with fibroid size (adjusted odds ratio 1.9; 95% CI (1.0-3.5). No other significant associations were noted between urinary phthalate concentrations and fibroid size within multivariate linear regression analyses.

Overall Quality Determination Medium

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Health Outcome(s) Assessed:	Reproductive/Developmental- uterine volume, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP); Mono-hydroxyisobutyl phthalate (MHiBP)
HERO ID:	5043589

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Key elements of study design were reported within this cross-sectional pilot study of a racially diverse population of premenopausal (n=57) women undergoing either hysterectomy or myomectomy for symptomatic uterine fibroids to examine the potential associations between urinary phthalate biomarkers and two measures of fibroid burden (uterine volume and fibroid size). Women within the Fibroids Observational Research on Genes and the Environment (FORGE) study presenting to the George Washington University (GWU) gynecology clinic for evaluation for symptomatic fibroid tumors and surgical management were recruited 2014-2017. Eligible women were nonpregnant, premenopausal, English speaking, older than 18 years of age, and intending to have their surgery at the GWU hospital. Women with small or large fibroids were oversampled to capture fibroid size variability. As larger fibroid size is associated with greater morbidity and participants were presenting to the clinic for fibroid surgical management, the representativeness of variability in fibroid size and potentially related exposures is uncertain. Recruitment was initially limited to non-Hispanic black or non-Hispanic white women, but later expanded to all racial/ethnic groups in 2017. Ninety percent (n=61) of the n=68 women initially approached consented to participate. Final analysis was limited to the women (n=57) with urinary phthalate metabolite data. Insufficient information regarding comparison of participants and non-participants with respect to demographic or other characteristics possibly related to exposure and outcome.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Methods used to quantify exposure to 14 urinary phthalate metabolites were well defined. Spot urines were obtained from participants during clinic visits prior to surgery for 91% of participants. Urines were not collected on the day of surgery to ensure participant samples more closely represented usual dietary practices however urine was collected up to 2 months after surgery in 9% (n=5) of participants. Quantification of urinary phthalate metabolite biomarkers was performed by the Centers for Disease Control and Prevention (CDC) utilizing online-solid phase extraction-high performance liquid chromatography-isotope dilution tandem mass spectrometry. Limits of detection (LOD) and percent detected were reported. Percent detected for exposure metabolites ranged from 42 percent (MiNP) to 100 percent (MEP, MCNP, MECPP). Biomarker concentrations below the LOD were replaced with the LOD divided by the square root of 2 prior to specific gravity (SG) adjustment or calculation of phthalate biomarker summary measures. There was uncertainty regarding the potential for reverse causality within this cross-sectional study of women presenting with symptomatic fibroids who might be undergoing more medical treatments with potentially higher phthalate concentrations due to parenteral exposure from medical devices. Given the short half-life of phthalates, it is unclear if a single spot urine measure adequately represents the intensity, frequency and potential peak exposures responsible for initiation and development of outcomes of interest.

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Health Outcome(s) Assessed:	Reproductive/Developmental- uterine volume, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP); Mono-hydroxyisobutyl phthalate (MHiBP)
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Domain	Metric		Rating	Comments
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Percent difference in largest fibroid size (cm), percent difference in uterine volume (cm^3), fibroid size >= median, and uterine volume >= median were the outcomes utilized within the final analyses for this study. Data regarding fibroid size was limited in many participants to one or two dimensions, and calculation of fibroid volume was lacking. Fibroid diagnosis and size data was collected from radiographic studies, electronic medical records and pathology reports. Fibroid size was reported in up to three dimensions with the largest recorded dimension utilized. Magnetic resonance imaging (MRI), the gold standard for fibroid detection and measurement, was available for 69 percent of patients who underwent myomectomy and 46 percent of those who had a hysterectomy. Data for fibroid size from those patients for whom MRI was unavailable within 12 months prior to surgery was obtained through ultrasound (n=19), operative (n=3) or surgical pathology (n=1) reports. Uterine size data was obtained through MRI within 12 months of surgery (n=35), ultrasound (n=20) and surgical pathology (n=1) reports. Uterine size was missing for n=1 participant (excluded from uterine volume analyses). Uterine volume was calculated using a referenced (Levens et al., 2009) equation. There was some uncertainty as MRI was more likely to have been utilized for fibroid size among patients undergoing myomectomy rather than hysterectomy, with the potentially less accurate methods utilized for many of those undergoing hysterectomies with potentially more complex medical histories and potentially higher medical procedural phthalate exposures.
	Metric 3B:	Selective Reporting	Medium	There were no concerns for selective reporting.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Final models for all analyses were adjusted for age, body mass index (BMI), and race/ethnicity. Potential confounders were assessed using prior knowledge on biological relevance and directed acyclic graphs. The variables considered as potential confounders included factors previously related to fibroid outcomes in this and other studies, as well as factors associated with phthalate exposures in this study. Data regarding potential confounding variables was obtained from patient medical records (race/ethnicity, age, parity, BMI, last menstrual period, insurance type, use of oral contraceptives or Lupron and medical history) and interviewer-administered surveys (smoking behavior and educational attainment). Time since diagnosis was obtained from medical record and cross-referenced with interview data. The distribution of potential confounders was presented across outcomes of interest, with amount of missing data noted. Data regarding time since diagnosis was missing for n=9 participants. There was uncertainty regarding potential for residual confounding due to a lack of consideration for non-oral hormonal contraceptive options and other estrogen-dependent gynecologic conditions, such as endometriosis and adenomyosis, potentially related to exposure in these participants.

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Health Outcome(s) Assessed:	Reproductive/Developmental- uterine volume, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP); Mono-hydroxyisobutyl phthalate (MHiBP)
HERO ID:	5043589

Domain	Metric		Rating	Comments
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Multivariate linear regression was utilized to examine the associations between natural log-transformed phthalate biomarker concentrations and natural log-transformed fibroid size with the percent difference in fibroid size and uterine volume calculated for a doubling, with the 95 percent confidence intervals (CIs), of phthalate biomarker concentrations. Multivariate logistic regression was utilized to evaluate the association between phthalate biomarker concentrations and fibroid size and uterine volume (below and at or above the median) with the estimated odds ratios (OR) and 95 percent CIs presented. Sensitivity analyses excluded n=6 women with previous fibroid surgery and potential surgically-induced alteration of fibroid biology. Additional sensitivity analyses excluded n=5 women providing a urine sample up to two months after surgery to assess potential for exposure misclassification. Examination of model fit, heteroscedasticity, and influence, as well as potential for examination of potential heterogeneity of effect were not described.
	Metric 5B:	Sensitivity	Medium	The analytic sample size (n=57) was limited for multivariate analyses. There was uncertainty regarding the potential for reverse causality within this cross-sectional study of women presenting with symptomatic fibroids who might be undergoing more medical treatments with potentially higher phthalate concentrations due to parenteral exposure from medical devices. There was additional uncertainty due to the 9 percent (n=5) of participants providing urine up to 2 months after surgery. However, there were reportedly no meaningful changes in associations between phthalate biomarkers and fibroid outcomes in sensitivity analyses excluding women with prior fibroid surgery or women with urine samples collected after surgery. Additionally, MRI (gold standard) measurements of fibroid detection and measurement were utilized for the majority (69 percent) of participants undergoing myomectomy, but only 46 percent of those undergoing hysterectomy, with the potential for fibroid size being measured with less accuracy in women undergoing hysterectomies, although measurements of fibroid size were highly correlated in the subset of participants with both measures. Uncertainty remains regarding potential for residual confounding from unassessed hormonal contraception, treatments or gynecological conditions potentially related to exposure, as well as the use of a single spot urine for analysis of phthalate exposures in adequately representing the intensity, frequency and potential peak exposures responsible for initiation and development of outcomes of interest.

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Health Outcome(s) Assessed:	Reproductive/Developmental- uterine volume, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP); Mono-hydroxyisobutyl phthalate (MHiBP)
HERO ID:	5043589

Domain	Metric	Rating	Comments
Additional Comments:	This cross-sectional pilot study included a racially diverse population of premenopausal women within the Fibroids Observational Research on Genes and the Environment (FORGE) study presenting to a university gynecology clinic and undergoing either hysterectomy or myomectomy for symptomatic uterine fibroids to examine the potential associations between urinary phthalate biomarkers and two measures of fibroid burden (uterine volume and fibroid size). Gold standard (MRI) measurements of fibroid size were utilized for the majority of, but not all, participants and urine phthalates were quantified by CDC labs. The number of participants for study (n=57) was limited, a single spot urine, taken prior to surgery in most (91 percent) but not all participants, was utilized for phthalate exposure, and potential for residual confounding remains from unassessed hormonal contraception, treatments and gynecological conditions. Higher urinary concentrations of MHiBP, MCOP, MCNP, MEHP, MEHHP, MEOHP, MECPP, the sum of DEHP metabolites and the sum of anti-androgenic metabolites (MnBP, MHBP, MiBP, MHiBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, MCOP, MEP) were significantly associated with adjusted odds of greater uterine volume. MCNP was the only phthalate biomarker marginally significantly associated with fibroid size (adjusted odds ratio 1.9; 95% CI (1.0-3.5). No other significant associations were noted between urinary phthalate concentrations and fibroid size within multivariate linear regression analyses.		

Overall Quality Determination Medium

Study Citation:	Jacobson, M. H., Stein, C. R., Liu, M., Ackerman, M. G., Blakemore, J. K., Long, S. E., Pinna, G., Romay-Tallon, R., Kannan, K., Zhu, H., Trasande, L. (2021). Prenatal exposure to bisphenols and phthalates and postpartum depression: The role of neurosteroid hormone disruption. Journal of Clinical Endocrinology and Metabolism 106(7):1887-1899.
Health Outcome(s) Assessed:	Neurological/Behavioral- postnatal depression, postpartum depression, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP); Mono-isononyl phthalate (MiNP)
HERO ID:	7978436

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This longitudinal cohort study examined urinary phthalate metabolite levels (MCiOP, MiNP, MCNP, MEHP, MECPP, MEHHP, MEOHP, MCMHP, MBzP, MBP, MiBP, phthalic acid) during pregnancy and the associations with sex hormone levels and postnatal depression/postpartum depression. 139 pregnant women from the New York University (NYU) Children's Health and Environment Study (CHES) were recruited between 2016 and 2018. Pregnant women were eligible if they were >=18 years old, under 18 weeks gestation, and had nonmedically threatened pregnancies. Recruitment occurred at three hospitals: NYU Langone Hospitals in Manhattan and Brooklyn, and Bellevue Hospital Center. While recruitment methods appear adequate, there is limited information comparing the eligible population with the study population. This impedes the ability to fully assess potential for selection bias.
Domain 2: Exposure Characterization				

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Study Citation:	Jacobson, M. H., Stein, C. R., Liu, M., Ackerman, M. G., Blakemore, J. K., Long, S. E., Pinna, G., Romay-Tallon, R., Kannan, K., Zhu, H., Trasande, L. (2021). Prenatal exposure to bisphenols and phthalates and postpartum depression: The role of neurosteroid hormone disruption. Journal of Clinical Endocrinology and Metabolism 106(7):1887-1899.
Health Outcome(s) Assessed:	Neurological/Behavioral- postnatal depression, postpartum depression, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP); Mono-isononyl phthalate (MiNP)
HERO ID:	7978436

Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Medium	Phthalate metabolite levels (DiNP metabolites: MCiOP, MiNP; DiDP metabolites: MCNP; DEHP metabolites: MEHP, MECPP, MEHHP, MEOHP, MCMHP; BBP metabolite: MBzP; DBP metabolites: MBP, MiBP; phthalic acid) were measured in urine samples collected from mothers in early (<18 weeks) and midpregnancy (>=18 - <25 weeks). While single measures of chemicals with short half-lives may lead to exposure misclassification, the multiple samples collected minimized concern that exposure was inaccurately measured. Phthalate levels were measured via "enzymatic deconjugation followed by off-line solid phase extraction with reversed phase HPLC electrospray MS/MS." Internal standards were incorporated for each metabolite. The LODs (ng/mL) were as follows: MCiOP = 0.15; MiNP = 0.02; MCNP = 0.17; MEHP = 0.30; MECPP = 0.05; MEHHP = 0.04; MEOHP = 0.02; MCMHP = 0.17; MBzP = 0.03; MBP = 0.04; MiBP = 0.02; phthalic acid = 0.12. Percent of samples detected were: MCiOP = 100%; MiNP = 66%; MCNP = 22%; MEHP = 72%; MECPP = 99%; MEHHP = 99%; MEOHP = 99%; MCMHP = 96%; MBzP = 89%; MBP = 99%; MiBP = 96%; phthalic acid = 99%. In analyses, urinary creatinine was used to adjust for urinary dilution. Ultimately, the molar sums of metabolites (MCiOP and MiNP only) were used to estimate total DiNP and total DEHP (MEHP, MEOHP, MEHHP, MECPP, MCMHP), total low molecular weight phthalates (MBP, MiBP), and total high molecular weight phthalates (MCiOP, MiNP, MCNP, MEHP, MEOHP, MEHHP, MECPP, MCMHP, MBP). Analysis was performed with HPLC coupled with electrospray MS/MS under negative mode of ionization. Assay precision was enhanced by incorporating the IS for each of the phthalate metabolites, allowing for LODs in the range of 0.02 to 0.3 ng/mL. Urinary Cr, used to adjust for urinary dilution, was analyzed using HPLC-MS/MS. The number of obtained samples was not specified.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Postnatal depression and postpartum depression (PPD) symptoms were measured in women at 4 months following delivery using the Edinburgh Postnatal Depression Scale (EPDS). Scores >=10 were categorized as postpartum depression cases. This threshold has the highest sensitivity for PPD and can capture a range of severity. While the questionnaire is a valid screening tool for depressive symptoms in mothers following birth, the study did not include a clinical diagnosis. There is risk of misclassification since mothers were self-reporting symptoms, particularly considering the stigma around mental health. Information is limited on the ideal time post-delivery to measure postpartum depression. There is some concern that four months may be too late to detect depression experienced before 4 months. Still, these concerns are not expected to introduce substantial bias.
	Metric 3B:	Selective Reporting	Medium	All anticipated results were reported for primary and secondary analyses.
Domain 4: Potential Confounding / Variability Control				

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Health Outcome(s) Assessed:	Neurological/Behavioral- postnatal depression, postpartum depression, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP); Mono-isononyl phthalate (MiNP)
HERO ID:	7978436

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	High	Confounders were selected for models a priori and using a directed acyclic graph. Appropriate key confounders were included in analyses. Models included urinary creatinine, gestational age at time of serum hormone sampling, maternal age, and prepregnancy BMI (phthalate-hormone models); urinary creatinine, maternal age, prepregnancy BMI, race/ethnicity, and education (phthalate-PPD models). Additional covariates were included in models (antenatal depressive symptoms, marital status, material hardship, pregnancy complications), but model results did not change. As a result, these covariates were not included in final models. Mothers reported information on potential confounders via questionnaire during each trimester. Information on clinical data (prepregnancy BMI, perinatal psychotropic medication use) were obtained from medical records.
Domain 5: Analysis				
	Metric 5A:	Analysis	High	Associations between phthalate metabolites and metabolite groups and PPD were examined via multiple informant models fit using generalize estimating equations with either logit or linear links (for dichotomous or continuous variables). Effect estimates and 95% CI are reported. Multiple informant models present a single integrated estimate for multiple exposure measures. EPDS scores were modeled as both dichotomous and continuous variables. 10 was used as the cutoff score for analyses of dichotomous EPDS. Phthalate measures were log-transformed for continuous analyses. Values <LOD were imputed using LOD/(sq rt. of 2). P-values were adjusted using a modified Bonferri approach to account for multiple testing. Sensitivity analyses examined urinary creatinine correction via standardization, exclusion of women taking antidepressants, anxiolytics, or antipsychotic medications, and assessed midpregnancy hormone concentrations in relation to EPDS scores to assess the influence of phthalate-associated hormonal shifts on PPD symptoms. Distributions of outcome and exposure variables are reported.
	Metric 5B:	Sensitivity	Medium	Sample size was fairly small (n = 139) but adequate to detect an effect. Exposure distributions for monoisononyl phthalate (44% <LOD; median, IQR = 1.0 ng/mL; <0.02-0.07) and MEHP (28%; median, IQR = 1.2; <0.3-3.9) were limited, but other metabolites had adequate distributions to detect an effect (median, IQR = MCiOP: 1.5 ng/mL, 0.79-3.6; MCNP: 0.97 ng/mL, 0.23-2.2; MECPP: 7.9 ng/mL, 3.6-13.6; MEHHP: 7.4 ng/mL, 3.6-13.9; MEOHP: 4.1 ng/mL, 2.2-7.7; MCMHP: 2.9 ng/mL, 1.5-8.0; MBzP: 11 ng/mL, 1.1-8.2).

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Health Outcome(s) Assessed:	Neurological/Behavioral- postnatal depression, postpartum depression, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP); Mono-isononyl phthalate (MiNP)
HERO ID:	7978436

Domain	Metric	Rating	Comments
Additional Comments:	This longitudinal cohort study assessed urinary phthalate metabolite (MCNP, MCiOP, MiNP, MEHP, MECPP, MEHHP, MEOHP, MCMHP, MBzP) levels in 139 pregnant women and the association with sex hormone levels and postpartum depression following deliver. The study population was from the NYU Children's Health and Environment Study. There were no major concerns for residual bias based on study design, as recruitment, exposure assessment and statistical analysis used adequate methods. While depression symptoms were self-reported using a validated scale, concern for resulting recall bias was minimal. The authors reported sum(DINP) metabolites were associated with reduced progesterone concentrations, with log-unit increases in Sum(DiNP) predicted 7.7% (95% CI –13.3%, –1.7%) lower progesterone. No statistically significant associations with phthalates were found when post-partum depression symptoms were represented by continuous EPDS scores.		

Overall Quality Determination Medium

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Health Outcome(s) Assessed:	Reproductive/Developmental- Sex hormones (allopregnanolone, pregnanolone, progesterone, pregnenolone), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP); Mono-isononyl phthalate (MiNP)
HERO ID:	7978436

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This longitudinal cohort study examined urinary phthalate metabolite levels (MCiOP, MiNP, MCNP, MEHP, MECPP, MEHHP, MEOHP, MCMHP, MBzP, MBP, MiBP, phthalic acid) during pregnancy and the associations with sex hormone levels and postnatal depression/postpartum depression. 139 pregnant women from the New York University (NYU) Children's Health and Environment Study (CHES) were recruited between 2016 and 2018. Pregnant women were eligible if they were >=18 years old, under 18 weeks gestation, and had nonmedically threatened pregnancies. Recruitment occurred at three hospitals: NYU Langone Hospitals in Manhattan and Brooklyn, and Bellevue Hospital Center. While recruitment methods appear adequate, there is limited information comparing the eligible population with the study population. This impedes the ability to fully assess potential for selection bias.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Phthalate metabolite levels (DiNP metabolites: MCiOP, MiNP; DiDP metabolites: MCNP; DEHP metabolites: MEHP, MECPP, MEHHP, MEOHP, MCMHP; BBP metabolite: MBzP; DBP metabolites: MBP, MiBP; phthalic acid) were measured in urine samples collected from mothers in early (<18 weeks) and midpregnancy (>=18 - <25 weeks). While single measures of chemicals with short half-lives may lead to exposure misclassification, the multiple samples collected minimized concern that exposure was inaccurately measured. Phthalate levels were measured via "enzymatic deconjugation followed by off-line solid phase extraction with reversed phase HPLC electrospray MS/MS." Internal standards were incorporated for each metabolite. The LODs (ng/mL) were as follows: MCiOP = 0.15; MiNP = 0.02; MCNP = 0.17; MEHP = 0.30; MECPP = 0.05; MEHHP = 0.04; MEOHP = 0.02; MCMHP = 0.17; MBzP = 0.03; MBP = 0.04; MiBP = 0.02; phthalic acid = 0.12. Percent of samples detected were: MCiOP = 100%; MiNP = 66%; MCNP = 22%; MEHP = 72%; MECPP = 99%; MEHHP = 99%; MEOHP = 99%; MCMHP = 96%; MBzP = 89%; MBP = 99%; MiBP = 96%; phthalic acid = 99%. In analyses, urinary creatinine was used to adjust for urinary dilution. Ultimately, the molar sums of metabolites (MCiOP and MiNP only) were used to estimate total DiNP and total DEHP (MEHP, MEOHP, MEHHP, MECPP, MCMHP), total low molecular weight phthalates (MBP, MiBP), and total high molecular weight phthalates (MCiOP, MiNP, MCNP, MEHP, MEOHP, MEHHP, MECPP, MCMHP, MBP). Analysis was performed with HPLC coupled with electrospray MS/MS under negative mode of ionization. Assay precision was enhanced by incorporating the IS for each of the phthalate metabolites, allowing for LODs in the range of 0.02 to 0.3 ng/mL. Urinary Cr, used to adjust for urinary dilution, was analyzed using HPLC-MS/MS. The number of obtained samples was not specified.
Domain 3: Outcome Assessment				

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Health Outcome(s) Assessed:	Reproductive/Developmental- Sex hormones (allopregnanolone, pregnanolone, progesterone, pregnenolone), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP); Mono-isononyl phthalate (MiNP)
HERO ID:	7978436

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Sex steroid hormones (allopregnanolone, pregnanolone, progesterone, and pregnenolone) were measured in midpregnancy (>=18-<25 weeks) serum samples. Samples were analyzed using gas chromatography mass spectrometry after separating steroid hormones using HPLC. Sex hormones were log-normally distributed and distributions are reported by demographic characteristics.
	Metric 3B:	Selective Reporting	Medium	All anticipated results were reported for primary and secondary analyses.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	High	Confounders were selected for models a priori and using a directed acyclic graph. Appropriate key confounders were included in analyses. Models included urinary creatinine, gestational age at time of serum hormone sampling, maternal age, and prepregnancy BMI (phthalate-hormone models); urinary creatinine, maternal age, prepregnancy BMI, race/ethnicity, and education (phthalate-PPD models). Additional covariates were included in models (antenatal depressive symptoms, marital status, material hardship, pregnancy complications), but model results did not change. As a result, these covariates were not included in final models. Mothers reported information on potential confounders via questionnaire during each trimester. Information on clinical data (prepregnancy BMI, perinatal psychotropic medication use) were obtained from medical records.
Domain 5: Analysis				
	Metric 5A:	Analysis	High	Associations between phthalate metabolites and metabolite groups and PPD were examined via multiple informant models fit using generalize estimating equations with either logit or linear links (for dichotomous or continuous variables). Effect estimates and 95% CI are reported. Multiple informant models present a single integrated estimate for multiple exposure measures. Phthalate and hormone measures were log-transformed for continuous analyses. Values <LOD were imputed using LOD/(sq rt. of 2). P-values were adjusted using a modified Bonferri approach to account for multiple testing. Sensitivity analyses examined urinary creatinine correction via standardization, exclusion of women taking antidepressants, anxiolytics, or antipsychotic medications, and assessed midpregnancy hormone concentrations in relation to EPDS scores to assess the influence of phthalate-associated hormonal shifts on PPD symptoms. Distributions of outcome and exposure variables are reported.
	Metric 5B:	Sensitivity	Medium	Sample size was fairly small (n = 139) but adequate to detect an effect. Exposure distribution for monoisononyl phthalate was limited (44% <LOD; median, IQR = 1.0 ng/mL; <0.02-0.07), but other metabolites had adequate distributions to detect an effect (median, IQR = MCiOP: 1.5 ng/mL, 0.79-3.6; MCNP: 0.97 ng/mL, 0.23-2.2).

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Study Citation:	Jacobson, M. H., Stein, C. R., Liu, M., Ackerman, M. G., Blakemore, J. K., Long, S. E., Pinna, G., Romay-Tallon, R., Kannan, K., Zhu, H., Trasande, L. (2021). Prenatal exposure to bisphenols and phthalates and postpartum depression: The role of neurosteroid hormone disruption. Journal of Clinical Endocrinology and Metabolism 106(7):1887-1899.
Health Outcome(s) Assessed:	Reproductive/Developmental- Sex hormones (allopregnanolone, pregnanolone, progesterone, pregnenolone), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP); Mono-isononyl phthalate (MiNP)
HERO ID:	7978436

Domain	Metric	Rating	Comments
Additional Comments:	This longitudinal cohort study assessed urinary phthalate metabolite (MCNP, MCiOP, MiNP, MEHP, MECPP, MEHHP, MEOHP, MCMHP, MBzP) levels in 139 pregnant women and the association with sex hormone levels and postpartum depression following deliver. The study population was from the NYU Children's Health and Environment Study. There were no major concerns for residual bias based on study design, as recruitment, exposure assessment and statistical analysis used adequate methods. While depression symptoms were self-reported using a validated scale, concern for resulting recall bias was minimal. The authors reported DINP metabolites were associated with reduced progesterone concentrations, with log-unit increases in Sum(DiNP) predicted 7.7% (95% CI –13.3%, –1.7%) lower progesterone. No statistically significant associations with phthalates were found when post-partum depression symptoms were represented by continuous EPDS scores.		

Overall Quality Determination Medium

Study Citation:	Merced-Nieves, F. M., Dzwilewski, C., K.L., Aguiar, A., Musaad, S., Korrick, S. A., Schantz, S. L. (2021). Associations of prenatal exposure to phthalates with measures of cognition in 4.5-month-old infants. International Journal of Environmental Research and Public Health 18(4):1838.
Health Outcome(s) Assessed:	Neurological/Behavioral- cognition (physical reasoning–looking time difference (seconds)), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP); Mono-isononyl phthalate (MiNP)
HERO ID:	7978433

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This prospective study included women enrolled within the Illinois Kids Development Study (IKIDS) from January 2014 to August 2018. Brochures were provided to women at their first prenatal clinic visit and interested women received a call from research study staff during which the study was described in more detail and eligibility was determined. Eligible women were between 18 and 40 years of age, fluent in English, not in a high-risk pregnancy or carrying multiples, lived within a 30-min drive of the University of Illinois at Urbana-Champaign campus, and were not planning to move out of the area before their child reached one year of age. Women who reported use of over-the-counter or prescription medications were not excluded from the study. Final sample size for analysis was n=159 women (infants). Participation rate not discussed. There is no comparison of characteristics of those excluded/included in the study.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Urine DiNP and DEHP metabolite concentrations were collected at 5 time points across pregnancy (10–14, 16–18, 22–24, 28–30, and 34–36 weeks of gestation) and were measured using high performance liquid chromatography-isotope dilution tandem mass spectrometry and were pooled to include the 5 time points. DINP was quantified as the molar sum of two urinary metabolites: mono-(2,6-dimethyl-7-carboxyheptyl) phthalate (MCOP) and mono-isononyl phthalate (mNP) and expressed as ΣDINP. DEHP was quantified as the molar sum of four urinary metabolites and was expressed as ΣDEHP: mono-2-ethyl-5-carboxypentyl phthalate (MECPP), mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), mono-2-ethyl-5-oxohexyl phthalate (MEOHP), and mono-2-ethylhexyl phthalate (MEHP)Sum(DINP) phthalate metabolite exposure was reported for 16-18 weeks gestation (n=158) as median (interquartile range, IQR) = 0.02 micromol/L (0.04) and for the pooled sample as (n=159) median (IQR) = 0.03 micromol/L (0.04). Sum(DEHP) phthalate metabolite exposure was reported for 16-18 weeks gestation (n=158) as median (interquartile range, IQR) = 0.06 micromol/L (0.05) and for the pooled sample as (n=159) median (IQR) = 0.07 micromol/L (0.05).LODs and percent of samples below the LOD (if any) not reported.
Domain 3: Outcome Assessment				

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Study Citation:	Merced-Nieves, F. M., Dzwilewski, C., K.L., Aguiar, A., Musaad, S., Korrick, S. A., Schantz, S. L. (2021). Associations of prenatal exposure to phthalates with measures of cognition in 4.5-month-old infants. International Journal of Environmental Research and Public Health 18(4):1838.
Health Outcome(s) Assessed:	Neurological/Behavioral- cognition (physical reasoning–looking time difference (seconds)), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP); Mono-isononyl phthalate (MiNP)
HERO ID:	7978433

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	High	A physical reasoning task, the difference in total looking time between videos of impossible and possible events (looking time at impossible minus possible in seconds), was assessed by using an automated version of the physical reasoning task designed by Baillargeon. Infants were assessed at 123-146 days of age (4.5 months). Infants sat upon parent's lap while watching videos on a screen, while parents wore dark sunglasses and were asked to remain silent during the test to prevent them from accidentally influencing the infants looking behavior. Infant looking behaviors were tracked using an EyeLink 1000 Plus infrared eye tracker. Physical reasoning ability was measured by calculating the difference in total looking time between the impossible and possible events (impossible minus possible) wherein a higher number meant the infant looked longer at the impossible than the possible event. Instrumentation was described as "state-of-the-art eye tracking technology" which allowed automated collection of precise looking behavior at a very early age.
	Metric 3B:	Selective Reporting	Medium	No concerns for selective reporting. Secondary analyses results presented in supplemental material.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Potential confounders were identified based on a priori knowledge, a directed acyclic graph. Potential confounders included were maternal age at birth, education, IQ, and parity, household income, infant's age at assessment, sex, and order of event presentation (possible first or impossible first). Only the order of event presentation and infant sex were associated with the outcome. Final models included covariates for order of event presentation, infant sex and maternal age.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Multivariable linear regression models were used to examine the association between an interquartile range (IQR) increase in each continuous maternal urinary biomarker of exposure (ΣDEHP, ΣDINP, MEP, ΣAA, and the Σall phthalates) and looking time difference (in seconds). Interaction of sex by exposure was assessed, as well as additional interactions, including interaction of exposure with order of event presentation. Sensitivity analyses included those removing women reporting any smoking, adjusted for first trimester alcohol intake, as well as analyses with models including additional demographic variables, including maternal education, household income, infant's age at time of testing, and maternal prenatal stress. Complex statistical methods for analyses of phthalate mixtures were not conducted.

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Study Citation:	Merced-Nieves, F. M., Dzwilewski, C., K.L., Aguiar, A., Musaad, S., Korrick, S. A., Schantz, S. L. (2021). Associations of prenatal exposure to phthalates with measures of cognition in 4.5-month-old infants. International Journal of Environmental Research and Public Health 18(4):1838.
Health Outcome(s) Assessed:	Neurological/Behavioral- cognition (physical reasoning–looking time difference (seconds)), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP); Mono-isononyl phthalate (MiNP)
HERO ID:	7978433

Domain	Metric	Rating	Comments
	Metric 5B: Sensitivity	Medium	Sample size (n=159) was fairly small, but results were robust to sensitivity analyses. Sum(DINP) phthalate metabolite exposure distribution for 16-18 weeks gestation (n=158) median (interquartile range, IQR) = 0.02 micromol/L (0.04) and for the pooled sample (n=159) median (IQR) = 0.03 micromol/L (0.04) was limited. Sum(DEHP) phthalate metabolite exposure for 16-18 weeks gestation (n=158) median (interquartile range, IQR) = 0.06 micromol/L (0.05) and for the pooled sample (n=159) median (IQR) = 0.07 micromol/L (0.05) was limited.

Additional Comments: In this study, the association of prenatal phthalate exposure with physical reasoning, as assessed by difference in looking times at physically impossible and possible events, was assessed in 159 (78 female; 81 male) 4.5-month-old infants from a prospective cohort of children enrolled in the Illinois Kids Development Study (IKIDS) from January 2014 to August 2018. Although the sample size was relatively small and complex statistical analyses for mixtures was thus not possible, results were consistent across sensitivity analyses, suggesting robustness. This study utilized pooled urine samples from multiple samples collected across pregnancy, providing a measure of average exposure throughout pregnancy. Additional analyses evaluated the associations with the sample collected between 16 and 18 weeks of gestation, an important window in the sexual differentiation of the brain. Results indicated that higher prenatal exposure to MEP (16–18 weeks of gestation and pooled sample), sumDINP (pooled sample), and the sum of all phthalates (16–18 weeks gestation and pooled sample) were each associated with male infants looking longer at the possible event than the impossible event. An IQR increase in sumDINP was associated with a negative looking time difference in males (Beta= -1.0; 95% CI: -1.8, -0.1; p-value = 0.03). No significant associations with sumDEHP.

Overall Quality Determination Medium

Study Citation:	Strassle, P. D., Smit, M., L.A., Hoppin, J. A. (2018). Endotoxin enhances respiratory effects of phthalates in adults: Results from NHANES 2005-6. Environmental Research 162:280-286.
Health Outcome(s) Assessed:	Lung/Respiratory- Asthma, wheeze, hay fever, rhinitis (symptoms in the past 12 months), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP); Mono-isononyl phthalate (MiNP)
HERO ID:	4728797

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	This study utilized the publicly available NHANES 2005-2006 data, designed to represent the US population. These data are the only recent NHANES that include information on respiratory and allergic symptoms and endotoxin measurements. The analysis sample included adults aged >= 18 years who had complete information on urinary phthalates, dust endotoxin levels, and potential confounders, and had not moved between the clinic visit and dust collection (n=1,091). NHANES methods including participation rates are documented (https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/overview.aspx?BeginYear=2005). The authors described the proportion of participants with complete data as about one third of NHANES participants with urinary phthalate measures. The sample analyzed in this study was similar to that in a previous study by these authors examining main effects of phthalates on these respiratory outcomes; the sample in this study was reduced as fewer participants had valid endotoxin measures. The authors noted some differences in the significance of main effects of some phthalates in this study vs their prior analysis (Hoppin et al., 2013 HEROID 1987636). For asthma, associations with the DiNP metabolite MCOP and the DiDP metabolite MCNP were statistically significant only in this study. Associations with these metabolites in the earlier study were not shown but were described as not significant. Nonetheless, there is no direct evidence that inclusion in this sample was selective.
Domain 2: Exposure Characterization			

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Study Citation:	Strassle, P. D., Smit, M., L.A., Hoppin, J. A. (2018). Endotoxin enhances respiratory effects of phthalates in adults: Results from NHANES 2005-6. Environmental Research 162:280-286.
Health Outcome(s) Assessed:	Lung/Respiratory- Asthma, wheeze, hay fever, rhinitis (symptoms in the past 12 months), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP); Mono-isononyl phthalate (MiNP)
HERO ID:	4728797

Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Medium	Phthalate metabolites were analyzed in spot urine samples collected during the NHANES clinic visit using high performance liquid chromatography-mass spectrometry. Concentrations below limits of detection (LOD) were imputed as the LOD divided by the square root of 2. Urine dilution was addressed by including creatinine as a covariate in regression models. Phthalate concentrations were log10 transformed for analysis. Any phthalates present in ≥50% of the sample were included. These included the DiDP metabolite mono(carboxynonyl) phthalate (MCNP), and the DiNP metabolite mono(carboxyoctyl) phthalate (MCOP). The proportion of samples above LOD was 89.9% for MCNP, 95.6% for MCOP. The DiNP metabolite mono-isononyl phthalate (MINP) was not included in the analysis as 13.3% of samples were above LOD. A primary aim was to examine whether endotoxin levels in the home modified associations between phthalates and respiratory symptoms. Endotoxin was measured in combined dust from the participants bed and bedroom floor within 7 days of the clinic visit. Limitations of exposure measurement include the use of a single spot urine to quantify exposure and the cross-sectional design. Given the relatively short half-life of phthalate metabolites in urine, exposure may be misclassified by a single sample. Reverse causation in a cross-sectional study cannot be ruled out, should some individuals experiencing respiratory and/or allergic symptoms adjust behaviors in ways that influence phthalates exposure. However, there is no evidence of such bias.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	The outcomes analyzed in this study were defined based on self-reported symptoms of asthma, hay fever, rhinitis, and wheeze during the past 12 months. Current asthma was defined based on both a doctor diagnosis of asthma and symptoms in the past year. Wheeze was defined as any episode of wheezing or whistling in the chest in the past year.
	Metric 3B:	Selective Reporting	Medium	The authors described their primary (and secondary) analyses in the methods section and results were reported for all primary analyses. Associations with hay fever and current rhinitis were described as null in the main manuscript and included in supplemental materials not available at the time of this assessment.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Models adjusted for variables included in a previous study on phthalates and allergy in NHANES 2005-2006 by these authors which did not analyze endotoxin interactions (Hoppin et al., 2013 HEROID 1987636). Covariates were selected a priori based on the literature, and included age, gender, race/ethnicity, BMI, urinary creatinine, and cotinine. Poverty-income ratio was excluded in the previous study as it did not confound associations and inclusion would have reduced sample size. To examine effect modification, endotoxin levels in dust were categorized in approximate tertiles (low: < 10 endotoxin units [EU]/mg, medium: 10–25 EU/mg, and high: ≥25 EU/mg). Potential co-exposure confounding was not discussed.

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Study Citation:	Strassle, P. D., Smit, M., L.A., Hoppin, J. A. (2018). Endotoxin enhances respiratory effects of phthalates in adults: Results from NHANES 2005-6. Environmental Research 162:280-286.
Health Outcome(s) Assessed:	Lung/Respiratory- Asthma, wheeze, hay fever, rhinitis (symptoms in the past 12 months), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP); Mono-isononyl phthalate (MiNP)
HERO ID:	4728797

Domain	Metric		Rating	Comments
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Multivariable logistic regression was used to analyze the association between phthalates and respiratory and allergic outcomes, potentially modified by endotoxin. Each phthalate was analyzed individually using log10 transformed variables. Results were reported as adjusted odds ratios for the main effects of phthalates alone and for effects stratified by endotoxin tertile. Phthalates-endotoxin interaction p-values were reported based on Wald tests for overall differences in slope across tertiles. Results were also presented graphically. As a sensitivity analysis, the authors analyzed interactions between phthalates and total dust weight to provide evidence that any interactions were due to the endotoxin content of dust vs. the dust itself. The previous study evaluated but did not find significant race/ethnicity interactions for main effects the DiNP or DiDP metabolites. Gender interactions were not discussed in either study.
	Metric 5B:	Sensitivity	Medium	The analysis sample included more than 1,000 adults. Detection rates were high and there was variability in the phthalate metabolites analyzed. The authors noted that the analysis sample was limited to participants who provided urine and household dust samples and included about one third of adults with urine samples in NHANES. Moreover, the sample of 1,546 adults in their previous study that did not incorporate endotoxin measures was reduced to 1,091 in this analysis. Main effects of phthalates were described as "approximately the same" as in their previous study, but with "additional significant findings for current asthma" and MCNP (a DiDP metabolite) and MCOP (a DiNP metabolite). The differences in magnitude of associations is unknown as detailed results for these metabolites were not shown previously.

Additional Comments: This study used NHANES 2005-2006 data to analyze whether dust endotoxin levels modified the association between phthalate exposures and respiratory symptoms in the past year, including symptoms of asthma (among doctor-diagnosed participants) and wheeze. The study utilized a sample (n =1,091) of nearly 1/3 of the NHANES sample size due to exclusions of from missing data such as lacking spot urine samples, home endotoxin measures, or confounding factors. For asthma, the authors reported significant ($p < 0.05$) interactions with endotoxins and phthalate metabolites MCOP (DiNP) and MCNP (DiDP). This study also observed significant main effects of these metabolites that were not observed in their previous study of NHANES 2005-06, which analyzed a larger sample as it did not exclude participants missing endotoxin data (N=1,546). Main effects for those associations were not shown in the previous study; results were described as not significant. The magnitude of difference in associations is unknown. For wheeze, main effect associations with these metabolites were not significant, but there was a significant ($p < 0.05$) interaction with endotoxin for MCOP (DiNP), MnBP (DBP) and ΣDEHP. Several characteristics of participants included in both studies were described by the authors and appeared to be similar (49% vs 46% non-Hispanic white, 50% vs 49% male, 28% vs 27% cotinine >10 ng/mL). Reasons for the differences in significance of some results are uncertain, and it is uncertain whether the magnitude of associations was meaningfully different. Nonetheless, there is no evidence that inclusion in this sample was selective.

Overall Quality Determination Medium

Study Citation:	Machtinger, R., Mansur, A., Baccarelli, A. A., Calafat, A. M., Gaskins, A. J., Racowsky, C., Adir, M., Hauser, R. (2018). Urinary concentrations of biomarkers of phthalates and phthalate alternatives and IVF outcomes. Environment International 111:23-31.
Health Outcome(s) Assessed:	Reproductive/Developmental- Total Oocytes, mature oocytes, fertilized oocytes, top quality embryos, live births, implantation, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP); Mono-isononyl phthalate (MiNP); Mono-oxononyl phthalate (MONP)
HERO ID:	5743382

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Authors provide ample details regarding participant selection and exclusion of participants. The study recruited 136 women undergoing IVF cycles in the Sheba Medical Center in Israel from January 2014-August 2016. To prevent potential confounders, authors only included women seeking IVF due to "male factor or unexplained infertility, who were oocyte donors, or couples undergoing preimplantation genetic diagnosis (PGD) of autosomal recessive diseases."Authors additionally provided the exclusion criteria (age >38 yrs., BMI>30 kg/m2, a diagnosis of polycystic ovary syndrome, endometriosis, social oocyte cryopreservation, poor responders according to Bologna criteria and frozen IVF cycles) and excluded participants who were not meant to undergo a fresh embryo transfer. Authors reported a 95% participation rate at the beginning of recruitment. Participation rate is incompletely reported but available information indicates participation is unlikely to be related to exposure.n=136
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Valid exposure assessment methods were used, and samples were collected during fertility treatment. In the study, 73% (n=99) of participants provided spot urine samples during ovarian stimulation (first week of gonadotropin injection) and the date of oocyte retrieval. Authors pooled these samples. In the other 26.7% of participants, only one spot urine sample was collected per participant, either during the ovarian stimulation or date of oocyte retrieval. Urinary analyses were quantified for 17 metabolites, including MCNP, MCOP, MiNP, and MONP. Authors utilized an approach based on solid phase extraction coupled with high performance liquid chromatography-isotope dilution tandem mass spectrometry, followed standard quality assurance/quality control procedures as previously described (Silva et al. 2013, HEROID 2215466; Silva et al. 2017, HEROID 3859089). To adjust for urinary dilution, presented median (IQR) levels were specific-gravity adjusted. Percent detection for DIDP and DINP metabolites ranged from 51.5% (MiNP) to 100% (MCOP). For metabolites where the percent of samples with detectable concentrations was> 66%, women were placed into tertiles based on each of their metabolite concentrations. For the one metabolite (mono-isononyl phthalate (MiNP)) where the percent of samples with detectable concentrations was< 66%, women with values below the LOD were placed in the first category and the women with detectable concentrations were placed in the remaining two levels based on the median metabolite concentration. Urine samples were described as shipped on dry ice for analysis, however details on sample storage were lacking.
Domain 3: Outcome Assessment				

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Study Citation:	Machtinger, R., Mansur, A., Baccarelli, A. A., Calafat, A. M., Gaskins, A. J., Racowsky, C., Adir, M., Hauser, R. (2018). Urinary concentrations of biomarkers of phthalates and phthalate alternatives and IVF outcomes. Environment International 111:23-31.
Health Outcome(s) Assessed:	Reproductive/Developmental- Total Oocytes, mature oocytes, fertilized oocytes, top quality embryos, live births, implantation, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP); Mono-isononyl phthalate (MiNP); Mono-oxononyl phthalate (MONP)
HERO ID:	5743382

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Outcome ascertainment is well described for both intermediate (total oocytes, mature oocytes, fertilized oocytes, and top quality embryos) and clinical (implantation, clinical pregnancy and live birth) outcomes, and authors note additional exclusions and treatments (all patients received controlled ovarian stimulation using GnRH antagonist) to avoid potential confounding. Reproductive outcomes (total Oocytes, mature oocytes, fertilized oocytes, top quality embryos, and live births) were measured during times of IVF treatment, development of oocytes, and births. Detail methodology regarding the IVF preparation process was provided. Authors note that "The total number of mature oocytes in a conventional IVF cycle was determined by summing the number of oocytes exhibiting one or more pronucleus combined with those without a pronucleus but exhibiting a polar body." An embryologist determined the results of a normal fertilization 16-18 hours following insemination. Clinical pregnancy was determined by an intrauterine gestation sac and fetal heartbeat detected via ultrasound at 7 weeks of gestation. Live birth was defined as the delivery of a live neonate 24 or more weeks of gestation. These clinical outcomes were sourced from medical records.
	Metric 3B:	Selective Reporting	Medium	The authors described their primary analyses in the methods section and results were adequately reported for all primary analyses. Additional analyses are located in the supplemental file.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Authors report that confounders were selected and identified using prior knowledge related to art outcomes and phthalate exposures. It is noted that the variables were explored using a directed acyclic graph (not found in main study or supplement). The final model included: maternal age, BMI, and current smoking status. Additionally, sensitive analyses were conducted to adjust for other phthalate metabolites.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Authors reported LODs and utilized instrumental reading values for metabolite concentrations below the LOD. Descriptive statistics were calculated for all metabolites before and after adjusting for specific gravity. All phthalate metabolites with detectable measures>66% were divided into tertiles (T1, T2, T3). Quantitative results were presented in adjusted means (95% CI), and statistical significance was reported with p-values. Results were unchanged when additional sensitivity analyses were conducted restricted to the 116 cycles with embryo transfer. The analyses are well described, but the confidence for this metric is rated medium/adequate due to the lack of considerations of nonlinear possibilities, and analyses to address robustness. MCOP (ug/L): [T1 (1.68-6.15); T2 (6.16-11.14); T3 (11.15-1344)]MiNP (ug/L): [T1 (<LOD); T2 (0.50-1.40); T3 (1.41-263)]MCNP (ug/L): [T1 (0.21-0.83); T2 (0.84-1.67); T3 (1.68-46)]

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Study Citation:	Machtinger, R., Mansur, A., Baccarelli, A. A., Calafat, A. M., Gaskins, A. J., Racowsky, C., Adir, M., Hauser, R. (2018). Urinary concentrations of biomarkers of phthalates and phthalate alternatives and IVF outcomes. Environment International 111:23-31.
Health Outcome(s) Assessed:	Reproductive/Developmental- Total Oocytes, mature oocytes, fertilized oocytes, top quality embryos, live births, implantation, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-carboxy-isooctyl phthalate (MCOP); Mono-isononyl phthalate (MiNP); Mono-oxononyl phthalate (MONP)
HERO ID:	5743382

Domain	Metric	Rating	Comments
	Metric 5B: Sensitivity	Medium	Authors note that the sample size is moderate and potentially limited the power of the findings. A total of n=136 participants were analyzed within the intermediate outcomes analyses, with n=121 analyzed for the live birth outcomes. The study population was sensitive to the development of outcomes of interest (women undergoing fertility treatment). Additionally, authors had a strict inclusion and exclusion criteria. This both strengthened their results and limited the generalizability.

Additional Comments: This cohort examined the association between urinary concentrations of phthalates with intermediate and clinical in vitro fertilization (IVF) outcomes. Authors note limitations such as the moderately sized sample, and the potential of IVF outcomes being much more sensitive when compared to clinical outcomes such as live birth. This study did not have any substantial flaws. No significant associations were noted between MONP and MCNP and the intermediate outcomes of assisted reproduction (total oocytes, mature oocytes, fertilized oocytes and top quality embryos). Significant associations were noted between total oocytes and MCOP and MiNP metabolites, and between mature oocytes and MCOP levels. None of the urinary phthalate metabolite concentrations were associated with a reduced probability of implantation, clinical pregnancy or live birth.

Overall Quality Determination Medium

Study Citation:	Watkins, D. J., Meeker, J. D., Tamayo-Ortiz, M., Sánchez, B. N., Schnaas, L., Peterson, K. E., Téllez-Rojo, M. M. (2021). Gestational and peripubertal phthalate exposure in relation to attention performance in childhood and adolescence. Environmental Research 196:110911.
Health Outcome(s) Assessed:	Reproductive/Developmental- Conners' Continuous Performance Test, Second Edition (CPT-II) at age 6-11 years and an updated version of the Conners' CPT (CPT-3) at age 9-18 years, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Monocarboxyoctyl phthalate (MCOP); Mono-iso-nonyl phthalate (MiNP)
HERO ID:	8348423

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This prospective cohort study analyzed associations between urinary phthalate metabolite levels and ADHD symptoms in childhood and adolescence. Women in Mexico City were recruited for the Early Life Exposure in Mexico to Environmental Toxicants (ELEMENT) birth cohort. The current study includes women recruited from 1997-2004 in maternity hospitals during the first trimester of pregnancy, those who participated in three prenatal study visits, and those who were followed through delivery. When their children were 6-11 years (n = 827), a follow up was initiated to assess ADHD symptoms. When children were 9-18, a second follow-up was initiated to collect urine samples and measure ADHD symptoms. 221 participants had prenatal phthalate measures and childhood outcome measures; 200 had prenatal phthalate measures and adolescent outcome measures; and 195 had prenatal phthalate measures and outcome measures at both timepoint. 491 participants had adolescent exposure and outcome measures. The current study population was not significantly different from the total eligible population, minimizing concern for selection bias. Some information on participation rates (e.g., total eligible population) was not reported.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	High	Phthalate metabolite levels were measured in urine samples collected both prenatally and during adolescence via liquid chromatography-tandem mass spectrometry. Maternal urine samples were collected throughout pregnancy (mean gestational weeks for each trimester: 1 = 13.4 weeks; 2 = 25.1 weeks; 3 = 34.3 weeks). Phthalate measures in each trimester were used to calculate geometric means for pregnancy (overall exposure in utero). Additional urine samples were collected from children during adolescent visits (between ages 9-18, mean age = 14.6 years). There is no information on quality control measures, but storage information is specified. Urine specific gravity was also measured in collected samples to account for dilution. The use of multiple phthalate measures throughout pregnancy reduces concerns for exposure misclassification.Exposure distribution information is available for both adolescent measures and pregnancy measures (available in Supplement). LODs are reported for each metabolite (ug/L: MEHP = 1.0; MEHHP = 0.1; MEOHP = 0.1; MECPP = 0.2; MBzP = 0.2; MBP = 0.5; MiBP = 0.2 or 0.1; MCOP = 0.2; MCNP = 0.2; MNP = 0.5), along with % of samples above the LOD (%, MEHP = 93.2; MEHHP = 99.6; MEOHP = 99.6; MECPP = 99.6; MBzP = 99.0; MBP = 99.6; MiBP = 99.6; MCOP = 99.6; MCNP = 98.6; MNP = 0.4). Samples <LOD were assigned values of LOD/ (sq. rt. 2). For analyses, DEHP metabolites were summed by dividing each metabolite by their molar mass and summing them.
Domain 3: Outcome Assessment				

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Study Citation:	Watkins, D. J., Meeker, J. D., Tamayo-Ortiz, M., Sánchez, B. N., Schnaas, L., Peterson, K. E., Téllez-Rojo, M. M. (2021). Gestational and peripubertal phthalate exposure in relation to attention performance in childhood and adolescence. Environmental Research 196:110911.
Health Outcome(s) Assessed:	Reproductive/Developmental- Conners' Continuous Performance Test, Second Edition (CPT-II) at age 6-11 years and an updated version of the Conners' CPT (CPT-3) at age 9-18 years, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Monocarboxyoctyl phthalate (MCOP); Mono-iso-nonyl phthalate (MiNP)
HERO ID:	8348423

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Attention Deficient Hyperactivity Disorder (ADHD) symptoms were measured using two editions of the Conners' Continuous Performance Test (CPT-II and CPT-3). CPT-II was administered during child visits at ages 6-11 years and CPT-3 was administered at adolescent visits at ages 9-18. The CPT is a "computer-based assessment of attention and impulsivity that provides information on specific ADHD behaviors." During these tests, participants at the computer press the spacebar when letters other than "X" appear on screen. "Letters are displayed for 250 ms at intervals of 1, 2, or 4 s, with a total of 360 trials over 14 min." The following indices are assessed using the scores: Omissions (missed targets); Commissions (incorrect response to non-target); Hit Reaction Time (HRT); HRT standard deviation (HRT-SD); HRT for Block Change (change in speed across blocks of trials); HRT for ISI Change (change in speed across different inter-stimulus intervals); Detectability (measure of differentiation of targets from non-targets); Variability (measure of variability of reaction time consistency across blocks of trials); Response Style (accuracy over speed or speed over accuracy). "Raw scores can be converted to age- and sex-adjusted t-scores with a mean of 50 and standard deviation of 10."Although the CPT-II and CPT-3 are both validated questionnaires, they are not official diagnostic tools for ADHD. In tandem with other measures of ADHD, these assessments may be useful for diagnosis; however, they are not used to officially diagnosis ADHD. Additionally, the use of two versions of the questionnaire from ages 6-11 to ages 9-18 may lead to varied scores for individuals. No information is provided on who performed the examinations and whether or not they were aware of participants' exposure status.
	Metric 3B:	Selective Reporting	Medium	Results for all anticipated analyses were reported in the main text or supplements, either quantitatively or qualitatively.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Confounders were collected a priori and included child age at assessment, sex, maternal education, and urinary specific gravity. Models assessing results from CPT-3 scores were also adjusted for the number of years the child attended school at the time of assessment. Sensitivity analyses also adjusted for household SES at CPT administration (as measured by the AMAI scale), ADHD medication use (n=5), gestational age at birth, and birth weight. Information on covariates was collected at prenatal, childhood, and adolescent visits. There is no information on missing covariates data. While maternal race/ethnicity was not considered, there is no evidence to suggest a high likelihood of residual confounding.
Domain 5: Analysis				

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Health Outcome(s) Assessed:	Reproductive/Developmental- Conners' Continuous Performance Test, Second Edition (CPT-II) at age 6-11 years and an updated version of the Conners' CPT (CPT-3) at age 9-18 years, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Monocarboxyoctyl phthalate (MCOP); Mono-iso-nonyl phthalate (MiNP)
HERO ID:	8348423

Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Medium	Associations between maternal and adolescent urinary phthalate metabolite levels and CPT t-scores were analyzed using linear regression. Effect estimates and 95% CI are provided. Phthalate measures and CPT t-scores for Response Style, Commissions, and Omissions at ages 6-11 and for Omissions, HRT, HRT-SD, Variability at ages 9-18 were natural-log transformed. Other CPT subindices were normally distributed. Maternal pregnancy phthalate measures were the sum of measures taken from the three trimesters. Samples <LOD were assigned values of LOD/(sq. rt. 2). Information on missing covariates data is not provided. Models assessed maternal phthalate measures and CPT outcomes at 6-11 years and at 9-18. Cross-sectional analyses examined adolescent phthalate measures and CPT scores at ages 9-18. Categorical analyses (phthalate tertiles) were also conducted.Exposure distribution information is provided for maternal and adolescent measures. Sensitivity analyses adjusted for additional confounders (household SES, ADHD medication, gestational age at birth, birth weight) and examined sex*exposure interactions.
	Metric 5B:	Sensitivity	Medium	The analytical sample sizes are adequate and would provide sufficient statistical power (longitudinal analyses: childhood CPT-II measures n = 221; adolescent CPT-3 measures n = 200 | cross-sectional analysis n = 491). Exposure levels appear to have adequate contrast to detect an effect, with the exception of MNP (median ug/L (25th-7th %ile): MEHP = 4.08 (2.30, 7.94); MEHHP = 29.5 (16.0, 53.0); MEOHP = 14.0 (7.89, 26.2); MECPP = 43.5 (24.6, 78.8); MBzP = 3.37 (1.94, 6.35); MBP = 128 (71.3, 238); MiBP = 11.3 (6.17, 19.2); MCOP = 4.85 (2.37, 9.56); MCNP = 0.80 (0.55, 1.36); MNP = <0.5 (<0.5, <0.5)).

Additional Comments: This prospective cohort study includes both longitudinal and cross-sectional analyses of urinary phthalate metabolites (DEHP: mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), mono-2-ethyl-5-oxohexyl phthalate (MEOHP), and mono-2-ethyl-5-carboxypentyl phthalate (MECPP); BBP: monobenzyl phthalate (MBzP); DIBP: monoisobutyl phthalate (MiBP); DBP: mono-n-butyl phthalate (MnBP)), measured during pregnancy and adolescence, and symptoms of ADHD measured by the CPT-II and CPT-3 scales. The study used an adequate design and methods to assess the association of interest, including for participant selection, exposure measurement, outcome ascertainment, and statistical analyses. The inclusion of multiple exposure measures is a particular strength of the study. There are no major deficiencies that raise concern for residual bias. In cross-sectional analyses, significantly increased HRT and HRT-SD scores were observed for summed DEHP and significantly decreased Block Change scores for MCOP and MCNP. In longitudinal analyses of adolescent CPT-3 scores, significant increases were found for the following: Response Style for MBP, Omissions for MBP and MBzP, and ISI Change and Variability for MiBP. Other results were not significant.

Overall Quality Determination — Medium

Study Citation:	Santana, Díaz, M. V., Hankinson, S. E., Bigelow, C., Sturgeon, , S. R., Zoeller, R. T., Tinker, L., Manson, E., J.A., Calafat, A. M., Meliker, , J. R., Reeves, K. W. (2019). Urinary concentrations of phthalate biomarkers and weight change among postmenopausal women: a prospective cohort study. Environmental Health 18(1):20.
Health Outcome(s) Assessed:	Nutritional/Metabolic- Weight change, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isobutyl phthalate (OH-MiBP)
HERO ID:	5613207

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This study performed cross-sectional and longitudinal analyses of postmenopausal women enrolled in the nested case-control Women's Health Initiative (WHI) study. Enrollment for the WHI was described briefly, and 50-79 year old women were enrolled from October 1, 1993 until December 21, 1998 at locations in Alabama, Pennsylvania, and Arizona. The WHI focused on individuals with breast cancer and had matched controls. Cases were comprised of women diagnosed with invasive breast carcinoma which occurred after a three-year follow-up through 2013. Controls were matched on numerous variables including enrollment date, length of follow-up, age at enrollment, and WHI study arm. Controls were matched to cases 2:1. The cross-sectional analysis included 337 cases and 660 controls with complete data available, while the longitudinal analysis only included the 660 controls from the parent study. The authors indicated that weight gain is common after breast cancer treatment, which is why the longitudinal analysis was restricted. The authors provided sufficient information about participant selection, contributing to minimal concerns of selection bias. The methods for determining the control group were also adequate, strengthened by the matching procedures.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	All participants provided first morning void urine samples at baseline, and the WHI used a standard collection, processing, and storage protocol. The samples were collected at home and processed upon arrival at the clinics. Phthalate metabolite concentrations were quantified via on-line solid phase extraction coupled to high performance liquid chromatography-electrospray ionization-isotope dilution tandem mass spectrometry after enzymatic hydrolysis of the metabolites. While the authors do not provide exact numbers for the LOD, they do link to the methods used for quantification and detail that the LODs were in the low ng/mL range. The LOD for creatinine was reported as 10 mg/mL. The methods utilized are appropriate for determining phthalate concentrations, and the samples represent the etiologically relevant time period. Concerns were raised about exposure misclassification because two clinics used urine collection containers that were not confirmed to be phthalate free. These concerns are lowered somewhat because the authors measured metabolite concentrations instead of parent phthalates, which should not reflect potential contamination. This contributes to more confidence in an adequate rating for this metric.
Domain 3: Outcome Assessment				

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Health Outcome(s) Assessed:	Nutritional/Metabolic- Weight change, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isobutyl phthalate (OH-MiBP)
HERO ID:	5613207

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	The authors report that measurements of height and weight were collected three times: at baseline, year 3, and year 6 clinic visits. These measurements were used to determine participants BMI as weight(kg)/height^2(m^2). Respondents were then grouped based on their BMI into underweight/normal weight (<25.0 kg/m^2), overweight (25.0-<30.0 kg/m^2), and obese (>/=30.0 kg/m^2). There is some uncertainty about misclassification because the authors did not report the tools used for height and weight, but in the discussion section the authors highlight the objectively measured data, reducing this concern. This metric is adequate because it is likely that the instruments were appropriate, but there is no discussion of validation.
	Metric 3B:	Selective Reporting	Medium	There were no major concerns of selective reporting in this reference, and results for the primary and secondary analyses outlined in the methods section are reported.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	The WHI collected extensive data on participants, and numerous variables were considered as confounders. These included age, race/ethnicity, education level, income, health insurance, smoking status, alcohol use, Healthy Eating Index-2005 score, dietary energy intake, total recreational physical activity, oral contraceptive use, any hormone therapy use, ever had diabetes, ever had cardiovascular disease, hypertension, and dyslipidemia. All models were adjusted for age and urinary creatinine concentration. Other covariates were included if they had a p-value of less than 0.25 in a univariable model in a preliminary multivariable model, and their significant was evaluated using backward selection and keeping those with a p-value less than 0.10. Covariates included in the final models include creatinine, age, ethnicity, alcohol use, physical activity, smoking status, health eating index, dietary energy intake, hormone replacement therapy use, education, income, and history of diabetes, hypertension, dyslipidemia, and cardiovascular disease. While numerous covariates were considered, inclusion in the model was based on statistical significance, contributing to an adequate rating. The authors also note in the discussion section that residual confounding may have impacted their results.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	All phthalate concentrations were natural log transformed for normality. Cross-sectional analyses included cases and controls, with phthalate concentrations grouped into quartiles. Linear regression and multinomial logistic regression analyses were conducted to examine relationships between the biomarkers and weight and BMI categories. All results were appropriately reported with effect estimates and corresponding confidence intervals. While there was not an optimal characterization of the outcome variable because specific tools were not mentioned, there was an adequate description of the exposure. LOD was not provided in the report, but specific methods were linked. Overall, the analyses performed were robust and appropriate.

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Study Citation:	Santana, Díaz, M. V., Hankinson, S. E., Bigelow, C., Sturgeon, , S. R., Zoeller, R. T., Tinker, L., Manson, E., J.A., Calafat, A. M., Meliker, , J. R., Reeves, K. W. (2019). Urinary concentrations of phthalate biomarkers and weight change among postmenopausal women: a prospective cohort study. Environmental Health 18(1):20.
Health Outcome(s) Assessed:	Nutritional/Metabolic- Weight change, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isobutyl phthalate (OH-MiBP)
HERO ID:	5613207

Domain	Metric	Rating	Comments
	Metric 5B: Sensitivity	Medium	Study sensitivity was sufficient due to a range of exposure levels, which provides enough variability to evaluate the primary hypotheses, and the study population was sensitive to the development of the outcomes of interest. Even though the longitudinal analysis only included controls, these contributing factors are still true. The cross-sectional analysis sample size (n=337 cases; n=660 controls) had adequate power, as well as the longitudinal analysis (n=660).

Additional Comments: This cross-sectional and longitudinal analysis of participants from a nested case-control included a moderate number of individuals, with a high-quality exposure assessment methodology. There were no major flaws noted in this study, other than a potential for residual confounding and possible Type 1 error resulting from numerous statistical analyses.

Overall Quality Determination Medium

Study Citation:	Jankowska, A., Polańska, K., Hanke, W., Wesołowska, E., Ligocka, D., Waszkowska, M., Stańczak, A., Tartaglione, A. M., Mirabella, F., Chiarotti, F., Garí, M., Calamandrei, G. (2019). Prenatal and early postnatal phthalate exposure and child neurodevelopment at age of 7 years - Polish Mother and Child Cohort. Environmental Research 177:108626.
Health Outcome(s) Assessed:	Neurological/Behavioral- Child behavior (domains: conduct problems, emotional symptoms, hyperactivity-inattention problems, peer relationship problems, total difficulties, prosocial behavior), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP)
HERO ID:	5933662

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This prospective cohort study examined associations between phthalates and measures of child behavior, cognition, and psychomotor development. Subjects were a subset of 134 maternal-child pairs participating in a larger multicenter cohort study (the Polish Mother and Child Cohort). Details on the larger cohort were reported in Polanska et al. 2009 (HERO ID 2092850) and Polanska et al. 2014 (HEROID 2347467). Women were recruited in their first trimester at maternity units/clinics in multiple regions across Poland; based on Polanska et al. 2014 it appears the current study was limited to participants from Lodz district (n=165 at age 2 years). Inclusion criteria were: singleton pregnancy up to 12 weeks gestation, no assisted conception, no pregnancy complications, and no chronic diseases. The current study was limited to participants with phthalate measurements who were assessed for neurodevelopmental outcomes at age 7. Information on participation rates, loss to follow-up, and the comparability of the current study population to the larger cohort was not provided; however, the information available on participation and recruitment does not raise major concerns regarding bias.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Phthalate metabolites (OH-MiNP, MiBP, MnBP, OH-MnBP, MBzP, OH-MEHP, oxo-MEHP) were measured prenatally in maternal 3rd trimester urine samples and postnatally in child urine samples collected at age 2 years. Additional details reported in Polanska et al. 2014 (HERO ID 2347467) indicate these were single spot urine samples, raising the potential for some degree of exposure misclassification although this is not a major concern. Phthalate and metabolite concentrations were measured using high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS). For OH-MiNP, MiBP, MnBP, OH-MnBP, OH-MEHP, and oxo-MEHP, at least 70% of samples were above the LOD. For MBzP, 84% of child samples were above the LOD but only 56% of maternal samples were above the LOD; as such, only child samples were used in analysis for this metabolite. Two other relevant metabolites (oxo-MiNP, MEHP) were measured but was not included in further analysis due to <70% of samples above the LOD. Maternal urine phthalate metabolite concentrations were adjusted for creatinine while postnatal samples were not; a rationale for this difference was not provided.
Domain 3: Outcome Assessment				

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Health Outcome(s) Assessed:	Neurological/Behavioral- Child behavior (domains: conduct problems, emotional symptoms, hyperactivity-inattention problems, peer relationship problems, total difficulties, prosocial behavior), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP)
HERO ID:	5933662

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	The outcomes of interest in this study were measures of child behavior, cognition, and psychomotor development assessed at age 7. Child behavior was measured using maternal report on the Strengths and Difficulties Questionnaire. The questionnaire is widely used and has been validated (e.g. Stone et al. 2010, PMID 20589428). Child cognition and psychomotor development was measured by trained psychologists using a Polish adaptation of the Intelligence and Development Scales. This scale is also widely used (Hagmann et al 2016, PMID: 27497247). The authors reported reliability of 0.94 for fluid and crystallized intelligence and cited a study reporting correlations of 0.80 with Wechsler Intelligence Scale for Children scores. The study did not state whether participants and/or trained psychologists were aware of exposure status, but this is unlikely to result in bias as the exposure was measured in biological samples.
	Metric 3B:	Selective Reporting	Medium	The authors described their primary and secondary analyses in the methods section and results were reported for all primary and secondary analyses.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	A wide array of potential confounders was considered. The inclusion of potential confounders in regression models was based on either hypothesized relevance to psychosocial epidemiologic studies, or statistical significance of the association with at least one outcome. Potential confounders included in models of outcomes assessed in the Strengths and Difficulties Questionnaire were: child's sex, child's age at examination, birth weight, SES, maternal educational level, prenatal and childhood tobacco smoke exposure, breastfeeding duration and maternal BMI. Potential confounders included in models of outcomes assessed in the Intelligence and Development Scales were: child's sex, child's age at examination, maternal educational level, place of residence, birth weight, prenatal and childhood tobacco smoke exposure and psychologist who have performed child examination. Tobacco smoke exposure was quantified using cotinine measurements in maternal saliva (prenatal) and child's urine (postnatal). Both pre- and postnatal measures of each phthalate were included simultaneously to address co-exposure confounding.
Domain 5: Analysis				

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Study Citation:	Jankowska, A., Polańska, K., Hanke, W., Wesołowska, E., Ligocka, D., Waszkowska, M., Stańczak, A., Tartaglione, A. M., Mirabella, F., Chiarotti, F., Garí, M., Calamandrei, G. (2019). Prenatal and early postnatal phthalate exposure and child neurodevelopment at age of 7 years - Polish Mother and Child Cohort. Environmental Research 177:108626.
Health Outcome(s) Assessed:	Neurological/Behavioral- Child behavior (domains: conduct problems, emotional symptoms, hyperactivity-inattention problems, peer relationship problems, total difficulties, prosocial behavior), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP)
HERO ID:	5933662

Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Medium	Analysis methods were largely appropriate. Outcomes assessed using the Strengths and Difficulties Questionnaire were dichotomized (normal vs. borderline/clinical) and analyzed using logistic regression, while outcomes assessed using the Intelligence and Development Scales were left as continuous variables and analyzed using linear regression. Models were adjusted for confounders and included both prenatal and postnatal phthalate metabolite concentrations simultaneously. Metabolite concentrations were log10-transformed prior to analysis. The study does not specify how missing data or values below the limit of detection were handled, although the proportion of participants with such values appears to be low. The authors did not discuss evaluating robustness of findings, stratifying by gender, or examining linearity of dose-response.
	Metric 5B:	Sensitivity	Medium	There was variability in both prenatal and postnatal measures of exposure. No additional concerns related to study sensitivity were identified.

Additional Comments: This prospective cohort study evaluated the association between prenatal and postnatal (age 2 years) phthalate metabolites and child behavior, cognition, and psychomotor development at age 7. The study included 134 mother-child pairs from central Poland, a subset of the Polish Mother and Child Cohort. Study methods were largely appropriate, with minor concerns largely due to a lack of information on some aspects of study design and analysis (e.g., loss to follow-up, handling of missing data). MnBP in child urine samples was inversely associated with fluid intelligence and cognition, while oxo-MEHP in maternal urine samples was positively associated with the same two outcomes. No statistically associations observed for other metabolites. For two measured phthalate metabolites (oxo-MiNP and MEHP), associations with outcomes were not quantified due to detection rates of less than 70% in both child and maternal urine samples.

Overall Quality Determination Medium

Study Citation:	Tanner, E. M., Hallerbäck, M. U., Wikström, S., Lindh, C., Kiviranta, H., Gennings, C., Bornehag, C. G. (2020). Early prenatal exposure to suspected endocrine disruptor mixtures is associated with lower IQ at age seven. Environment International 134:105185.
Health Outcome(s) Assessed:	Neurological/Behavioral- full scale IQ, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP)
HERO ID:	5933606

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	High	The association of prenatal urinary DiDP (MHiDP, MCNP), DiNP (MHiNP, MOiNP, MCiOP), DBP (MBP), BBP (MBzP), and DEHP (MEHP, MEHHP, MEOHP, MECPP) metabolites and child full scale IQ at age 7 was assessed in this cohort study of mother-child pairs (n = 718) from the Swedish Environmental Longitudinal Mother and Child, Asthma and Allergy (SELMA) study. 2300 pregnant women were recruited for the study from November 2007 - March 2010 in prenatal clinics in Varmland county during the first trimester. Families were invited to participate in child cognitive functioning studies consecutively based on child age. 943 were assessed, but full data were only available for 718 children. Inverse probability weights were used to incorporate baseline characteristics (child sex, maternal age, education, and smoking) with significant differences between the recruited population (n=943) and the study population. Concern for selection bias is minimal.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	MBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, MHiDP, MCNP, MHiNP, MOiNP, and MCiOP were assessed in first morning void urine samples from pregnant women during the first prenatal clinic visit (median = 10 weeks gestation). Samples were analyzed via LC-MS/MS and creatinine (measured enzymatically) was used to adjust for urine dilution. Limits of detection are reported (MBP: 0.100 ng/mL; MBzP: 0.04 ng/mL; MEHP: 0.100 ng/mL; MEHHP: 0.02 ng/mL; MEOHP: 0.03 ng/mL; MECPP: 0.02 ng/mL; MHiDP and MCNP: 0.031 ng/mL, MHiNP: 0.020 ng/mL, MOiNP: 0.010 ng/mL, MCiOP: 0.020 ng/mL) and 100% of metabolite samples were >LOD. DiNP was calculated as the molar sum of 3 metabolites (MHiNP, MOiNP, and MCiOP) and DEHP was calculated as the molar sum of 4 metabolites (MEHP, MEHHP, MEOHP, MECPP).Urinary measure during pregnancy is the etiologically window to measure exposure. However, the use of single measurements for chemicals with short half-lives to represent exposure during pregnancy may lead to misclassification. Impacts expected to be minor.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Trained psychologists evaluated full scale IQ in children at age 7 using the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV). Scores were indexed to have a mean of 100 and SD of 15. There is no discussion of validation in the study population, but the WISC-IV is a well-established tool to assess cognitive function.
	Metric 3B:	Selective Reporting	Medium	All anticipated results are reported from primary and secondary analyses.
Domain 4: Potential Confounding / Variability Control				

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Study Citation:	Tanner, E. M., Hallerbäck, M. U., Wikström, S., Lindh, C., Kiviranta, H., Gennings, C., Bornehag, C. G. (2020). Early prenatal exposure to suspected endocrine disruptor mixtures is associated with lower IQ at age seven. Environment International 134:105185.
Health Outcome(s) Assessed:	Neurological/Behavioral- full scale IQ, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP)
HERO ID:	5933606

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	Medium	Covariates were selected for inclusion through examination of the literature and bivariate associations with study data. Child sex and the maternal characteristics (parity, age, weight, education, IQ (RAVEN), and smoking) were included as confounders in final models. Maternal fish consumption and breast feeding were also considered as confounders. Additionally, child sex, maternal age, maternal education, maternal smoking, and prenatal creatinine-corrected MEP and MBzP, trans-nonachlor, and PCBs were included via inverse probability weights to adjust for potential selection bias. These variables were summarized in a directed acyclic graph. Analyses were also stratified by child sex. Information on potential confounders was collected from mothers during visits via questionnaire. Subsequent information was collected via follow-up questionnaires (i.e., information on breast feeding). Gestational age, birth weight, and maternal weight data were obtained from the Swedish Medical birth register.
Domain 5: Analysis				
	Metric 5A:	Analysis	High	Weighted quantile sum (WQS) regression was used to examine the association between exposure to mixtures of EDC chemicals (natural log-transformed), including the phthalate metabolites of interest, and child full scale IQ. For these regressions, a WQS index (of all chemicals) is included in a multivariable linear model to assess the effects on the outcome. Effect estimates and 95% CI are reported from WQS regression. Construction of the WQS used negative weights from 100 bootstrap samples for each chemical, anchored by an assumption that IQ would decrease with increasing exposure. Chemicals with weights >3.8% were considered chemicals of concern. Authors deemed this an explanatory approach.A repeated holdout validation was conducted to simulate a distribution of validated results from the underlying population. The resulting mean estimate is reported along with the range of values representing the uncertainty in a weight uncertainty plot.Additional sensitivity analyses were conducted with the population stratified by child sex, with the addition of covariates (maternal fish consumption, breastfeeding). The WQS regression was conducted with 40% of the data to assess the origin of differences between the explanatory approach and repeated holdout validation. Additional analyses were conducted without the highest weight chemical and with an assumption of a positive association between exposure and outcome (i.e., using positive weights instead of negative).Analyses were conducted on individuals with complete data; thus, treatment of missing values was not necessary.
	Metric 5B:	Sensitivity	Low	Study had adequate sample size (n = 718 mother-child pairs) and exposure distribution to detect an effect. Importantly, the study analyzes the effect of EDC mixtures on child cognitive functioning (IQ). As a result, single chemical effects cannot be gleaned from the findings.

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Study Citation:	Tanner, E. M., Hallerbäck, M. U., Wikström, S., Lindh, C., Kiviranta, H., Gennings, C., Bornehag, C. G. (2020). Early prenatal exposure to suspected endocrine disruptor mixtures is associated with lower IQ at age seven. Environment International 134:105185.
Health Outcome(s) Assessed:	Neurological/Behavioral- full scale IQ, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP)
HERO ID:	5933606

Domain	Metric	Rating	Comments
Additional Comments:	This cohort study examined mother-child pairs (n=718) from the SELMA study and the association between prenatal urinary phthalate exposure (MBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, MHiDP, MCNP, MHiNP, MOiNP, MCiOP) and child IQ at age 7. The study used a robust analysis and appropriate recruiting, outcome, and exposure assessment methods. However, the results are reported for mixtures of EDCs only, limiting the study's sensitivity to determine single-pollutant effects. DEHP (calculated as the molar sum of MEHP, MEHHP, MEOHP, and MECPP), DiNP (calculated as the molar sum of MHiNP, MOiNP, and MCiOP), MBP, MHiDP, and MCiNP were below the threshold of concern, however, in some analyses with positive weights, DiNP was above the threshold. MBzP was above the threshold of concern in the full sample explanatory approach (weight: 6%).		

Overall Quality Determination Medium

Study Citation:	Lee, G., Kim, S., Bastiaensen, M., Malarvannan, G., Poma, G., Casero, N. C., Gys, C., Covaci, A., Lee, S., Lim, J. E., Mok, S., Moon, H. B., Choi, G., Choi, K. (2020). Exposure to organophosphate esters, phthalates, and alternative plasticizers in association with uterine fibroids. Environmental Research 189:109874.
Health Outcome(s) Assessed:	Reproductive/Developmental- Uterine fibroids, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-carboxy-isononyl phthalate (cx-MiNP)
HERO ID:	7274600

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	The case control study examined the relationship between phthalate metabolites and uterine fibroids in pre-menopausal Korean women. Women (20-49 years of age) were recruited 2015-2016 from public health centers or gynecology clinics of universities in Seoul, Ansan, Incheon, and Jeju South Korea. A subset (n=70) of participants (n=516 originally recruited) were randomly chosen from the Children's Health and Environmental Chemicals of Korea (CHECK) cohort. Of the women initially recruited, those with current pregnancy (n=38) were excluded. Of the n=95 cases of uterine fibroids initially identified, n=40 were selected as cases as defined by 'severe' degree of fibrosis. Severe fibrosis cases were chosen based on the criteria of size of uterine fibroids (> 4cm), the number of fibroids (>2), or concurrent diagnosis of adenomyosis. Women of the same age without uterine fibroids were randomly chosen as controls with a 1:2 (case : control) ratio. Cases and controls with insufficient samples for chemical analysis were excluded, leaving a total of 32 cases and 79 controls for final analysis within the current study. Comparisons with respect to demographic and other factors potentially associated with exposure and outcomes of interest between participants and non-participants were not detailed.
Domain 2: Exposure Characterization			

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Study Citation:	Lee, G., Kim, S., Bastiaensen, M., Malarvannan, G., Poma, G., Casero, N. C., Gys, C., Covaci, A., Lee, S., Lim, J. E., Mok, S., Moon, H. B., Choi, G., Choi, K. (2020). Exposure to organophosphate esters, phthalates, and alternative plasticizers in association with uterine fibroids. Environmental Research 189:109874.
Health Outcome(s) Assessed:	Reproductive/Developmental- Uterine fibroids, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-carboxy-isononyl phthalate (cx-MiNP)
HERO ID:	7274600

Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Low	Urine samples were taken at the health examination where subjects were asked to fast for more than 8 hours before sample. Phthalates were extracted using a solid phase extraction and analyzed using HPLC and an ESI-MS/MS. cxMINP, OH-MINP, MiBP, MBP, MBzP, MCHP, MEOHP, MEHHP, MECPP, MCMHP, and MEHP detection frequencies in cases were 78.1, 93.8, 100, 100, 100, 3.1, 100, 100, 100, 100, 50 respectively. Control cxMINP, OH-MINP, MiBP, MBP, MBzP, MCHP, MEOHP, MEHHP, MECPP, MCMHP, and MEHP detection frequencies were noted as 78.5, 91.1, 93.7, 100, 100, 3.8, 87.3, 98.7, 100, 100, and 44.3, respectively. For chemicals with a detection frequency of 75% or more, the non-detected concentrations were imputed with the limit of quantification (LOQ) divided by the square root of 2. Urinary chemical concentrations were adjusted by specific gravity (SG) to correct for urine dilutions. Median (25th, 75th percentiles) concentrations for case OH_MINP, cxMINP, MiBP, MBP, MBzP, MCHP, MEOHP, MEHHP, MECPP, MCMHP, and MEHP were 2.05 ng/mL (1.12, 3.80 ng/mL), 2.34 ng/mL (1.51, 4.65 ng/mL), 2.81 ng/mL (1.18, 5.16 ng/mL), 6.73 ng/mL (4.46, 12.61 ng/mL), 0.66 ng/mL (0.44, 1.15 ng/mL), <LOQ, 1.73 ng/mL (1.09, 2.57 ng/mL), 3.21 ng/mL (2.21, 4.02 ng/mL), 14.33 ng/mL (9.99, 23.50 ng/mL), 4.95 ng/mL (3.36, 7.27 ng/mL), 0.09 ng/mL (<LOQ, 3.55 ng/mL), respectively. Median (25th, 75th percentiles) concentrations for controls OH_MINP, cxMINP, MiBP, MBP, MBzP, MCHP, MEOHP, MEHHP, MECPP, MCMHP, and MEHP were 1.37 ng/mL (0.83-2.39 ng/mL), 2.57 ng/mL (1.52, 3.50 ng/mL), 2.54 ng/mL (1.22, 4.15 ng/mL), 5.60 ng/mL (3.66, 8.29 ng/mL), 0.65 ng/mL (0.41, 1.26 ng/mL), <LOQ ng/mL , 1.23 ng/mL (0.72, 2.26 ng/mL), 2.59 ng/mL (1.55, 4.25 ng/mL), 11.67 ng/mL (7.42, 18.06 ng/mL), 4.04 ng/mL (2.38, 6.07 ng/mL), <LOQ (<LOQ, 1.18 ng/mL). The biological half-lives of most phthalates are less than 24 h and it is unclear if a single spot urine adequately represents the intensity, duration and potential peak exposures responsible for the initiation of the outcome of interest. Due to the instructions for fasting more than 8 hours prior to sampling, the concentrations of metabolites measured in the urine of the participating women may be lower than those expected in normal situations. The timing of diagnosis of uterine fibroids and measurement of urinary phthalates were similar, so a reasonable inference of causation and contribution of chemical exposure to uterine fibroids cannot be made.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Uterine fibrosis and adenomyosis were diagnosed via a gynecologic ultrasonography. Severe fibrosis was defined as a uterine fibroid size >4cm, >2 fibroids, or a concurrent diagnosis of adenomyosis.
	Metric 3B:	Selective Reporting	Medium	Analyses reported in the methods and results were described for primary analyses.
Domain 4: Potential Confounding / Variability Control				

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Study Citation:	Lee, G., Kim, S., Bastiaensen, M., Malarvannan, G., Poma, G., Casero, N. C., Gys, C., Covaci, A., Lee, S., Lim, J. E., Mok, S., Moon, H. B., Choi, G., Choi, K. (2020). Exposure to organophosphate esters, phthalates, and alternative plasticizers in association with uterine fibroids. Environmental Research 189:109874.
Health Outcome(s) Assessed:	Reproductive/Developmental- Uterine fibroids, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-carboxy-isononyl phthalate (cx-MiNP)
HERO ID:	7274600

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	Medium	Key confounders included age, BMI, income, parity, urinary cotinine, and alcohol consumption and were determined from previous reports that reported association with uterine fibroids. Data regarding confounding factors was indicated as obtained from participant questionnaire and based upon previous reports. Urinary cotinine was measured by an Immulite 2000 Nicotine Metabolite kit.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Multivariate linear regression models were constructed to compare metabolite concentrations between cases and controls while adjusting for covariates of interest. Multivariate logistic regression analysis was used to examine the association between chemical exposure and uterine fibroids. Concentrations were log-transformed due to distribution skewness. Additional multivariate logistic regression models with factors derived from factor analyses were run within multiple chemical exposure models. Non-linear relationships were explored within analyses presented across dichotomous, tertiles and quartiles of exposure. Consideration for additional sensitivity analyses was not detailed.
	Metric 5B:	Sensitivity	Medium	Sample size is somewhat small (n=111 total) which may lead to insufficient statistical power. and exposure range is adequate. It is unclear if a single spot urine adequately represents the intensity, duration and potential peak exposures responsible for the initiation of the outcome of interest. Urinary concentrations might not reflect normal daily levels due to the more than 8 hours fasting requirement prior to urine specimen collection.

Additional Comments: This case-control study assessed the relationship between uterine fibroids and phthalate metabolite concentrations. The limitations included a smaller sample size which may lead to insufficient statistical power, half-lives of phthalates are less than 24 h and the concentrations of metabolites measured in the urine of the participating women may be lower than those expected in normal situations. In addition, the spot urine measurements may not represent longer term exposure profile of the target chemicals. Study design and diagnosis of uterine fibroids and measurement of urinary chemicals were similar, the inference of causation and contribution of chemical exposure to uterine fibroids cannot be made. These limitations show that chance findings cannot be ruled out which affect the overall validity of the study.

Overall Quality Determination — Medium

Study Citation:	Engel, S. M., Villanger, G. D., Nethery, R. C., Thomsen, C., Sakhi, A. K., Drover, M., S.S., Hoppin, J. A., Zeiner, P., Knudsen, G. P., Reichborn-Kjennerud, T., Herring, A. H., Aase, H. (2018). Prenatal phthalates, maternal thyroid function, and risk of attention-deficit hyperactivity disorder in the Norwegian mother and child cohort. Environmental Health Perspectives 126(5):057004.
Health Outcome(s) Assessed:	Neurological/Behavioral- Attention-deficit hyperactivity disorder (ADHD), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-carboxy-isononyl phthalate (cx-MiNP); Mono-isononyl phthalate (MiNP)
HERO ID:	4728558

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	The participants within this population-based nested case-control study were part of the Norwegian Mother and Child Cohort (MoBa) 2003-2008. Of 112,762 participants enrolled between 1999 and 2008, mother-child pairs were eligible for the current study if they were singleton pregnancies in 2003 or later, completed the 36 month questionnaire, did not have Down Syndrome or cerebral palsy, had maternal urine and blood samples during pregnancy, and resided in geographic areas eligible for the MoBa Preschool ADHD Substudy (born at one of the larger hospitals in Norway between April 2004 and January 2008). The final eligible population was 24,035 from which cases (n=297) were randomly sampled from the Norwegian Patient Registry (NPR), a national database capturing 90 to 95% of ADHD diagnoses and containing all persons with diagnoses recorded from 2008 onward within government funded facilities. Controls (n=553 mother-child pairs) were randomly sampled from the eligible population. There were case-control differences in variables that included maternal age, education, depression, and smoking status, as well as in child sex and year of birth. However, multivariate models were adjusted for these variables. Comparisons between those included and excluded for the current study with regards to population characteristics possibly related to exposure or outcome were not presented, but there was no evidence of bias. The authors noted that to some extent, the MoBa cohort under-represent young mothers, those living alone, and women who report smoking during pregnancy, but there was no evidence that this would introduce bias.
Domain 2: Exposure Characterization				

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Study Citation:	Engel, S. M., Villanger, G. D., Nethery, R. C., Thomsen, C., Sakhi, A. K., Drover, M., S.S., Hoppin, J. A., Zeiner, P., Knudsen, G. P., Reichborn-Kjennerud, T., Herring, A. H., Aase, H. (2018). Prenatal phthalates, maternal thyroid function, and risk of attention-deficit hyperactivity disorder in the Norwegian mother and child cohort. Environmental Health Perspectives 126(5):057004.
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Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-carboxy-isononyl phthalate (cx-MiNP); Mono-isononyl phthalate (MiNP)
HERO ID:	4728558

Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Medium	Quantification of 12 maternal urinary phthalate metabolites using spot urine samples collected at approximately 17 weeks gestation was conducted utilizing on-line column switching liquid chromatography coupled with tandem mass spectrometry at the Norwegian Institute of Public Health. Individual metabolites of DiBP, DBP and BBP were analyzed; DiNP and DEHP were analyzed as the molar sums of multiple metabolites. Concentrations of relevant metabolites were reported across case and control status in ug/L. Appropriate quality control procedures were summarized. Limits of quantification (LOQ) and percent greater than the LOQ were summarized for metabolites and summation of metabolites variables. All reported concentrations were adjusted for batch and standardized to the geometric mean of specific gravity to account for dilution. Raw measured values for individual phthalates were greater than the LOQ; 98.5% or more of batch- and specific-gravity adjusted concentrations were also above LOQs. Given the short half-life of phthalates, it is unclear to what extent a single spot urine measure adequately represents gestational exposure. Concentrations of postnatal phthalates in children were not measured.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Clinically diagnosed cases of ADHD born in 2003 or later were randomly sampled from the Norwegian Patient Registry (NPR) national database, which contains all persons with clinical diagnoses within government funded facilities recorded from 2008 onward. Current study cases (n=297) were randomly sampled from the NPR clinician diagnosed ADHD cases born in 2003 or later based upon ICD-10 classification of at least two registrations of “Hyperkinetic disorder” (codes F90, F90.0, F90.1, F90.8 or F90.9). Cases were limited to those with two registrations to exclude erroneous registrations or false diagnoses. These ICD-10 codes exclude attention deficit disorder (ADD) without hyperactivity. The distribution of age at diagnosis, and the year of follow-up through which cases were identified, were not reported. Cases were more likely than controls to have been born in 2003-2004 (44.1% vs. 10.0%), and less likely to have been born in 2007-2008 (11.8% vs. 31.5%). Despite this imbalance, there was no evidence of resulting bias as final models were adjusted for year of birth. The possibility of ADD, undiagnosed ADHD, or other related disorders among controls was not discussed. However, there was no evidence that the case definition, or the criteria used to obtain controls, resulted in bias.
	Metric 3B:	Selective Reporting	Medium	There were no concerns for selective reporting.
Domain 4: Potential Confounding / Variability Control				

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Study Citation:	Engel, S. M., Villanger, G. D., Nethery, R. C., Thomsen, C., Sakhi, A. K., Drover, M., S.S., Hoppin, J. A., Zeiner, P., Knudsen, G. P., Reichborn-Kjennerud, T., Herring, A. H., Aase, H. (2018). Prenatal phthalates, maternal thyroid function, and risk of attention-deficit hyperactivity disorder in the Norwegian mother and child cohort. Environmental Health Perspectives 126(5):057004.
Health Outcome(s) Assessed:	Neurological/Behavioral- Attention-deficit hyperactivity disorder (ADHD), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-carboxy-isononyl phthalate (cx-MiNP); Mono-isononyl phthalate (MiNP)
HERO ID:	4728558

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	Medium	The strategy for selection of potential confounding factors incorporated a priori knowledge with directed acyclic graphs based on knowledge of covariates that could potentially influence both phthalate levels and ADHD. Final models were adjusted for child sex and year of birth, as well as maternal age at delivery, education level, marital status, smoking in the first or second trimester, parity, and depression during pregnancy. Several maternal thyroid hormones during pregnancy were evaluated as potential mediators. Supplementary models evaluated analytic batch and specific gravity as confounders vs. as integrated in phthalates measures. Information on confounders was obtained from maternal self-report and from records. Missing data was somewhat higher in cases vs. controls, but numbers were not excessive (e.g. highest n=29 vs. n=7 missing values for maternal education). There was no evidence of inadequate or inappropriate confounding adjustment.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Bayesian logistic regression with binary ADHD status as the outcome in a complete case analysis framework was used to examine associations between maternal urinary phthalate concentrations and clinical diagnosis of ADHD. Models examined associations using either quintiles or log-transformed phthalates exposure variables. Primary analyses included all phthalates simultaneously; associations with single phthalates were examined in supplementary analyses. A Bayesian framework was selected as estimates are more stable in the presence of correlated exposures. Models were run for all children as well as stratified by child sex; additive interactions between each phthalate variables and child sex were examined. Mediation analyses using measures of three maternal thyroid hormones and preterm delivery was also examined for phthalates found to be significantly associated with ADHD. Results were presented as odds ratios with corresponding 95% credible intervals. Sensitivity analyses examined additional adjustment for maternal or paternal income, and for month and year of urine collection, with no substantial changes reported.
	Metric 5B:	Sensitivity	Medium	The analytic sample size for cases (n=297) and controls (n=533) was adequate; the authors reported an estimated 90% power to detect additive interactions between phthalates and child sex. There was substantial variability in individual phthalate metabolites, and very few participants had exposure levels below LOQ. Potential concerns that may reduce the ability to detect an association include exposure misclassification due to the use of a single spot urine from early pregnancy to characterize prenatal exposure.

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Study Citation:	Engel, S. M., Villanger, G. D., Nethery, R. C., Thomsen, C., Sakhi, A. K., Drover, M., S.S., Hoppin, J. A., Zeiner, P., Knudsen, G. P., Reichborn-Kjennerud, T., Herring, A. H., Aase, H. (2018). Prenatal phthalates, maternal thyroid function, and risk of attention-deficit hyperactivity disorder in the Norwegian mother and child cohort. Environmental Health Perspectives 126(5):057004.
Health Outcome(s) Assessed:	Neurological/Behavioral- Attention-deficit hyperactivity disorder (ADHD), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-carboxy-isononyl phthalate (cx-MiNP); Mono-isononyl phthalate (MiNP)
HERO ID:	4728558

Domain	Metric	Rating	Comments
Additional Comments:	This was a relatively large (n=297 cases, n=533 controls) population-based nested case-control study of ADHD in children born in the Norwegian MoBa cohort between 2003 and 2008. The authors examined associations between odds of clinically diagnosed ADHD and metabolites of DiNP, DEHP, BBP, DBP and DiBP. The study reported significant associations with the sum of DEHP phthalate metabolites. Strengths include the prospective design. A potential limitation is an imbalance in the birth years of cases vs. controls: the earlier birth years of cases may have contributed to higher concentrations of some phthalates. However, associations remained significant after adjusting for birth year, as well as month and year of sample collection. Other potential limitations include the heterogeneity of ADHD, and estimating exposure based on a single spot urine sample from early pregnancy.		

Overall Quality Determination Medium

Study Citation:	Kamai, E. M., Villanger, G. D., Nethery, R. C., Thomsen, C., Sakhi, A. K., Drover, M., S.S., Hoppin, J. A., Knudsen, G. P., Reichborn-Kjennerud, T., Zeiner, P., Overgaard, K., Herring, A. H., Aase, H., Engel, S. M. (2021). Gestational phthalate exposure and preschool attention deficit hyperactivity disorder in Norway. Environmental Epidemiology 5(4):e161.
Health Outcome(s) Assessed:	Neurological/Behavioral- Attention Deficit Hyperactivity Disorder (ADHD), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-carboxy-isononyl phthalate (cx-MiNP); Mono-isononyl phthalate (MiNP)
HERO ID:	9559555

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This case-cohort study of prenatal phthalates exposure and preschool ADHD was nested within the population-based Norwegian MoBa (Mother, Father and Child) birth cohort study. The participation rate for the parent cohort of more than 100,000 mother-child pairs was 41% (Magnus et al 2016, PMID: 27063603). This study included 260 children defined as ADHD cases and 549 non-cases born between April 2004 and January 2008 and who lived proximate to or within a direct flight to Oslo (n=33,050). Cases were identified from among 2,798 children aged 3.1 to 3.8 years who scored at or above the 90th percentile on ADHD screening questions included in the 36-month questionnaire. Of 1,195 (35%) who agreed to participate in a 1-day clinical assessment in Oslo used to identify cases, 870 had stored maternal gestational urine samples and 260 (115 girls, 44%) were confirmed as cases. From the eligible cohort of 27,347 children with 36-month questionnaire and stored maternal urine samples, 556 (274 girls, 50%) were randomly selected and frequency matched to cases on year of birth. 549 remained after removing 7 identified as cases during the ADHD clinic screening (6 from among 147 non-cases who agreed to the clinical exam, 22.5%). There was no evidence that selection into either the parent cohort or the sub-study was biased. Moreover, models included adjustment for maternal age, education, and parity, factors associated with selection into MoBa.
Domain 2: Exposure Characterization				

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Study Citation:	Kamai, E. M., Villanger, G. D., Nethery, R. C., Thomsen, C., Sakhi, A. K., Drover, M., S.S., Hoppin, J. A., Knudsen, G. P., Reichborn-Kjennerud, T., Zeiner, P., Overgaard, K., Herring, A. H., Aase, H., Engel, S. M. (2021). Gestational phthalate exposure and preschool attention deficit hyperactivity disorder in Norway. Environmental Epidemiology 5(4):e161.
Health Outcome(s) Assessed:	Neurological/Behavioral- Attention Deficit Hyperactivity Disorder (ADHD), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-carboxy-isononyl phthalate (cx-MiNP); Mono-isononyl phthalate (MiNP)
HERO ID:	9559555

Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Medium	Three DiNP metabolites (OH-MiNP, oxo-MiNP, and cx-MiNP), DiBP metabolite (MiBP), DBP metabolite (MnBP), BBP metabolite (MBzP), and DEHP metabolites (MEHP, MEHHP, MEOHP, MECPP, and MMCHP) were measured in maternal spot urine samples collected at about 17 weeks' gestation. The molar sum of its metabolites was analyzed as DiNP and DEHP exposure; individual metabolites were not analyzed. Concentrations of phthalates were measured at the Norwegian Institute of Public Health. Analysis methods, as described elsewhere, used liquid chromatography/mass spectrometry with procedural blanks and control samples in each randomized batch. The coefficient of variation was <0.1% for control urine samples and average batch coefficients of variation were less than 5%. LOQ and the percentage above LOQ for DiNP metabolites OH-MiNP, oxo-MiNP, and cx-MiNP were 0.2 ug/L and 100%, 0.2 ug/L and 98.5%, and 1.0 ug/L and 100%, respectively. For MiBP, MnBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, MMCHP the LOQ was 0.5 ug/L, 0.5 ug/L, 0.2 ug/L, 0.5 ug/L, 0.4 ug/L, 0.4 ug/L, 2.0 ug/L, and 2.0 ug/L respectively, and 100% of samples had detectable levels. Specific gravity was used to account for urine dilution. Exposure at ~17 weeks' gestation is thought to be a relevant window of vulnerability for perturbations in fetal growth that can impact long-term neurodevelopmental outcomes. As noted by the authors, single spot urine samples collected in this study may not accurately reflect a woman's exposure to phthalates throughout her pregnancy as the half -lives of phthalates are short. However, there was no evidence of potential differential misclassification of exposure by case status.

Domain 3: Outcome Assessment

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HERO ID:	9559555

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Cases defined as having either ADHD or subthreshold ADHD were identified in an assessment by trained graduate psychology students under the supervision of child psychologists/psychiatrists. The assessment used diagnostic interviews based on the Preschool Age Psychiatric Assessment (PAPA), a validated tool designed to evaluate children aged 2-6 years. Reliability was assessed by a second rater, blind to parent and teacher ratings, who re-scored 79 randomly selected recorded audiotapes (ICC 0.98 for number of ADHD symptoms). The PAPA defines ADHD symptoms as present when reported by parents to be pervasive across at least two settings. Only symptoms lasting >=3 months were counted. Impairment or impact of symptoms was evaluated in six functional domains (e.g., friends, learning, play/leisure). ADHD (n=114) was defined as the presence of both (b) > 6 symptoms on the PAPA that met DSM-IV-TR criteria and (b) impairment. Subthreshold preschool ADHD (n=146) was defined as children with 6+ ADHD symptoms but no evidence of impairment, or with 3-5 ADHD symptoms and evidence of impairment. The authors did not discuss separately analyzing associations with subthreshold ADHD. While outcome assessment was rigorous, evaluating behavioral outcomes during preschool years is challenging; the authors noted the potential for undetected preschool ADHD among non-cases. Most cases were identified among children screened at >= the 90th percentile on items in the 36-month questionnaire, which included 6 items from the Child Behavior Checklist and five items from the DSM-IV-TR criteria for ADHD. However, 6 children not identified in the screening were characterized as cases in the assessment. As noted by the authors, some symptoms may be less noticeable to caretakers.
	Metric 3B:	Selective Reporting	Medium	No concerns for selective reporting.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Confounders were selected a priori using directed acyclic graphs and previous literature. Covariates included specific gravity, analytic batch, child sex, maternal age, parity, maternal education, maternal depression during pregnancy, and maternal ADHD-like symptom. Marital status and maternal smoking were considered but ultimately excluded as they did not meaningfully influence effect estimates and removal improved model fit. Confounding by co-exposure to correlated phthalate metabolites was assessed in a sensitivity analysis. Variables such as maternal BMI and pregnancy complications were not discussed, but may have been excluded as potential intermediates. The authors presented crude and adjusted associations with phthalate quintiles; results were generally very similar.
Domain 5: Analysis				

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Study Citation:	Kamai, E. M., Villanger, G. D., Nethery, R. C., Thomsen, C., Sakhi, A. K., Drover, M., S.S., Hoppin, J. A., Knudsen, G. P., Reichborn-Kjennerud, T., Zeiner, P., Overgaard, K., Herring, A. H., Aase, H., Engel, S. M. (2021). Gestational phthalate exposure and preschool attention deficit hyperactivity disorder in Norway. Environmental Epidemiology 5(4):e161.
Health Outcome(s) Assessed:	Neurological/Behavioral- Attention Deficit Hyperactivity Disorder (ADHD), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-carboxy-isononyl phthalate (cx-MiNP); Mono-isononyl phthalate (MiNP)
HERO ID:	9559555

Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Medium	Descriptive data included participant characteristics and phthalate distributions. Logistic regression models were used to calculate odds ratios of association between phthalates and preschool ADHD. Analyses in the full sample analyzed exposure using both exposure quintile and natural log transformed variables; sex-stratified models used only natural log transformed exposure variables. Augmented product terms were used to evaluated sex specific effects; statistical significance of interaction was set at $p < 0.20$. Cubic splines and Wald tests were used to assess the significance of nonlinear associations: the association between ADHD and prenatal concentrations of both DiNP and DiBP metabolites were significantly non-linear. While evaluating this non-linearity was a strength, a limitation is that this non-linear relationship was not taken into account in sex-stratified analyses, which used a continuous exposure variable. Positive trends between increasing levels of ΣDEHP and odds of preschool ADHD. Statistically significant modification by child sex of the linear association between MnBP and preschool ADHD. Sensitivity analyses evaluated the influence of adjusting for correlated phthalate co-exposures.
	Metric 5B:	Sensitivity	Medium	The sample size of 260 cases and 549 non-cases was likely adequate to estimate associations in the sample as a whole; power may have been limited for stratified analyses. Exposure distributions were had substantial variability among both cases and non-cases. The geometric means and standard deviation of the sum of DiNP metabolites for cases was 0.02 and 2.04 umol/L with a range of 0.01 to 0.96 umol/L. For DiBP, the geometric mean (SD) among cases was 19.7 (2.12) ug/L. For the sum of DEHP, the geometric mean (SD) among cases was 0.29 (2.13) ug/L. For DBP, the geometric mean (SD) among cases was 20.0 (2.22) ug/L. For BBP, the geometric mean (SD) among cases was 5.40 (2.49) ug/L.

Additional Comments: This case-cohort study (260 cases, 549 non-cases) nested in the Norwegian MoBa cohort analyzed the association between prenatal phthalates measured in spot urines at about 17 weeks' gestation and odds of ADHD at age 3 years. Prenatal phthalate metabolites were detected in virtually all participants. Associations in the full sample were analyzed using both exposure quintiles and natural log transformed continuous exposure variables. Intermediate quintiles of DiNP (2nd and 5th) and DiBP (3rd and 4th) metabolites were associated with significantly increased odds of preschool ADHD, suggesting potential non-linear relationships. This non-linearity was not addressed in sex-stratified analyses to evaluate gender differences, which used only continuous natural log transformed exposure. In stratified analyses, there was a significant sex difference in associations with the DBP metabolite MBP, which were positive and significant only among boys. Associations with the highest quintile of the sum of DEHP metabolites were marginally non-significant overall and reached significance among boys. A limitation noted by the authors is the use of a single spot urine sample to characterize exposure during pregnancy, which may misclassify exposures. However, there is no evidence of bias. The authors acknowledged the possibility of undetected preschool ADHD among the non-case group, as only 22.5% were examined by study psychologists. The authors also discussed a possibility of bias due to self-selection into the MoBa cohort, but the statistical model adjusted for variables such as maternal education, which may mitigate residual bias. There was no evidence of important bias that would affect the validity of the overall results.

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Health Outcome(s) Assessed:	Neurological/Behavioral- Attention Deficit Hyperactivity Disorder (ADHD), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-carboxy-isononyl phthalate (cx-MiNP); Mono-isononyl phthalate (MiNP)
HERO ID:	9559555

Domain	Metric	Rating	Comments
Overall Quality Determination		**Medium**	

Study Citation:	Choi, G., Keil, A. P., Villanger, G. D., Richardson, D. B., Daniels, J. L., Hoffman, K., Sakhi, A. K., Thomsen, C., Herring, A. H., Drover, M., S.S., Nethery, R., Aase, H., Engel, S. M. (2021). Pregnancy exposure to common-detect organophosphate esters and phthalates and maternal thyroid function. Science of the Total Environment 782:146709.
Health Outcome(s) Assessed:	Thyroid- Thyroid function: total triiodothyronine (TT3), total thyroxine (TT4), TT3:TT4 ratio, thyroid stimulating hormone (TSH), thyroid peroxidase autoantibodies (TPOAb), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-carboxy-isononyl phthalate (cx-MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP)
HERO ID:	7978495

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	Participants in this study were a subset of individuals from the Norwegian Mother, Father, and Child Cohort (MoBa), an ongoing prospective population-based cohort. Participants were women recruited at routine prenatal ultrasound visits across Norway between 1999 and 2008, who provided urine and blood samples. Participants were recruited at approximately 17 gestational weeks. From the overall cohort of 114,500 children, 95,200 mothers, and 75,200 fathers, 33,050 participants met eligibility criteria that included giving birth to a singleton without Down syndrome or cerebral palsy between April 2004 and January 2008 and living in proximity to Oslo. This study used data from a sample of 555 women with available urine and blood specimens who had completed the 36-month questionnaire, who were randomly sampled and frequency matched by birth year to cases in a study on phthalates, maternal thyroid function and ADHD (Engel et al. 2018, HEROID 4728558). Of 539 women with measures of thyroid function organophosphate esters and urinary phthalate metabolites, primary analyses included 473 euthyroid women with no missing data (excluding women with self-reported thyroid disease, using thyroid medications, with measured thyroid biomarkers that could imply thyroid dysfunction, or missing covariate data). Non-euthyroid individuals were excluded since their measured thyroid markers may have been affected by medical interventions. The overview of recruitment and selection for this study was adequate, and there was no evidence to suggest biased participation.
Domain 2: Exposure Characterization			

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Study Citation:	Choi, G., Keil, A. P., Villanger, G. D., Richardson, D. B., Daniels, J. L., Hoffman, K., Sakhi, A. K., Thomsen, C., Herring, A. H., Drover, M., S.S., Nethery, R., Aase, H., Engel, S. M. (2021). Pregnancy exposure to common-detect organophosphate esters and phthalates and maternal thyroid function. Science of the Total Environment 782:146709.
Health Outcome(s) Assessed:	Thyroid- Thyroid function: total triiodothyronine (TT3), total thyroxine (TT4), TT3:TT4 ratio, thyroid stimulating hormone (TSH), thyroid peroxidase autoantibodies (TPOAb), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-carboxy-isononyl phthalate (cx-MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP)
HERO ID:	7978495

Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Medium	Maternal spot urine samples collected at approximately 17 weeks of gestation were used to measure three DiNP metabolites: OH-MiNP, oxo-MiNP, and cx-MiNP. DiNP exposure was analyzed as the molar sum of these three metabolites. Metabolites were analyzed using on-line column switching liquid chromatography coupled with tandem mass spectrometry. As reported by the reference cited for additional information on exposure assessment (Engel et al., 2018, HERO 4728558), quality controls, blank and control samples were used, and coefficients of variation across batches were <5%. Urinary dilution was addressed by standardizing for specific gravity. Detection rates for raw measures were 100%; after batch and specific gravity adjustment detection rates for the three metabolites were 100%, 98.5%, and 100% respectively. Values below LOD for other exposures analyzed in this study were imputed as LOD divided by the square root of 2. A limitation is that given the high variability and short half-lives of these phthalate metabolites, a single urine sample may misclassify habitual exposure to DiNP. However, there was no evidence of potential differential misclassification that might contribute to bias. Although thyroid hormone function was measured in blood samples collected at the same time as the spot urines used to estimate exposure, there was no evidence of reverse causality.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Thyroid function was assessed by examining thyroid hormone biomarkers in maternal blood samples collected at approximately 17 weeks' gestation, along with urine samples. The TT3 to TT4 ratio was used as an indicator of thyrotoxicosis mechanisms distinct from hyper- or hypo-active stimulation of the thyroid gland (Ross et al 2016 PMID: 27521067). Electro- chemiluminescent immunoassays were used to measure total triiodothyronine (TT3), total thyroxine (TT4), and thyroid stimulating hormone (TSH) in plasma. The inter- and intra-assay coefficients of variation were <5% for TSH, triiodothyronine uptake, TT3, and TT4. An analysis smple with normal thyroid function was identified using measures of TSH, free T4 index, and thyroid peroxidase autoantibodies (TPOAb), along with reported preexisting thyroid disease or medication use reported by mothers or identified by data linkage to the Medical Birth Registry of Norway. The reliability of TT3, TT5 and TSH during pregnancy measured in plasma rather than serum (the gold standard) was evaluated by the authors in an independent study of 17 pregnant women; Spearman correlations were 0.97 to 1.00 (Villanger et al, 2017; PMID: 27984425). Overall, outcome measures appeared to be appropriate. While there was no mention of blinding in the methods, it is unlikely that the researchers had knowledge of an individual's exposure levels.
	Metric 3B:	Selective Reporting	Medium	The results reported by the study author are consistent with the primary and secondary analyses described. No major concerns of selective reporting were noted.

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Study Citation:	Choi, G., Keil, A. P., Villanger, G. D., Richardson, D. B., Daniels, J. L., Hoffman, K., Sakhi, A. K., Thomsen, C., Herring, A. H., Drover, M., S.S., Nethery, R., Aase, H., Engel, S. M. (2021). Pregnancy exposure to common-detect organophosphate esters and phthalates and maternal thyroid function. Science of the Total Environment 782:146709.
Health Outcome(s) Assessed:	Thyroid- Thyroid function: total triiodothyronine (TT3), total thyroxine (TT4), TT3:TT4 ratio, thyroid stimulating hormone (TSH), thyroid peroxidase autoantibodies (TPOAb), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-carboxy-isononyl phthalate (cx-MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP)
HERO ID:	7978495

Domain	Metric	Rating	Comments
Domain 4: Potential Confounding / Variability Control			
	Metric 4A: Potential Confounding	Medium	The authors constructed a directed acyclic graphic to identify a minimally sufficient adjustment set of covariates that included study year, maternal age, education, parity, dietary iodine, dietary selenium, depression, smoking during pregnancy, season of urine collection, and urinary concentrations of other phthalates and organophosphate esters. Covariate information was obtained through a variety of tools, including a questionnaire at 15 weeks' gestation, a food frequency questionnaire at approximately 22 weeks' gestation, and linkage with the Medical Birth Registry of Norway (MBRN). Characteristics obtained from the 15-week questionnaire included education, depression before or during pregnancy, smoking during the first or second trimester of pregnancy, and alcohol intake during pregnancy. Iodine and selenium intake was estimated from the food frequency questionnaire. Co-pollutant confounding was addressed by simultaneously adjusting for 4 other phthalate metabolites and 2 organophosphate esters, as well as using Bayesian Kernel Machine regression to analyze mixtures. Models did not adjust for maternal BMI, which was characterized as a collider in their directed acyclic graph. Comorbidities such as hypertension and diabetes were not discussed; the authors did not discuss whether depression may have been a collider or overadjustment. However, there was no evidence of important residual confounding bias.
Domain 5: Analysis			
	Metric 5A: Analysis	Medium	Analysis methods were appropriate. Descriptive data included sample characteristics as well as exposure and outcome variable distributions. Associations between DiNP exposure and each outcome were estimated using multivariate general linear models. Estimates were presented as the difference in each marker per IQR increase in log-transformed exposure with 95% confidence intervals. The primary analysis was a complete case analysis of 473 euthyroid women, i.e. excluding women who had a preexisting thyroid disease or had measured biomarkers of TSH, TPOAb, and FT4i concentrations that could imply thyroid dysfunction. In addition to adjusting for co-pollutants, the authors performed a Bayesian Kernal Machine Regression to analyze mixtures of pollutants. The BKMR analysis allowed the authors to confirm that there were no important deviations from linearity in associations. The authors reported the absolute difference in thyroid biomarkers expected with increasing exposure from the 25th to the 75th percentile while keeping other exposures at their 25th percentile,and adjusting for confounders (both exact and approximate methods used). A sensitivity analysis included the 49 non-euthyroid women in the analysis sample; results were inferentially similar to the primary models. Additional sensitivity analyses examined batch effects and alternative definitions of OPE exposure variables.

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Health Outcome(s) Assessed:	Thyroid- Thyroid function: total triiodothyronine (TT3), total thyroxine (TT4), TT3:TT4 ratio, thyroid stimulating hormone (TSH), thyroid peroxidase autoantibodies (TPOAb), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-carboxy-isononyl phthalate (cx-MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP)
HERO ID:	7978495

Domain	Metric	Rating	Comments
	Metric 5B: Sensitivity	Medium	There were no major concerns raised related to sensitivity. The range of exposure levels (geometric ± mean SD for DINP 0.02 ±1.19 mmol/L) appeared to provide adequate variability. There was also variability in outcome variables (e.g., TT3 163.2 ± 1.2 ng/dL, TT4 10.4 ± 1.1 ug/dL, TSH 1.60 ± 1.6 mU/L). The sample used for the primary analyses included 473 women with complete data.

Additional Comments: This cross-sectional study analyzed data on a subset of 473 pregnant women in the Norwegian MoBa cohort who had available spot urine and blood samples, had completed a 36-month postnatal questionnaire, and had normal thyroid function. The authors reported that there was an inverse association between the sum of DiNP metabolites and a significantly lower ratio of total triiodothyronine (TT3) to total thyroxine (TT4) in plasma. Associations with lower TT3 and higher TT4, individually, were less precise and did not reach significance. There were no major concerns. Potential limitations include misclassification of habitual DiNP exposure, which was measured based on metabolites in a single spot urine sample collected at approximately 17 weeks gestation. The cross-sectional design is also a limitation.

Overall Quality Determination Medium

Study Citation:	Choi, G., Keil, A. P., Villanger, G. D., Richardson, D. B., Daniels, J. L., Hoffman, K., Sakhi, A. K., Thomsen, C., Herring, A. H., Drover, M., S.S., Nethery, R., Aase, H., Engel, S. M. (2021). Pregnancy exposure to common-detect organophosphate esters and phthalates and maternal thyroid function. Science of the Total Environment 782:146709.
Health Outcome(s) Assessed:	Thyroid- Thyroid function: total triiodothyronine (TT3), total thyroxine (TT4), TT3:TT4 ratio, thyroid stimulating hormone (TSH), thyroid peroxidase autoantibodies (TPOAb), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-carboxy-isononyl phthalate (cx-MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP)
HERO ID:	7978495

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	Participants in this study were a subset of individuals from the Norwegian Mother, Father, and Child Cohort (MoBa), an ongoing prospective population-based cohort. Participants were women recruited at routine prenatal ultrasound visits across Norway between 1999 and 2008, who provided urine and blood samples. Participants were recruited at approximately 17 gestational weeks. From the overall cohort of 114,500 children, 95,200 mothers, and 75,200 fathers, 33,050 participants met eligibility criteria that included giving birth to a singleton without Down syndrome or cerebral palsy between April 2004 and January 2008 and living in proximity to Oslo. This study used data from a sample of 555 women with available urine and blood specimens who had completed the 36-month questionnaire, who were randomly sampled and frequency matched by birth year to cases in a study on phthalates, maternal thyroid function and ADHD (Engel et al. 2018, HEROID 4728558). Of 539 women with measures of thyroid function organophosphate esters and urinary phthalate metabolites, primary analyses included 473 euthyroid women with no missing data (excluding women with self-reported thyroid disease, using thyroid medications, with measured thyroid biomarkers that could imply thyroid dysfunction, or missing covariate data). Non-euthyroid individuals were excluded since their measured thyroid markers may have been affected by medical interventions. The overview of recruitment and selection for this study was adequate, and there was no evidence to suggest biased participation.
Domain 2: Exposure Characterization			

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Study Citation:	Choi, G., Keil, A. P., Villanger, G. D., Richardson, D. B., Daniels, J. L., Hoffman, K., Sakhi, A. K., Thomsen, C., Herring, A. H., Drover, M., S.S., Nethery, R., Aase, H., Engel, S. M. (2021). Pregnancy exposure to common-detect organophosphate esters and phthalates and maternal thyroid function. Science of the Total Environment 782:146709.
Health Outcome(s) Assessed:	Thyroid- Thyroid function: total triiodothyronine (TT3), total thyroxine (TT4), TT3:TT4 ratio, thyroid stimulating hormone (TSH), thyroid peroxidase autoantibodies (TPOAb), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-carboxy-isononyl phthalate (cx-MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP)
HERO ID:	7978495

Domain	Metric	Rating	Comments
	Metric 2A: Exposure Measurement	Medium	Maternal spot urine samples collected at approximately 17 weeks of gestation were used to measure several primary and secondary metabolites of DiNP, DEHP, DBP, DiBP, and BBP. DiNP exposure was analyzed as the molar sum of three metabolites, and DEHP as the molar sum of five metabolites. Metabolites were analyzed using on-line column switching liquid chromatography coupled with tandem mass spectrometry. As reported by the reference cited for additional information on exposure assessment (Engel et al., 2018, HERO 4728558), quality controls, blank and control samples were used, and coefficients of variation across batches were <5%. Urinary dilution was addressed by standardizing for specific gravity. Detection rates for raw measures were 100%; after batch and specific gravity adjustment detection rates for the various metabolites ranged from a low of 98.5% for oxo-MiNP to a high of 100% for all other metabolites. Values below LOD for other exposures analyzed in this study were imputed as LOD divided by the square root of 2. A limitation is that given the high variability and short half-lives of these phthalate metabolites, a single urine sample may misclassify habitual exposure to parent phthalates. However, there was no evidence of potential differential misclassification that might contribute to bias. Although thyroid hormone function was measured in blood samples collected at the same time as the spot urines used to estimate exposure, there was no evidence of reverse causality.
Domain 3: Outcome Assessment			
	Metric 3A: Outcome Ascertainment	Medium	Thyroid function was assessed by examining thyroid hormone biomarkers in maternal blood samples collected at approximately 17 weeks' gestation, along with urine samples. Electro-chemiluminescent immunoassays were used to measure total triiodothyronine (TT3), total thyroxine (TT4), and thyroid stimulating hormone (TSH) in plasma. The TT3 to TT4 ratio was used as an indicator of thyroid homeostasis mechanisms distinct from hyper- or hypo-active stimulation of the thyroid gland (Ross et al 2016 PMID: 27521067). Free TT3 and TT4 were not directly measured due to the uncertain influence of large changes in levels of plasma binding proteins and total thyroid hormones. The inter- and intra-assay coefficients of variation were <5% for TSH, triiodothyronine uptake, TT3, and TT4. The analysis sample was limited to women with normal thyroid function based on levels of TSH, estimated free T4 index, and thyroid peroxidase autoantibodies (TPOAb), along with preexisting thyroid disease or medication self-reported or identified by data linkage to the Medical Birth Registry of Norway. The reliability of TT3, TT5 and TSH during pregnancy measured in plasma rather than serum (the gold standard) was evaluated by the authors in an independent study of 17 pregnant women; Spearman correlations were 0.97 to 1.00 (Villanger et al, 2017; PMID: 27984425). Overall, outcome measures appeared to be appropriate. While there was no mention of blinding in the methods, it is unlikely that the researchers had knowledge of an individual's exposure levels.

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Health Outcome(s) Assessed:	Thyroid- Thyroid function: total triiodothyronine (TT3), total thyroxine (TT4), TT3:TT4 ratio, thyroid stimulating hormone (TSH), thyroid peroxidase autoantibodies (TPOAb), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-carboxy-isononyl phthalate (cx-MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP)
HERO ID:	7978495

Domain	Metric	Rating	Comments
	Metric 3B: Selective Reporting	Medium	The results reported by the study author are consistent with the primary and secondary analyses described. No major concerns of selective reporting were noted.
Domain 4: Potential Confounding / Variability Control			
	Metric 4A: Potential Confounding	Medium	The authors constructed a directed acyclic graphic to identify a minimally sufficient adjustment set of covariates that included study year, maternal age, education, parity, dietary iodine, dietary selenium, depression, smoking during pregnancy, season of urine collection, and urinary concentrations of other phthalates and organophosphate esters. Covariate information was obtained through a variety of tools, including a questionnaire at 15 weeks' gestation, a food frequency questionnaire at approximately 22 weeks' gestation, and linkage with the Medical Birth Registry of Norway (MBRN). Characteristics obtained from the 15-week questionnaire included education, depression before or during pregnancy, smoking during the first or second trimester of pregnancy, and alcohol intake during pregnancy. Iodine and selenium intake was estimated from the food frequency questionnaire. Co-pollutant confounding was addressed by simultaneously adjusting for 4 other phthalate metabolites and 2 organophosphate esters, as well as using Bayesian Kernel Machine regression to analyze mixtures. Models did not adjust for maternal BMI, which was characterized as a collider in their directed acyclic graph. Comorbidities such as hypertension and diabetes were not discussed; the authors did not discuss whether depression may have been a collider or overadjustment. However, there was no evidence of important residual confounding bias.
Domain 5: Analysis			

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Health Outcome(s) Assessed:	Thyroid- Thyroid function: total triiodothyronine (TT3), total thyroxine (TT4), TT3:TT4 ratio, thyroid stimulating hormone (TSH), thyroid peroxidase autoantibodies (TPOAb), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-carboxy-isononyl phthalate (cx-MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP)
HERO ID:	7978495

Domain	Metric	Rating	Comments
	Metric 5A: Analysis	Medium	Analysis methods were appropriate. Descriptive data included sample characteristics as well as exposure and outcome variable distributions. Associations between phthalate exposure and each outcome were estimated using multivariate general linear models. Estimates were presented as the difference in each marker per IQR increase in log-transformed exposure with 95% confidence intervals. The primary analysis was a complete case analysis of 473 euthyroid women, i.e. excluding women who had a preexisting thyroid disease or had measured biomarkers of TSH, TPOAb, and FT4i concentrations that could imply thyroid dysfunction. In addition to adjusting for co-pollutants, the authors performed a Bayesian Kernal Machine Regression to analyze mixtures of pollutants, and to illustrate the shape of dose-response relationships. The authors reported the absolute difference in thyroid biomarkers expected with increasing exposure from the 25th to the 75th percentile while keeping other exposures at their 25th percentile and adjusting for confounders. The authors presented results from both “exact” and “approximate” BKMR methods; a rationale for this comparison was not discussed. A sensitivity analysis included the 49 non-euthyroid women in the analysis sample; results were inferentially similar to the primary models. Additional sensitivity analyses examined analytic batch effects and alternative definitions of mixtures.
	Metric 5B: Sensitivity	Medium	There were no major concerns raised related to sensitivity. The range of exposure levels for all measured phthalate metabolites appeared to provide adequate variability for analysis. There was also variability in outcome variables (e.g., geometric mean $\pm$ geometric SD: TT3 163.2 $\pm$ 1.2 ng/dL, TT4 10.4 $\pm$ 1.1 ug/dL, TSH 1.60 $\pm$ 1.6 mU/L). The sample used for the primary analyses included 473 women with complete data.

Additional Comments: This cross-sectional study analyzed data on a subset of 473 pregnant women in the Norwegian MoBa cohort who had available spot urine and blood samples, had completed a 36-month postnatal questionnaire, and had normal thyroid function. The authors reported that there was an inverse association between the sum of DiNP metabolites and a significantly lower ratio of total triiodothyronine (TT3) to total thyroxine (TT4) in plasma. The study also found that several other phthalate metabolites were associated with non-significant increases in TT3, but were not meaningfully associated with TT4, including MnBP, MiBP and MBzP. There were no major concerns. Potential limitations include the cross-sectional design, and possible misclassification of habitual phthalate exposure, which was measured based on metabolites in a single spot urine sample at about 17 weeks of gestation. All models shown adjusted simultaneously for multiple phthalates along with several organophosphate ester metabolites and included adjustments for maternal depression. However, there was no evidence of resulting bias.

Overall Quality Determination — Medium

Study Citation:	Choi, G., Villanger, G. D., Drover, M., S.S., Sakhi, A. K., Thomsen, C., Nethery, R. C., Zeiner, P., Knudsen, G. P., Reichborn-Kjennerud, T., Øvergaard, K. R., Herring, A. H., Skogan, A. H., Biele, G., Aase, H., Engel, S. M. (2021). Prenatal phthalate exposures and executive function in preschool children. Environment International 149:106403.
Health Outcome(s) Assessed:	Neurological/Behavioral- Executive function symptoms, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-isononyl phthalate (MiNP); Mono-carboxy-isononyl phthalate (cx-MiNP)
HERO ID:	8010273

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Choi et al 2021 HEROID 8010273 examined the relationship between prenatal phthalates and executive function at age 3.5 years among 340 participants in the Preschool ADHD sub study nested within the MoBa (Norwegian Mother, Father, and Child Cohort) birth cohort. MoBa recruited pregnant women from 1999-2008 (n= 114,500 children, 41% maternal participation rate). The ADHD sub-study included births after April 1, 2004, residing within a direct flight to Oslo, oversampled based on summed scores for ADHD-like symptoms reported using the Child Behavior Checklist and DMS-IV-TR criteria in the 36-month questionnaire (62% completion rate). Of 3,452 invitees (2,798 with symptom scores >90th percentile, 654 randomly selected without), 1,195 (34.6%) children took part in the one-day clinical assessment used for this study. 870 (72.8%) had prenatal urine samples. This study included 262 children with clinically significant or subthreshold symptoms of ADHD and 78 children confirmed as neurotypical (39.1% of 870). Further details on selection criteria at this final stage were not provided. Multivariate analyses included 310 of the 340 participants. As noted by the authors, selection into this study involved oversampling based on ADHD scores and was not random. Therefore, the primary analyses used inverse probability sampling weights calculated based on ADHD summed scores. There was no evidence that sample selection was not adequately addressed, or that the selection process induced bias.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Prenatal exposure to phthalates was measured using a single maternal spot urine sample from approximately 17 weeks of gestation. Several phthalates were investigated using individual metabolites (MBzP, MiBP, MnBP). Exposure to DiNP was estimated as the molar sum of three metabolites (OH-MiNP, oxo-MiNP and (cx-MiNP), and DEHP as the molar sum of five metabolites (MEHP, MEHHP, MEOHP, MECPP, MMCHP). Assays used online column switching liquid chromatography coupled with tandem mass spectrometry; procedural blanks and control samples were analyzed in each randomized batch. Specific gravity was used to account for urine dilution. Prenatal exposure preceded the assessments of executive function outcomes at age 3.5 years. Given the short half-life of phthalates, misclassification due to the use of a single sample to characterize exposure is a potential concern. However, there was no evidence of factors that would contribute to differential misclassification of exposure.
Domain 3: Outcome Assessment				

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Study Citation:	Choi, G., Villanger, G. D., Drover, M., S.S., Sakhi, A. K., Thomsen, C., Nethery, R. C., Zeiner, P., Knudsen, G. P., Reichborn-Kjennerud, T., Øvergaard, K. R., Herring, A. H., Skogan, A. H., Biele, G., Aase, H., Engel, S. M. (2021). Prenatal phthalate exposures and executive function in preschool children. Environment International 149:106403.
Health Outcome(s) Assessed:	Neurological/Behavioral- Executive function symptoms, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-isononyl phthalate (MiNP); Mono-carboxy-isononyl phthalate (cx-MiNP)
HERO ID:	8010273

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	The study analyzed executive function symptoms in a pooled sample of children with clinically significant/subthreshold ADHD and neurotypical children. The sample did not include children with high levels of autistic symptoms, severe medication conditions that might affect ability to complete clinic assessments, or using psychopharmacological treatment (Baumgartner et al 2014, PMID 24884579). Data were collected in two ways. Habitual executive function over the previous 6 months was evaluated by parent and teacher-rated reports completed using the Behavior Rating Inventory of Executive Function-Preschool [BRIEF-P]. Emotional control, inhibition, and working memory scores were age and sex- standardized to calculate T-scores (n=6 outcome measures). In addition, three performance-based assessments were administered by psychologists in the study clinic with a parent present: Stanford Binet IV short version [SB5]; a developmental Neuro PSYchological Assessment [NEPSY] test subtask; and cookie delay task [CDT]. SB5 performance was used to assess non-verbal and verbal working memory; the CDT to evaluate self-control, and the NEPSY subtask to assess motor persistence and inhibition (n=4 outcome measures). Raters were blinded to child selection status. Scores were standardized to facilitate comparisons across instruments. Strengths include the assessment of multiple domains of executive function using accepted methods, the use of clinical assessments at the same age under the same testing conditions, and availability of assessments based on recent behavior over a longer period from teachers as well as parents. The lower ADHD symptom group was described as confirmed as neurotypical after the on-site assessment. Interestingly, however, mean clinic assessment scores, but not parent or teacher ratings, were higher in the neurotypical vs ADHD group. The authors did not discuss inter-rater reliability or validity within the study population. However, there was no evidence to suggest bias.
	Metric 3B:	Selective Reporting	Medium	Results of primary analyses for all outcomes were reported for all children and stratified by child sex. There was no evidence of selective reporting.

Domain 4: Potential Confounding / Variability Control

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HERO ID:	8010273

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	Medium	The authors used a directed acyclic graph (DAG) to identify potential confounders. Models adjusted for maternal ADHD, BMI, age at delivery, parity, childbirth year, and child sex, specific gravity, and analytic batch effect. For phthalates significantly associated with outcomes, the authors examined the influence of additionally adjusting for other phthalates with significant results. Several confounders considered were omitted from the final models; the authors used the minimally sufficient adjustment set to improve variance and selection bias. Additional variables considered included marital status, maternal education, self-reported depression before or during pregnancy, smoking during pregnancy, alcohol intake during pregnancy, fish intake during pregnancy, folate use during pregnancy, child age at the clinical exam. The authors considered extensive confounders, though potential residual confounding cannot be ruled out (e.g., by other pre- or postnatal neurotoxicant exposures, assessor, timing of urine sample collection).
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Analyses used appropriate methods. Descriptive data were shown for phthalates exposures and for test scores. Associations were estimated using weighted multiple linear regression models per inter-quartile increase in each phthalate exposure after confirming that relationships were not non-linear. Sample weights were calculated separately for neurotypical and ADHD children; an alternative approach to weighting based on the population prevalence of ADHD was also examined. Results of several supplementary analyses to assess robustness of results were shown for phthalates significantly associated with child outcomes. These included results stratified by ADHD status and adjusting for phthalate co-exposure, as well as associations with individual metabolites. There was no evidence that additional supplementary analyses for phthalates for which primary results were non-significant would meaningfully influence conclusions.
	Metric 5B:	Sensitivity	Medium	Though mean concentrations of some phthalates were low, each exposure measure had variability. Concentrations were lowest for DiNP: geometric mean (SD) 0.02 (1.60) umol/L. Though the size of an IQR increase in DiNP was small (0.01 umol/L) there was no direct evidence of low sensitivity. However, statistical power was likely limited for analyses stratified by child sex or by ADHD group. Variability was considerably larger for all other phthalate exposure measures.

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HERO ID:	8010273

Domain	Metric	Rating	Comments
Additional Comments:	This study analyzed the association between several phthalate metabolites and measures of executive function symptoms in a subset of 310 children from the longitudinal MoBa ((Norwegian Mother, Father, and Child) cohort. The sample was selected by recruiting two groups of children – with and without high ADHD symptoms – to participate; sample weights were used to account for oversampling children with these symptoms. The final sample included 77% of children with elevated symptoms. Phthalates were measured in a single spot urine sample collected at around 17 weeks gestation. Outcomes were measured using widely used, externally validated instruments, and included separate parent and teacher reports of emotional control, inhibition, and working memory, and in-clinic assessments of non-verbal and verbal working memory, self-control, and inhibition. The study found evidence of associations with several phthalate metabolites [monobenzyl phthalate (MBzP), mono-n-butyl phthalate (MnBP) and monoisobutyl phthalate (MiBP)], some of which appeared to be sex-specific. There were no significant associations with DiNP, and few with DEHP. Strengths include the longitudinal design and including multiple measures of a range of executive function symptoms based on multiple assessors. Limitations include the use of a single maternal spot urine to estimate exposure. Another potential limitation is the relatively small sample of neurotypical children in the study. In addition to sex differences for some metabolites, supplementary analyses conducted for MBzP found stronger associations for 6 of 8 outcomes among children with low vs. high ADHD summed scores. The oversampling of ADHD participants was addressed using sample weight adjustments. There was no evidence of important bias or error that would meaningfully affect conclusions.		

Overall Quality Determination Medium

Study Citation:	Burns, J. S., Sergeyev, O., Lee, M. M., Williams, P. L., Mínguez-Alarcón, L., Plaku-Alakbarova, B., Sokolov, S., Kovalev, S., Koch, H. M., Lebedev, A. T., Hauser, R., Korrick, S. A., Study, R.C. (2022). Associations of prepubertal urinary phthalate metabolite concentrations with pubertal onset among a longitudinal cohort of boys. Environmental Research 212(Pt A):113218.
Health Outcome(s) Assessed:	Reproductive/Developmental- age at pubertal onset (as measured by testicular volume, genitalia Tanner stage, and pubarche Tanner stage_, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	10294569

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	This prospective cohort study measured urinary phthalate metabolite levels at age 8-9 and the association with age at puberty onset in boys from the Russian Children's Study (RCS). Phthalate metabolites included mono-isobutyl phthalate (MiBP), mono-benzyl phthalate (MBzP), mono-n-butyl phthalate (MnBP), mono (2-ethylhexyl) phthalate (MEHP), mono (2-ethyl-5-hydroxy-hexyl) phthalate (MEHHP), mono (2-ethyl-5-oxo-hexyl) phthalate (MEOHP), mono (2-ethyl-5-carboxy-pentyl) phthalate (MECPP), mono-hydroxy-iso-nonyl phthalate (MHiNP), mono-oxo-iso-nonyl phthalate (MOiNP), mono-carboxy-iso-octyl phthalate (MCOP), mono-(hydroxy-iso-decyl) phthalate (MHiDP), mono-(oxo-iso-decyl) phthalate (MOiDP), mono-(carboxy-iso-nonyl) phthalate (MCNP), and mono-(3-carboxypropyl) phthalate (MCPP). Recruitment of boys at ages 8-9 occurred from 2003-2005 in Chapaevsk, Russia, and boys were followed annually through ages 18-19 (total n=516). Boys with at least one urinary metabolite measure prior to pubertal onset were eligible (n = 320). Boys were excluded if they were orphans without birth or parental information or had chronic diseases that could impact puberty, leaving a final sample size of 304. There is no comparison of the included study population with the broader population of the RCS, making it difficult to assess the potential for selection bias. However, there is no direct evidence of bias.
Domain 2: Exposure Characterization			

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Health Outcome(s) Assessed:	Reproductive/Developmental- age at pubertal onset (as measured by testicular volume, genitalia Tanner stage, and pubarche Tanner stage_, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	10294569

Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Medium	Phthalate metabolites were measured in spot urine samples via liquid chromatography tandem mass spectrometry (LC-MS/MS). Metabolites included the following: DIBP: MiBP; BBP:MBzP; DBP: MnBP; DEHP: MEHP, MEHHP, MEOHP, MECPP; DiNP: MHiNP, MOiNP, MCOP; DiDP: MHiDP, MOiDP, MCNP, MCPP. Summed DEHP, summed DiNP, and summed DiDP were also analyzed. Urine samples were collected at enrollment and during annual study visits, with each boy having 1-6 samples (median = 2). Pooled samples were used in the analyses by combining individual annual samples. Urine samples collected during the first 10 months of the study (n = 216) were not analyzed, as they were stored at Harvard and could not be shipped to Moscow for analyses. There is no additional information on these samples, but they would not be expected to greatly bias the observed results. LODs ranged from 0.05 - 0.125 ng/mL. Samples were all >LOD except for the following (%): MBzP: <1%; MEHP: <1%; MHiDP: 3%; MOiDP: 23%; MCNP: <1%. Standards were used to perform instrument calibrations (including commercial reference standards, custom synthesized standards from Koch/IPA, and isotopically labelled internal standards from LGC). All batches were run with two randomly selected samples analyzed in duplicate, two QC samples, and 1 field blank for QA/QC purposes. Specific gravity was measured and metabolite concentrations were adjusted for specific gravity to account for urinary dilution. While not every participant had multiple urine samples, a median of 2 urine samples across the analytic sample is a strength as it increases certainty in the exposure assessment.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Age at pubertal onset was determined via clinical examinations. At enrollment, boys underwent a standardized anthropometric examination. Pubertal staging was determined by a single physician at study entry and during annual visits. Staff did not have knowledge of urinary phthalate metabolite measures during assessments. Staging included the following: 1-5 (immature to sexually mature) for genitalia and pubic hair (according to Tanner Stages). A prader orchidometer was used to measure testicular volume (TV). Boys with TV of 1 or 2 and genitalia at stage 1 or 2 were determined to be in prepuberty. Prepuberty was also defined as TV at 3 and genitalia at stage 1. Genitalia and pubic hair at stage 2 or TV above 3 were marked as pubertal onset. Some boys in early puberty (at genitalia or pubic hair stage 2) were included in prepubertal urinary pools due to discordant sexual maturity measures. Although this suggests the outcome definition was not sufficiently specific, the authors conducted a sensitivity analysis to exclude these boys and findings were largely similar, minimizing concern for misclassification.
	Metric 3B:	Selective Reporting	Medium	Results for all anticipated analyses were reported.
Domain 4: Potential Confounding / Variability Control				

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Health Outcome(s) Assessed:	Reproductive/Developmental- age at pubertal onset (as measured by testicular volume, genitalia Tanner stage, and pubarche Tanner stage_, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	10294569

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	Medium	All key confounders were considered. All models were adjusted for urine specific gravity. Models of testicular volume were also adjusted for prenatal tobacco smoke exposure, birthweight, breastfed, and household income. Models of genitalia stage were also adjusted for prenatal tobacco smoke exposure, mother's age at son's birth, breastfed, and biological father living in home. Models of pubarche were also adjusted for prenatal maternal alcohol intake. Height, BMI, gestational age, dietary intake (calories, calories from carbohydrates, calories from fat, calories from protein), and parental education were also considered as potential confounders. Age was considered as part of the outcome (age at pubertal onset) and thus not needed as a covariate.Most information was collected from questionnaires completed by parents during study entry and annual visits. Self-report by parents may be subject to some recall bias, particularly for food frequency questionnaires. Few data were missing. A complete case analysis was conducted. Potential confounders were identified a priori. Covariates were selected for inclusion in models using backwards selection to exclude covariates with p>0.10 (association with pubertal onset). Covariates with <0.20 were re-entered into the final model and those with >=10% change in trend test were retained.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	The association between urinary phthalate metabolite concentrations and the mean age at pubertal onset as measured by three separate parameters was measured via interval-censored survival analyses, which allows for pubertal onset between study visits, before the study entry visit, or after the final visit. Urinary phthalate metabolite levels were analyzed categorically (quartiles). Effect estimates and 95% CI are reported for the models. Analyses were conducted for MnBP, MiBP, MBzP, and summed DEHP, summed DiNP, and summed DiDP. Sensitivity analyses excluded boys with genitalia or pubarche at stage 2 in the prepubertal urine pool and excluded boys with only one urine sample in their pooles samples. Information on the exposure distribution and % of samples <LOD is provided for all metabolites.
	Metric 5B:	Sensitivity	Medium	The sample size was adequate (n = 304). Exposure levels in the study were adequate to detect an effect. There are no other concerns for sensitivity.

Additional Comments: This prospective cohort study examined age at pubertal onset that the association with prepubertal urinary phthalate metabolite levels among boys from the Russia Child's Study (RCS). Measured metabolites included DIBP: MiBP; BBP:MBzP; DBP: MnBP; DEHP: MEHP, MEHHP, MEOHP, MECPP; DiNP: MHiNP, MOiNP, MCOP; DiDP: MHiDP, MOiDP, MCNP, MCPP. The study used an adequate approach to participant selection, exposure measurement, outcome ascertainment, account for confounders, and statistical analyses. Pubertal onset occurred at older ages among higher quartiles of MiBP, MBzP, summed DEHP, and summed DiNP.

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Health Outcome(s) Assessed:	Reproductive/Developmental- age at pubertal onset (as measured by testicular volume, genitalia Tanner stage, and pubarche Tanner stage_, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	10294569

Domain	Metric	Rating	Comments
Overall Quality Determination		**Medium**	

Study Citation:	Shu, H., Wikstrom, S., Jönsson, G., B.A., Lindh, C. H., Svensson, Å., Nånberg, E., Bornehag, C. G. (2018). Prenatal phthalate exposure was associated with croup in Swedish infants. Acta Paediatrica 107(6):1011-1019.
Health Outcome(s) Assessed:	Lung/Respiratory- Wheeze, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4728698

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This prospective birth cohort study examined the association between phthalate metabolites measured in prenatal urine samples among pregnant women in the SELMA cohort and respiratory/immune outcomes in infants up until 12 months of age. Study participants were a subset of maternal-child pairs included in the Swedish Environmental Longitudinal, Mother and Child, Asthma and Allergy study (SELMA). For the overall SELMA cohort, 6,658 women were invited to participate during their first visit to a public antenatal care center (2007-2010), of which 2,582 (39%) agreed to participate. Exclusion criteria as described in Bornehag et al., 2012 (HERO ID 1597769) were: did not understand written Swedish questionnaire, > 22 weeks gestational age, and plans to move outside the study area. The current study population was limited to a subset of SELMA participants (n=1062) with complete data on relevant variables; this subset was similar to the overall cohort on most covariates and exposure levels. Participating families differed from non-participants in characteristics such as the prevalence of allergy and asthma symptoms (Bornehag et al., 2012). However, mean concentrations of phthalate metabolites were similar in the study population and the entire SELMA study. There is no evidence to suggest that entry into or continuation in the study population was jointly related to exposure and outcome.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Prenatal exposure to phthalates was characterized using measures in maternal urine collected during pregnancy. Phthalate metabolites were measured in morning void urine samples collected at enrollment; enrollment was during the first trimester for 96% of participants (median 10 weeks, range 4-27 weeks). Metabolites were measured using liquid chromatography-tandem mass spectrometer (LC-MS/MS). For all relevant metabolites, 100% of samples were above the LOD with the exception of MEHP (99.6% above LOD). Urine dilution was addressed by adjusting for creatinine in regression models. There is potential for some exposure misclassification due to the use of a single urine sample; this misclassification is expected to be non-differential. The study authors state that they were not able to separate the two DiDP metabolites (MHiDP, MCiNP) from DPHP metabolites with similar retention time and mass spectrometry; further details on this issue were not provided. Results for these metabolites were reported as reflecting DiDP/DPHP exposure. While there is concern for potential additional error, there is no direct evidence of bias. Monitoring data from other European studies report low levels of DPHP exposure (Schmidtkunz et al., 2019, PMID 30772154).
Domain 3: Outcome Assessment				

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Health Outcome(s) Assessed:	Lung/Respiratory- Wheeze, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4728698

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	The outcomes of interest in this study were any episode of wheeze, along with croup and otitis media, within the infant's first 12 months of life. Outcomes were assessed via maternal report at a single time point by maternal report. For wheeze, the study used the standardized International Study of Asthma and Allergies in Childhood (ISAAC) core health questions, which include questions on wheeze reported as adequately sensitive and specific in other settings and age groups (e.g., Asher et al., 2020 PMID 32972987). Nonetheless, there is potential for some misclassification due to the use of parent reported symptoms to define outcomes.
	Metric 3B:	Selective Reporting	Medium	The authors described their primary and secondary analyses in the methods section and results were reported for all primary and secondary The authors described their primary and secondary analyses in the methods section. Results were presented for croup and wheeze. For otitis media, however, the authors stated that no significant associations were found in either crude or adjusted analysis, and data were not shown..
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Potential confounders were included in regression models if they were significantly correlated with two or more urinary phthalate metabolites concentrations. Information on how the full set of potential confounders evaluated in bivariate analyses were identified was not provided. The final set of confounders included in regression models was: maternal age, maternal education, maternal smoking, child sex, asthma and allergies in the family, categories of creatinine in urine. Maternal smoking was evaluated via measurement of cotinine in blood samples collected at enrollment, while other variables were measured using self-administered questionnaires. No information on how creatinine was categorized in analysis was provided. Co-exposure confounding was not discussed.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	The association between each phthalate metabolite and each outcome was evaluated using logistic regression. Metabolites were log 10 transformed prior to analysis. Individual metabolites were analyzed separately, analyses using the sum of metabolites from the same parent phthalate were not mentioned. Metabolites were evaluated in models as a continuous variable as well as categorized into quartiles. Sex-stratified analyses were conducted. No sensitivity analyses were described. No missingness was described, as expected given the study population was limited to maternal-infant pairs in the SELMA cohort with complete data.
	Metric 5B:	Sensitivity	Medium	The sample size was large (n=1062) and there was variability in and high detection rates for phthalate metabolites. No concerns related to study sensitivity were identified.

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Health Outcome(s) Assessed:	Lung/Respiratory- Wheeze, Non-cancer
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HERO ID:	4728698

Domain	Metric	Rating	Comments
Additional Comments:	This analysis of a subset of maternal-infant pairs in the SELMA cohort (n=1,062 of 2,356 participants) had a large sample size and appropriate participant recruitment methods. There is potential for outcome misclassification as outcomes were classified based on maternal reports of infant symptoms of wheeze, otitis media, and croup during the first year of life. For wheeze, outcomes were reported using standardized questions; questions about croup were based on specific characterization of symptoms. Questions on otitis media were not described. DiDP metabolites results were reported as DiDP/DPHP due to difficulty separating these metabolites in the assays used. In quartile-based analyses, DINP metabolites were significantly associated with wheeze (for example, OR [95% CI] for Q4 vs. Q1: MHiNP 1.83 [1.24, 2.71], MOiNP 1.69 [1.13, 2.51], MCiOP 1.72 [1.17, 2.54]) although there was no clear dose-response relationship. Associations for Q4 vs Q1 were somewhat stronger and reached significance in girls but not boys for DiNP metabolites (MHiNP, MOiNP, and MCiOP). Associations between wheeze and metabolites of other phthalates (DiDP/DPHP, DEHP, BBP, and DBP) did not reach significance. Overall, no significant associations were found between DiNP or DiDP/DPHP metabolites and croup. However, isolated quartiles of the DiNP metabolite MHiNP and the DiDP metabolite MHiDP had significant associations among boys. The BBP metabolite (MBzP) as well as the DEHP metabolites were significantly positively associated with croup among all study participants; most associations remained significant among boys when stratified by sex. There were no significant associations with otitis media, for which results were not shown.		

Overall Quality Determination Medium

Study Citation:	Shu, H., Wikstrom, S., Jönsson, G., B.A., Lindh, C. H., Svensson, Å., Nånberg, E., Bornehag, C. G. (2018). Prenatal phthalate exposure was associated with croup in Swedish infants. Acta Paediatrica 107(6):1011-1019.
Health Outcome(s) Assessed:	Lung/Respiratory- Croup, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4728698

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This prospective birth cohort study examined the association between phthalate metabolites measured in prenatal urine samples among pregnant women in the SELMA cohort and respiratory/immune outcomes in infants up until 12 months of age. Study participants were a subset of maternal-child pairs included in the Swedish Environmental Longitudinal, Mother and Child, Asthma and Allergy study (SELMA). For the overall SELMA cohort, 6,658 women were invited to participate during their first visit to a public antenatal care center (2007-2010), of which 2,582 (39%) agreed to participate. Exclusion criteria as described in Bornehag et al., 2012 (HERO ID 1597769) were: did not understand written Swedish questionnaire, $>$ 22 weeks gestational age, and plans to move outside the study area. The current study population was limited to a subset of SELMA participants (n=1062) with complete data on relevant variables; this subset was similar to the overall cohort on most covariates and exposure levels. Participating families differed from non-participants in characteristics such as the prevalence of allergy and asthma symptoms (Bornehag et al., 2012). However, mean concentrations of phthalate metabolites were similar in the study population and the entire SELMA study. There is no evidence to suggest that entry into or continuation in the study population was jointly related to exposure and outcome.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Prenatal exposure to phthalates was characterized using measures in maternal urine collected during pregnancy. Phthalate metabolites were measured in morning void urine samples collected at enrollment; enrollment was during the first trimester for 96% of participants (median 10 weeks, range 4-27 weeks). Metabolites were measured using liquid chromatography-tandem mass spectrometer (LC-MS/MS). For all relevant metabolites, 100% of samples were above the LOD with the exception of MEHP (99.6% above LOD). Urine dilution was addressed by adjusting for creatinine in regression models. There is potential for some exposure misclassification due to the use of a single urine sample; this misclassification is expected to be non-differential. The study authors state that they were not able to separate the two DiDP metabolites (MHiDP, MCiNP) from DPHP metabolites with similar retention time and mass spectrometry; further details on this issue were not provided. Results for these metabolites were reported as reflecting DiDP/DPHP exposure. While there is concern for potential additional error, there is no direct evidence of bias. Monitoring data from other European studies report low levels of DPHP exposure (Schmidtkunz et al., 2019, PMID 30772154).
Domain 3: Outcome Assessment				

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Study Citation:	Shu, H., Wikstrom, S., Jönsson, G., B.A., Lindh, C. H., Svensson, Å., Nånberg, E., Bornehag, C. G. (2018). Prenatal phthalate exposure was associated with croup in Swedish infants. Acta Paediatrica 107(6):1011-1019.
Health Outcome(s) Assessed:	Lung/Respiratory- Croup, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4728698

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Low	The outcomes of interest in this study were any episode of croup or otitis media, along with wheeze, within the infant's first 12 months of life. All three outcomes were assessed via maternal report at a single time point by maternal report. Croup was defined as breathing difficulties with a barking cough ("Has your child suffered from croup (breathing difficulties with a barking cough?" Preece et al., 2021 HEROID 7975690). Otitis media questions were not specified in this manuscript. Prevalence of these outcomes was 9.5% for croup, and 15.4% for otitis media. There is some concern for potential outcome misclassification due to the use of parent reported symptoms to define outcomes and uncertainty regarding reliability of the questions used. However, there is no direct evidence of low sensitivity, specificity, or differential misclassification.
	Metric 3B:	Selective Reporting	Medium	The authors described their primary and secondary analyses in the methods section. Results were presented for croup and wheeze. For otitis media, however, the authors stated that no significant associations were found in either crude or adjusted analysis, and data were not shown.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Potential confounders were included in regression models if they were significantly correlated with two or more urinary phthalate metabolites concentrations. Information on how the full set of potential confounders evaluated in bivariate analyses were identified was not provided. The final set of confounders included in regression models was: maternal age, maternal education, maternal smoking, child sex, asthma and allergies in the family, categories of creatinine in urine. Maternal smoking was evaluated via measurement of cotinine in blood samples collected at enrollment, while other variables were measured using self-administered questionnaires. No information on how creatinine was categorized in analysis was provided. Co-exposure confounding was not discussed.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	The association between each phthalate metabolite and each outcome was evaluated using logistic regression. Metabolites were log 10 transformed prior to analysis. Individual metabolites were analyzed separately, analyses using the sum of metabolites from the same parent phthalate were not mentioned. Metabolites were evaluated in models as a continuous variable as well as categorized into quartiles. Sex-stratified analyses were conducted. No sensitivity analyses were described. No missingness was described, as expected given the study population was limited to maternal-infant pairs in the SELMA cohort with complete data.
	Metric 5B:	Sensitivity	Medium	The sample size was large (n=1062) and there was variability in and high detection rates for phthalate metabolites. No concerns related to study sensitivity were identified.

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Study Citation:	Shu, H., Wikstrom, S., Jönsson, G., B.A., Lindh, C. H., Svensson, Å., Nånberg, E., Bornehag, C. G. (2018). Prenatal phthalate exposure was associated with croup in Swedish infants. Acta Paediatrica 107(6):1011-1019.
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HERO ID:	4728698

Domain	Metric	Rating	Comments
Additional Comments:	This analysis of a subset of maternal-infant pairs in the SELMA cohort (n=1,062 of 2,356 participants) had a large sample size and appropriate participant recruitment methods. There is potential for outcome misclassification as outcomes were classified based on maternal reports of infant symptoms of wheeze, otitis media, and croup during the first year of life. For wheeze, outcomes were reported using standardized questions; questions about croup were based on specific characterization of symptoms. Questions on otitis media were not described. DiDP metabolites results were reported as DiDP/DPHP due to difficulty separating these metabolites in the assays used. In quartile-based analyses, DINP metabolites were significantly associated with wheeze (for example, OR [95% CI] for Q4 vs. Q1: MHiNP 1.83 [1.24, 2.71], MOiNP 1.69 [1.13, 2.51], MCiOP 1.72 [1.17, 2.54]) although there was no clear dose-response relationship. Associations for Q4 vs Q1 were somewhat stronger and reached significance in girls but not boys for DiNP metabolites (MHiNP, MOiNP, and MCiOP). Associations between wheeze and metabolites of other phthalates (DiDP/DPHP, DEHP, BBP, and DBP) did not reach significance. Overall, no significant associations were found between DiNP or DiDP/DPHP metabolites and croup. However, isolated quartiles of the DiNP metabolite MHiNP and the DiDP metabolite MHiDP had significant associations among boys. The BBP metabolite (MBzP) as well as the DEHP metabolites were significantly positively associated with croup among all study participants; most associations remained significant among boys when stratified by sex. There were no significant associations with otitis media, for which results were not shown.		

Overall Quality Determination Medium

Study Citation:	Shu, H., Wikstrom, S., Jönsson, G., B.A., Lindh, C. H., Svensson, Å., Nånberg, E., Bornehag, C. G. (2018). Prenatal phthalate exposure was associated with croup in Swedish infants. Acta Paediatrica 107(6):1011-1019.
Health Outcome(s) Assessed:	Immune/Hematological- Otitis media, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4728698

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This prospective birth cohort study examined the association between phthalate metabolites measured in prenatal urine samples among pregnant women in the SELMA cohort and respiratory/immune outcomes in infants up until 12 months of age. Study participants were a subset of maternal-child pairs included in the Swedish Environmental Longitudinal, Mother and Child, Asthma and Allergy study (SELMA). For the overall SELMA cohort, 6,658 women were invited to participate during their first visit to a public antenatal care center (2007-2010), of which 2,582 (39%) agreed to participate. Exclusion criteria as described in Bornehag et al., 2012 (HERO ID 1597769) were: did not understand written Swedish questionnaire, $>$ 22 weeks gestational age, and plans to move outside the study area. The current study population was limited to a subset of SELMA participants (n=1062) with complete data on relevant variables; this subset was similar to the overall cohort on most covariates and exposure levels. Participating families differed from non-participants in characteristics such as the prevalence of allergy and asthma symptoms (Bornehag et al., 2012). However, mean concentrations of phthalate metabolites were similar in the study population and the entire SELMA study. There is no evidence to suggest that entry into or continuation in the study population was jointly related to exposure and outcome.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Prenatal exposure to phthalates was characterized using measures in maternal urine collected during pregnancy. Phthalate metabolites were measured in morning void urine samples collected at enrollment; enrollment was during the first trimester for 96% of participants (median 10 weeks, range 4-27 weeks). Metabolites were measured using liquid chromatography-tandem mass spectrometer (LC-MS/MS). For all relevant metabolites, 100% of samples were above the LOD with the exception of MEHP (99.6% above LOD). Urine dilution was addressed by adjusting for creatinine in regression models. There is potential for some exposure misclassification due to the use of a single urine sample; this misclassification is expected to be non-differential. The study authors state that they were not able to separate the two DiDP metabolites (MHiDP, MCiNP) from DPHP metabolites with similar retention time and mass spectrometry; further details on this issue were not provided. Results for these metabolites were reported as reflecting DiDP/DPHP exposure. While there is concern for potential additional error, there is no direct evidence of bias. Monitoring data from other European studies report low levels of DPHP exposure (Schmidtkunz et al., 2019, PMID 30772154).
Domain 3: Outcome Assessment				

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Study Citation:	Shu, H., Wikstrom, S., Jönsson, G., B.A., Lindh, C. H., Svensson, Å., Nånberg, E., Bornehag, C. G. (2018). Prenatal phthalate exposure was associated with croup in Swedish infants. Acta Paediatrica 107(6):1011-1019.
Health Outcome(s) Assessed:	Immune/Hematological- Otitis media, Non-cancer
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HERO ID:	4728698

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Low	The outcomes of interest in this study were any episode of croup or otitis media, along with wheeze, within the infant's first 12 months of life. All three outcomes were assessed via maternal report at a single time point by maternal report. Croup was defined as breathing difficulties with a barking cough ("Has your child suffered from croup (breathing difficulties with a barking cough?" Preece et al., 2021 HEROID 7975690). Otitis media questions were not specified in this manuscript. Prevalence of these outcomes was 9.5% for croup, and 15.4% for otitis media. There is some concern for potential outcome misclassification due to the use of parent reported symptoms to define outcomes and uncertainty regarding reliability of the questions used. However, there is no direct evidence of low sensitivity, specificity, or differential misclassification.
	Metric 3B:	Selective Reporting	Low	The authors described their primary and secondary analyses in the methods section. Results were presented for croup and wheeze. For otitis media, however, the authors stated that no significant associations were found in either crude or adjusted analysis, and data were not shown.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Potential confounders were included in regression models if they were significantly correlated with two or more urinary phthalate metabolites concentrations. Information on how the full set of potential confounders evaluated in bivariate analyses were identified was not provided. The final set of confounders included in regression models was: maternal age, maternal education, maternal smoking, child sex, asthma and allergies in the family, categories of creatinine in urine. Maternal smoking was evaluated via measurement of cotinine in blood samples collected at enrollment, while other variables were measured using self-administered questionnaires. No information on how creatinine was categorized in analysis was provided. Co-exposure confounding was not discussed.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	The association between each phthalate metabolite and each outcome was evaluated using logistic regression. Metabolites were log 10 transformed prior to analysis. Individual metabolites were analyzed separately, analyses using the sum of metabolites from the same parent phthalate were not mentioned. Metabolites were evaluated in models as a continuous variable as well as categorized into quartiles. Sex-stratified analyses were conducted. No sensitivity analyses were described. No missingness was described, as expected given the study population was limited to maternal-infant pairs in the SELMA cohort with complete data.
	Metric 5B:	Sensitivity	Medium	The sample size was large (n=1062) and there was variability in and high detection rates for phthalate metabolites. No concerns related to study sensitivity were identified.

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Study Citation:	Shu, H., Wikstrom, S., Jönsson, G., B.A., Lindh, C. H., Svensson, Å., Nånberg, E., Bornehag, C. G. (2018). Prenatal phthalate exposure was associated with croup in Swedish infants. Acta Paediatrica 107(6):1011-1019.
Health Outcome(s) Assessed:	Immune/Hematological- Otitis media, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	4728698

Domain	Metric	Rating	Comments
Additional Comments:	This analysis of a subset of maternal-infant pairs in the SELMA cohort (n=1,062 of 2,356 participants) had a large sample size and appropriate participant recruitment methods. There is potential for outcome misclassification as outcomes were classified based on maternal reports of infant symptoms of wheeze, otitis media, and croup during the first year of life. For wheeze, outcomes were reported using standardized questions; questions about croup were based on specific characterization of symptoms. Questions on otitis media were not described. DiDP metabolites results were reported as DiDP/DPHP due to difficulty separating these metabolites in the assays used. In quartile-based analyses, DINP metabolites were significantly associated with wheeze (for example, OR [95% CI] for Q4 vs. Q1: MHiNP 1.83 [1.24, 2.71], MOiNP 1.69 [1.13, 2.51], MCiOP 1.72 [1.17, 2.54]) although there was no clear dose-response relationship. Associations for Q4 vs Q1 were somewhat stronger and reached significance in girls but not boys for DiNP metabolites (MHiNP, MOiNP, and MCiOP). Associations between wheeze and metabolites of other phthalates (DiDP/DPHP, DEHP, BBP, and DBP) did not reach significance. Overall, no significant associations were found between DiNP or DiDP/DPHP metabolites and croup. However, isolated quartiles of the DiNP metabolite MHiNP and the DiDP metabolite MHiDP had significant associations among boys. The BBP metabolite (MBzP) as well as the DEHP metabolites were significantly positively associated with croup among all study participants; most associations remained significant among boys when stratified by sex. There were no significant associations with otitis media, for which results were not shown.		

Overall Quality Determination Medium

Study Citation:	Chang, W. H., Tsai, Y. S., Wang, J. Y., Chen, H. L., Yang, W. H., Lee, C. C. (2019). Sex hormones and oxidative stress mediated phthalate-induced effects in prostatic enlargement. Environment International 126:184-192.
Health Outcome(s) Assessed:	Oxidative stress/Inflammation- Oxidative stress/Inflammation (malondialdehyde, inducible nitric oxide synthetase, 8-hydroxy-2'-deoxyguanosine), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP)
HERO ID:	5499417

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This is a cross-sectional study from 2015 to 2017 that enrolled and collected data from 207 elderly men with urologist-diagnosed benign prostatic hyperplasia (BPH) and prostatic enlargement in their first visit to urology clinics at the National Cheng Kung University Hospital (NCKUH). Patients with either storage, or voiding problems, or both, a positive DRE, and biopsy samples histologically confirmed as benign prostatic hyperplasia (BPH) were enrolled in the study. The mean age of the participants was 62.5 years old, but no specific age exclusion was discussed. Patients with liver dysfunction, diabetes, urinary tract infection, kidney stones, neuropathic bladder, using hormonal therapy or steroid medication, or occupational exposure to phthalates or other agents (metals, radiation, heat, pesticide, polychlorinated biphenyls, dioxins, etc.) were excluded. The participation rate was over 90%. Distributions of relevant exposure, outcome, demographic and other variables between those included and excluded were not detailed. No serious concern for selection bias.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Eleven phthalate metabolites were measured in first morning spot-urine samples collected from each participant and mono-iso-nonyl phthalate [MiNP], a major metabolite of diisononyl phthalate [DiNP] and mono-iso-decyl phthalate [MiDP], a major metabolite of diisodecyl phthalate [DiDP] were analyzed. MINP and MIDP were detected in only 2.4%, 1.0%, of participants, respectively. Samples were processed using a solid-phase extraction method and were analyzed as described using high-performance liquid chromatography (HPLC 1200; Agilent, Waldbronn, Germany) coupled with tandem mass spectrometry (6410B tandem quadrupole mass spectrometer; Agilent) with electrospray ionization. Quality control procedures were detailed. Values below the lower limit of detection (LOD) were assigned a value of the limit of detection divided by 2. Urinary phthalate metabolites were adjusted for urinary creatinine. The median (25th-75th percentile) concentration for MINP was 0.50 ng/mL (<LOD-0.50 ng/mL)and for MIDP was 0.50 ng/mL (<LOD-0.50 ng/mL). Given the short half-life of phthalates, it is unclear if a single spot urine measure adequately represents the intensity, frequency and potential peak exposures responsible for initiation and development of the outcomes of interest.
Domain 3: Outcome Assessment				

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Study Citation:	Chang, W. H., Tsai, Y. S., Wang, J. Y., Chen, H. L., Yang, W. H., Lee, C. C. (2019). Sex hormones and oxidative stress mediated phthalate-induced effects in prostatic enlargement. Environment International 126:184-192.
Health Outcome(s) Assessed:	Oxidative stress/Inflammation- Oxidative stress/Inflammation (malondialdehyde, inducible nitric oxide synthetase, 8-hydroxy-2'-deoxyguanosine), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP)
HERO ID:	5499417

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	The study analyzed changes in serum sex hormones (leutenizing hormone (LH), follicle-stimulating hormone (FSH), sex hormone binding globulin (SHBG), Inhibin B, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAs), androstenedione (AD), estrone (E1), estradiol (E2), total testosterone (TT), free testosterone (FT), dihydrotestosterone (DHT), DHT/TT ratio, E2/TT ratio, and E2/E1 ratio), oxidative stress and inflammation markers (malondialdehyde (MDA), inducible nitric oxide synthetase (iNOS), and 8-hydroxy-2'-deoxyguanosine (8-OHdG)), and indicators for benign prostatic hyperplasia (BPH)(prostate specific antigen (PSA), prostate volume). Venous blood samples for sex hormones were quantified using an electrochemical luminescence immunoassay. Inhibin B was quantified utilizing a double-antibody enzyme-linked immunosorbent assay. SHBG was assayed using an electrochemical luminescence immunoassay. Serum MDA and iNOS were assessed using TBARS Assay kits and ELISA, respectively. Urinary 8-OHdG analyses were conducted utilizing a competitive ELISA kit. The presence of clinical BPH was assessed using the following variables: the International Prostate Symptom Score (I-PSS), PSA, urinary creatinine, and uro-flowmetry (=prostate volume [PV], voided volume, and peak flowrate [Qmax]), digital rectal examination (DRE) results, and a confirmed prostate biopsy. Patients with either storage, or voiding problems, or both, a positive DRE, and biopsy samples histologically confirmed as BPH were enrolled in the study. All patients were examined in urology clinics and evaluated by the NCKUH Pathology Department. The duration of BPH symptoms could not precisely be determined, but patients reported symptoms continued for more than one month.
	Metric 3B:	Selective Reporting	Medium	No concern for selective reporting
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Models were adjusted for age, body mass index [BMI], and season for which blood was collected for hormone analysis. Total testosterone/estradiol were additionally adjusted for SHBG. Strategy for selection of potential confounders was not detailed. Data regarding confounding variables was assumed to have been obtained from the interview of participants described as utilizing a standardized questionnaire.
Domain 5: Analysis				

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Health Outcome(s) Assessed:	Oxidative stress/Inflammation- Oxidative stress/Inflammation (malondialdehyde, inducible nitric oxide synthetase, 8-hydroxy-2'-deoxyguanosine), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP)
HERO ID:	5499417

Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Medium	Multivariate linear regression was used to determine the association between the urinary phthalate metabolites and sex hormone levels, PSA, PV, and OS markers. A ridge regression analysis was used to determine the interactive effects of the concurrent exposure of BPH patients to various phthalates. Results were reported with 95% CIs, IQR, geometric mean, and standard deviations are provided in the main and supplemental documents. Mediation analysis was used to estimate the size of the effect of the exposure of patients to phthalates on the prostatic enlargement that was mediated by sex hormones, oxidative stress and inflammation, with total, direct and indirect effects estimated and reported. Multiple comparisons were adjusted using the false-discovery rate. Missing data is not noted. Natural logs were used to transform skewed variables.
	Metric 5B:	Sensitivity	Low	MINP and MIDP were detected in only 2.4% and 1.0% of participants, respectively. The sample size (n=207) is relatively limited. The range of exposure does not greatly vary for MINP and MIDP– the median (25th-75th percentile) concentration for MINP was 0.50 ng/mL (<LOD-0.50 ng/mL) and for MIDP was 0.50 ng/mL (<LOD-0.50 ng/mL). Given the short half-life of phthalates, it is unclear if a single spot urine measure adequately represents the intensity, frequency and potential peak exposures responsible for initiation and development of the outcomes of interest.

Additional Comments: MINP and MIDP were detected in only 2.4% and 1.0% of participants, respectively. There is a possibility that other contaminants resulted in the outcome findings. The single spot measures of urinary phthalate metabolizes may not represent long-term exposure and since BPH and BPE are chronic disease, the development of these outcomes and their relationship to the exposure may be inaccurate. Finally, the short half-lives of phthalates and the fluctuations of the outcomes measured might contribute to variations in symptom intensity throughout the day.

Overall Quality Determination Medium

Study Citation:	Fernandez, Moreira, M. A., Cardeal, Z. L., Carneiro, M. M., André, L. C. (2019). Study of possible association between endometriosis and phthalate and bisphenol A by biomarkers analysis. Journal of Pharmaceutical and Biomedical Analysis 172:238-242.
Health Outcome(s) Assessed:	Reproductive/Developmental- Endometriosis, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP)
HERO ID:	5432788

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Low	This case-control study evaluated the association between phthalate metabolites and endometriosis. Participants were aged 18-45 years. Diagnosis or the absence of disease was confirmed at the Endometriosis Center of the Hospital School of the Federal University of Minas Gerais, Brazil. 30 endometriosis cases and 22 controls without endometriosis were recruited in Brazil. No information was provided on the recruitment process, participation rates, inclusion/exclusion criteria, or on the underlying population(s) from which the cases and controls arose. The potential for selection bias cannot be ruled out.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Phthalate metabolites were measured in urine samples using an Agilent 7890 "GC system...coupled to a MS equipped with a quadrupole mass analyser." Details on the analytic method were previously published (Fernandez et al 2016, HEROID 3466575). Concentrations were adjusted for creatinine. Measured metabolites included MiNP, MiBP, MBP, MCHP, MBzP, and MEHP. Limits of quantification (LOQ) ranged from 2.91 ug/L for MBzP to 38.9 ug/L for MiBP. Values below the LOQ were replaced with 0. The proportion of participants above LOQ was typically <50%. Of 30 cases and 22 controls, case/control Ns above LOQ were: MiNP 9/6, MiBP 18/7, MBP 8/3, MCHP 10/3, MBzP 2/0, and MEHP 10/6. The authors' stated that metabolites were categorized at the median for analysis, or effectively as any vs no detectable amounts. No information on the details or timing of urine sample collection was provided (e.g., spot urine sample vs. first morning void). Given the case control design, samples were collected after diagnosis. However, timing of diagnosis relative to enrollment (e.g., inclusion of incident vs. prevalent cases) was not discussed. As such, there is uncertainty as to whether the exposure represents the etiologically relevant time period. However, there is no direct evidence of bias (e.g. post-diagnosis behavior changes or treatments that affected exposure).
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Presence or absence of endometriosis was confirmed in cases and controls using "videolaparoscopy surgery with visual inspection of the pelvis and biopsy of suspected lesions" for most participants. For three participants, diagnosis was done via MRI. Though the rationale for the use of a different method for these three participants was not provided, both methods are valid, and the different approaches may be medically justified. The authors did not discuss whether cases were incident diagnosis or had prevalent disease. There was no discussion of the stage of disease. The authors did not discuss whether controls were patients who had been examined in relation to ongoing medical concerns (e.g. pelvic pain, infertility) to exclude a diagnosis of endometriosis.

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Study Citation:	Fernandez, Moreira, M. A., Cardeal, Z. L., Carneiro, M. M., André, L. C. (2019). Study of possible association between endometriosis and phthalate and bisphenol A by biomarkers analysis. Journal of Pharmaceutical and Biomedical Analysis 172:238-242.
Health Outcome(s) Assessed:	Reproductive/Developmental- Endometriosis, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP)
HERO ID:	5432788

Domain	Metric		Rating	Comments
	Metric 3B:	Selective Reporting	Medium	The authors described their primary and secondary analyses in the methods section and results were reported for all primary and secondary analyses.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Low	No potential confounders accounted for either by design or adjustment. Descriptive data indicated differences in cases and controls in variables including BMI (24.7 vs 27.6 kg/m2), family history of endometriosis (16.7% vs 9.1%), oral contraceptive use (43.3 vs. 31.8%), and frequent intake of microwaved food (36.6 vs 45.4%); there was no significance testing. Associations between potential risk factors for endometriosis and phthalate metabolites were not shown. Though residual confounding is likely, there is no direct evidence of substantial bias.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	The association between creatinine adjusted phthalate metabolites and endometriosis was assessed using a chi-square test and via calculation of an odds ratio and 95% confidence interval. Phthalate metabolite concentrations were dichotomized at the median for analysis. Only bivariate analyses were conducted. No sensitivity analyses were conducted to assess robustness of findings.
	Metric 5B:	Sensitivity	Low	The overall sample size was relatively small (n=52). In addition to a small number of cases (n=30) this study did not increase the number of controls (n=22) to enhance statistical power. Few participants had urinary concentrations of phthalate metabolites above LOQ. For example, only 15 participants (9 cases, 6 controls) had quantifiable MiNP. However, among participants with detectable amounts, there was variability in exposure (e.g., MiNP median 21.8 ug/L, range 8.4 to 249 among cases). The unclear timing of outcome diagnosis vs. exposure ascertainment and the use of a single urine sample to characterize exposure may have contributed to misclassification that would further reduce statistical power.

Additional Comments: This case-control study of women in Brazil evaluated the association between phthalate metabolites and endometriosis. The sample included 30 cases and 22 controls. An important concern was the potential for residual confounding, as no potential confounders were controlled for by design or by adjustment. Descriptive data indicated that cases and controls differed in several characteristics, including BMI. Additional concerns include the lack of information on the participant recruitment process, and whether cases were incident diagnoses vs. women with prevalent disease. It was also unclear whether controls were screened laparoscopically for endometriosis because they were patients being attended at the same hospital center with other unnamed gynecologic or reproductive disorders.

Overall Quality Determination Low

Study Citation:	Liao, K. W., Kuo, P. L., Huang, H. B., Chang, J. W., Chiang, H. C., Huang, P. C. (2018). Increased risk of phthalates exposure for recurrent pregnancy loss in reproductive-aged women. Environmental Pollution 241:969-977.
Health Outcome(s) Assessed:	Reproductive/Developmental- Recurrent pregnancy loss, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP)
HERO ID:	4728516

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This case-control study evaluated the association between phthalate exposure and recurrent pregnancy loss (RPL) among cases and controls recruited from the Obstetrics and Gynecology Department at the National Cheng Kung University Hospital in Taiwan, August 2013-August 2017. Cases (n=103) were reproductive-aged women between ages 20-49 who were diagnosed with RPL. Controls were women of similar age (22.8-47.8) who did not have RPL but were diagnosed with other "mild gynecological conditions" (not further specified). Controls were further excluded if they had endometriosis, adenomyosis and leiomyoma, polycystic ovary syndrome, or ovary- or uterus-related diseases; the study did not specify whether these exclusion criteria also applied to cases. No further inclusion/exclusion criteria were stated. No information on participation rates was provided. All cases and controls were of Chinese descent. There is some concern for selection bias given the lack of information of some aspects of participation recruitment.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Phthalate metabolites were analyzed from single spot urine samples provided by the participants using an "online system coupled with liquid chromatography-electrospray tandem mass spectrometry." The LOD and the percentage of samples above the LOD for each metabolite is documented in Table 2. The LOD for MBzP, MCMHP, and MiNP were 0.3 ng/mL, 0.1 ng/mL, and 0.1 ng/mL, respectively. <50% of both the controls and the cases had MBzP values above the LOD. Only 40.8% of controls and 58.3% of the cases had MCMHP values above the LOD. Notably, only 2.6% of controls and 2.9% of cases had values of MiNP above the LOD. The timing of urine sample collection was not provided, although presumably this took place at enrollment given the case-control design. There is some concern for exposure misclassification due to the use of a single spot urine sample to represent exposure levels prior to the development of the outcome (recurrent pregnancy loss).
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	High	Authors stated that diagnosis of RPL was clinically defined as having two or more consecutive miscarriages (terminated pregnancy before 20 weeks of gestation). Although the source of the clinical definition is not specified, there is minimal concern for outcome misclassification as the diagnosis was conducted by a physician.
	Metric 3B:	Selective Reporting	Medium	The results reported are consistent with the analyses described in the methods section.
Domain 4: Potential Confounding / Variability Control				

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Study Citation:	Liao, K. W., Kuo, P. L., Huang, H. B., Chang, J. W., Chiang, H. C., Huang, P. C. (2018). Increased risk of phthalates exposure for recurrent pregnancy loss in reproductive-aged women. Environmental Pollution 241:969-977.
Health Outcome(s) Assessed:	Reproductive/Developmental- Recurrent pregnancy loss, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP)
HERO ID:	4728516

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	Low	The association between the relevant metabolites (MBzP, MCMHP, and MiNP) and RPL was examined only in bivariate analyses given the low percent of samples with detectable concentrations for each metabolite (i.e., no adjustment for potential confounders). The lack of adjustment for confounders in analyses for each metabolite is the major driver of the low confidence rating in this domain.
Domain 5: Analysis				
	Metric 5A:	Analysis	Low	The association between the relevant metabolites (MBzP, MCMHP, and MiNP) and RPL was examined only in bivariate analyses (Mann-Whitney U test for each metabolite in cases vs. controls) given the low percent of samples with detectable concentrations. Handling of missing data are not discussed. Additional analyses to evaluate bias, such as sensitivity analyses, are not discussed in this study.
	Metric 5B:	Sensitivity	Low	A major concern regarding study sensitivity is the low percentage of cases and controls with detectable levels of MBzP, MCMHP, and MiNP.

Additional Comments: This case-control study examined associations between phthalate exposures measured in urine samples and recurrent pregnancy loss among women in Taiwan. A major concern is that MBzP, MCMHP, and MiNP were only examined in bivariate analyses given the very low percentage of samples with values above the limit of detection. In particular, detectable MiNP exposure was less than 3% in both cases and controls). Other concerns include the lack of information on some aspects of participant selection and the use of a single spot urine sample to assess exposure.

Overall Quality Determination Low

Study Citation:	Shin, H. M., Schmidt, R. J., Tancredi, D., Barkoski, J., Ozonoff, S., Bennett, D. H., Hertz-Picciotto, I. (2018). Prenatal exposure to phthalates and autism spectrum disorder in the MARBLES study. Environmental Health 17(1):85.
Health Outcome(s) Assessed:	Neurological/Behavioral- Autism spectrum disorder (ASD), non-typical development (Non-TD), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP)
HERO ID:	5043457

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	High	This cohort study examined a subset of participants (186 mothers and their 201 children) from the MARBLES (Markers of Autism Risk in Babies – Learning Early Signs) cohort, which follows pregnant women at a high risk of delivering another child who will develop autism spectrum disorder (ASD). Recruitment for the larger cohort was conducted from 2006-2014 "mostly in Northern California" primarily from "lists of children receiving services for autism through the California Department of Developmental Services, as well as from other studies, by self- or provider referrals and obstetrics/gynecology clinics. Participation rates and inclusion/exclusion criteria were not provided for the overall cohort. For the subset of mothers and children included in the current study, participants were limited to mothers who provided first morning voids and/or 24 hour urine samples during pregnancy between 2007-2014 and had a child who completed the study at age 3 (flow chart available in Figure S1). 43 mothers were excluded due to miscarriage or loss to follow-up. While there was a moderate degree of loss to follow-up, the information provided does not suggest that this was jointly related to exposure and outcome.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	High	Valid exposure assessment methods were used. Phthalate metabolites were measured in multiple maternal urine samples during pregnancy. Mothers were asked to provide three first morning voids (FMVs) each one week apart, as well as one 24-hour urine sample each trimester (collected between January 2007-February 2014). When mothers provided 3+ urine specimens a trimester, authors kept the first FMV as an individual sample and pooled the extra urine samples. Samples were refrigerated or frozen and sent to the UC Davis lab for analyses. The LODs (% above the LOD) were 0.2 ug/L (100%) for MCNP, 0.3 ug/L (100%) for MCOP, and 0.9 ug/L (50%) for MiNP, 0.4 ug/L (99%) for MBP, 0.4 ug/L (82% for MHBP, 0.8 ug/L (98%) for MiBP, 0.4 ug/L (97%) for MHiBP, 0.3 ug/L (99%) for MBzP, 0.8 ug/L (83%) for MEHP, 0.4 ug/L (100%) for MEHHP, 0.2 ug/L (100%) for MEOHP, and 0.4 ug/L (100%) for MECPP. DEHP metabolites were summed (molar sum). The number of urine samples actually provided varied among participants; as such, weighted averages were estimated across mid-to-late pregnancy as well as for the 2nd and 3rd trimesters separately, with weights proportional to the number of individual and pooled samples. Some non-differential exposure misclassification may be present particularly among participants with fewer samples across pregnancy, but this is not a major concern. Concentrations were corrected for specific gravity.
Domain 3: Outcome Assessment				

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Study Citation:	Shin, H. M., Schmidt, R. J., Tancredi, D., Barkoski, J., Ozonoff, S., Bennett, D. H., Hertz-Picciotto, I. (2018). Prenatal exposure to phthalates and autism spectrum disorder in the MARBLES study. Environmental Health 17(1):85.
Health Outcome(s) Assessed:	Neurological/Behavioral- Autism spectrum disorder (ASD), non-typical development (Non-TD), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP)
HERO ID:	5043457

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	High	There is high confidence in the validity in the outcome definition. ASD was assessed in children by licensed clinical psychologists using the gold standard, the Autism Diagnostic Observation Schedules (ADOS). Children were also administered the Mullen Scales of Early Learning (MSEL). Scores from ADOS and MEL were used to categorize children into those with ASD outcomes, non-typical development outcomes, and typical development outcomes. The study does not state whether outcome assessors were aware of exposure status, but this seems unlikely given the exposure was measured in a biological matrix (urine).
	Metric 3B:	Selective Reporting	Medium	The authors described their primary and secondary analyses in the methods section and results were reported for all primary and secondary analyses.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Uninformative	As only 50% of samples were above the LOD for MiNP, only bivariate analyses were conducted with no adjustment for potential confounders. Substantial confounding is likely present.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	As only 50% of samples were above the LOD for MiNP, only bivariate analyses were conducted. Wilcoxon rank-sum tests were used to compare MiNP levels among ASD vs. TD children, and among non-TD vs. TD children. No further analyses were conducted on this metabolite.
	Metric 5B:	Sensitivity	Low	Concentrations of MiNP were relatively low (median = 1.1 ug/L, 5th percentile = <LOD, 95th percentile = 8.1 ug/L), with only 50% of samples above the LOD.

Additional Comments: Overall, this cohort of mother-child pairs from MARBLES provided detailed methodology using the gold standard regarding the exposure assessment and outcome ascertainment. However, only 50% of samples were above the limit of detection for MiNP and only bivariate analyses were conducted for this metabolite with no consideration of potential confounding.

Overall Quality Determination — Uninformative

Study Citation:	Dzwilewski, C., K.L., Woodbury, M. L., Aguiar, A., Shoaff, J., Merced-Nieves, F., Korrick, S. A., Schantz, S. L. (2021). Associations of prenatal exposure to phthalates with measures of cognition in 7.5-month-old infants. NeuroToxicology 84:84-95.
Health Outcome(s) Assessed:	Neurological/Behavioral- Cognition at 7-8 months as assessed by information processing speed (average run duration during familiarization trial), visual attention (time to reach familiarization criterion during familiarization trial), and visual recognition memory (novelty preference in test trial) using eye tracking within a paired comparison visual recognition memory (VRM) test., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	7978460

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Participants were a subset of pregnant women enrolled in the Illinois Kids Development Study (IKIDS) from two obstetric clinics in the Champaign-Urbana, IL area between December 2013 and August 2018. IKIDS enrolled pregnant women aged 18 and 40 years at enrollment, with singleton non-high-risk pregnancies, fluent in English, residing within a 30-minute drive of the University of Illinois at Urbana-Champaign campus. The analysis sample included 244 of 558 women enrolled: 481 (86%) had urinary phthalates data, of which 328 (68%) participated in the cognitive assessment at 7-8 months and had useable data (e.g., not too fussy or sleepy), and 244 of these (74.3%) had complete covariate data. Demographic data presented indicated that the subset was similar to the parent cohort. There was no evidence of selectivity.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Phthalates were measured via appropriate metabolites in a pooled urine sample from each mother. The sample combined aliquots of multiple first morning urines collected at about 10–14, 16–18, 22–24, 28–30, and 34–36 weeks of gestation. Pooling reduced concern for misclassification due to exposure variability and the short half-life of these metabolites. The number of samples per participant was not provided, however analysis was restricted to those infants completing all five faces trials and no missing covariate data for analyses of [sum (DEHP) and sum (DINP2), n=244] and analyses of exposure measures including MONP [sum (DINP3) and MONP, n=142]. Urinary specific gravity was used to account for differences in dilution. Phthalate metabolites were measured at the Centers for Disease Control using online solid phase extraction-high performance liquid chromatography-isotope dilution tandem mass spectrometry. Values below detection limits were imputed using machine readings. Proportions below detection were not shown; the minimum 0 for MINP and MEHP suggests some samples of this metabolite were below LOD. Where metabolite concentrations were below the limit of detection, instrument readings provided by the CDC were used in data analysis. Because urine was sent to the CDC laboratory in batches and new methods for phthalate metabolite measurement were developed between batches, MONP measures were available only for 58 % of the infants. Concern of potential bias associated with this change was mitigated by the transparent approach of analyzing DINP exposure as the molar sum of either two or three metabolites (DINP2, n=244; DINP3, n=142), as well as analyzing associations with MONP individually. This enabled comparison of associations with and without MONP. Exposure variables also included weighted molar sums of anti-androgenic metabolites, which included DINP metabolites. Distributions of phthalates for the subset of infants included vs excluded from this study were compared and were similar. There was no evidence of bias.

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Study Citation:	Dzwilewski, C., K.L., Woodbury, M. L., Aguiar, A., Shoaff, J., Merced-Nieves, F., Korrick, S. A., Schantz, S. L. (2021). Associations of prenatal exposure to phthalates with measures of cognition in 7.5-month-old infants. NeuroToxicology 84:84-95.
Health Outcome(s) Assessed:	Neurological/Behavioral- Cognition at 7-8 months as assessed by information processing speed (average run duration during familiarization trial), visual attention (time to reach familiarization criterion during familiarization trial), and visual recognition memory (novelty preference in test trial) using eye tracking within a paired comparison visual recognition memory (VRM) test., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	7978460

Domain	Metric		Rating	Comments
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Infant cognition was assessed at 7-8 months using a visual recognition memory (VRM) paradigm modified from prior studies (Rose et al., 1992 PMID 1446544). Outcomes were based on the duration or proportion of time infants spent looking at sets of images of faces, using automated measurement of eye movements (EyeLink 1000 Plus infrared eye tracker). The test comprised a familiarization trial (two identical photos presented side by side) followed by test phases (familiar image paired with a novel photo on either the left or right). Results were used to assess three cognitive domains: (i) information processing speed (run duration during familiarization trial); (ii) visual attention (time to familiarization); and (iii) visual recognition memory (novelty preference or attention time in test trial). The protocol was administered seated in a caregiver's lap in a booth with black curtains, with caregivers instructed to remain neutral and direct their gaze downward. Measures from the original protocol were variably predictive of subsequent IQ (e.g. Rose et al., PMIDs 12760523, 9306643 and 1446544). Infants were randomized to different image sets and sequencing. However, performance varied by testing set (Dzwilewski et al., 2020, PMID 32485220). Validity was not discussed. Information processing (run duration) and visual attention (time to familiarization) were correlated (Pearson's r = -0.49), but visual recognition memory (novelty preference) was not correlated with either outcome (r = 0.01 and -0.04). There were no clear associations between demographic factors or other potential predictors of cognitive development with outcome measures (in supplement not available at time of assessment). The sensitivity and specificity of outcomes measures within this study is uncertain. However, there was no evidence of bias, and caregivers were asked to remain neutral throughout testing and to direct their gaze downward so as not to affect the infant's behavior.
	Metric 3B:	Selective Reporting	Medium	Results were presented for all analyses described in the methods section. Additional results are included in a supplement with sex-stratified sensitivity analyses results for the entire cohort (n=244) and the subset (n=142) with additional MONP measures (and sum(DINP3) which included MONP).
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Potential confounders were identified based on a priori knowledge and using directed acyclic graphs (DAGs). Parental sociodemographic covariates were obtained from interviews held before or after birth. Models adjusted for maternal age, race/ethnicity (white, non-Hispanic vs. other), education (<bachelor's degree vs, bachelor's degree or higher), parity (nulliparous vs. $\geq$ 1), annual household income (<$50,000, $50,000-$99,999, $\geq$$100,000), and verbal IQ (VIQ), as well as infant sex, gestational age at birth, postnatal age at assessment, and test protocol stimulus set. Maternal smoking and alcohol intake during pregnancy were evaluated in a sensitivity analysis excluding participants with those behaviors. The authors did not discuss evaluating gestational age at birth as a potential intermediate. Co-exposure confounding was not discussed. However, there was no evidence of important residual confounding bias.

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Study Citation:	Dzwilewski, C., K.L., Woodbury, M. L., Aguiar, A., Shoaff, J., Merced-Nieves, F., Korrick, S. A., Schantz, S. L. (2021). Associations of prenatal exposure to phthalates with measures of cognition in 7.5-month-old infants. NeuroToxicology 84:84-95.
Health Outcome(s) Assessed:	Neurological/Behavioral- Cognition at 7-8 months as assessed by information processing speed (average run duration during familiarization trial), visual attention (time to reach familiarization criterion during familiarization trial), and visual recognition memory (novelty preference in test trial) using eye tracking within a paired comparison visual recognition memory (VRM) test., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	7978460

Domain	Metric		Rating	Comments
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Descriptive data for the study sample as a whole were presented for exposure and outcome variables. Stratified descriptive data were not presented, and unadjusted or minimally adjusted associations were not shown. Multivariable generalized linear regression was shown to assess associations between each phthalate exposure variable and each outcome. The authors reported that unspecified regression diagnostics "generally supported" the use of continuous, untransformed biomarker measures and linear models, despite the right skewed exposure variables. Associations were presented per interquartile range increase in exposure. Models including both two-way interactions and a three-way sex-by-stimulus set-by exposure interaction were explored for every exposure-outcomerelationship. Interaction terms with p-values 0.10 were then considered as part of final model specification. Sensitivity analyses evaluated the impact of excluding influential data points identified by Cook's D values and included analyses adjusting for maternal alcohol intake, removing mothers who smoked, or removing potential high leverage observations from the analysis. Because analyses were hypothesis based, the authors did not adjust for multiple comparisons. Although the adequacy of using linear models with untransformed exposures to estimate associations is uncertain, there was no evidence that analyses were inappropriate.
	Metric 5B:	Sensitivity	Medium	There was variability in exposure and outcome variables. For ΣDINP2, for example, the median (IQR) was 0.0388 (0.0543) uumol/L. The sample size was moderate (n = 244), which may have limited statistical power particularly for sex-stratified analyses and to detect significant interactions ($p<0.10$ used). Sample sizes for analyses of Σ DINP3 and MONP (n=142) were less than optimal for analyses involving sex- and set-specific interaction assessment.

Additional Comments: This study used data from a subset of 244 participants in the Illinois Kids Development Study (IKIDS) to explore associations between prenatal exposure to phthalates, including DINP, and infant cognition assessed at 7-8 months of age. Evaluating cognition in infancy is challenging. The study used a "visual recognition memory" testing protocol to assess three cognitive domains: information processing speed ('run duration'), visual attention ('time to familiarization'), and visual recognition memory ('novelty preference'), based on the duration or proportion of time infants spent looking at sets of familiar vs. novel images. Gaze was tracked and measured using an automated eye tracking system. Two DINP metabolites (MINP and MCOP) were available for the full sample. A third (MONP) became available during the study because of improvements in analytic methods and was available for 142 infants. The authors presented results of analyses using the sum of 2 (DINP2) or 3 (DINP3) metabolites, and MONP individually. Associations varied by infant sex and by the set of images used in testing. DINP2 was associated with longer processing time for image set 2, and DINP3 with longer processing time among males viewing set 2. DINP2 and DINP3 had weak negative associations with visual recognition memory (novelty preference). A strength of the study was the use of pooled aliquots from multiple maternal urine samples throughout pregnancy to estimate prenatal phthalates exposure. Sample size is a potential limitation, as the study may have had limited power to detect interactions. Specificity and sensitivity of outcome measures is uncertain and reasons for variable performance by image testing set were unclear. However, previous literature in other populations suggests these measures may predict later cognition.

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Study Citation:	Dzwilewski, C., K.L., Woodbury, M. L., Aguiar, A., Shoaff, J., Merced-Nieves, F., Korrick, S. A., Schantz, S. L. (2021). Associations of prenatal exposure to phthalates with measures of cognition in 7.5-month-old infants. NeuroToxicology 84:84-95.
Health Outcome(s) Assessed:	Neurological/Behavioral- Cognition at 7-8 months as assessed by information processing speed (average run duration during familiarization trial), visual attention (time to reach familiarization criterion during familiarization trial), and visual recognition memory (novelty preference in test trial) using eye tracking within a paired comparison visual recognition memory (VRM) test., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	7978460

Domain	Metric	Rating	Comments
Overall Quality Determination		**Medium**	

Study Citation:	Shoaff, J. R., Coull, B., Weuve, J., Bellinger, D. C., Calafat, A. M., Schantz, S. L., Korrick, S. A. (2020). Association of exposure to endocrine-disrupting chemicals during adolescence with attention-deficit/hyperactivity disorder-related behaviors. JAMA Network Open 3(8):e2015041.
Health Outcome(s) Assessed:	Neurological/Behavioral- Attention Deficit-Hyperactivity Disorder (ADHD) related behaviors, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	9419487

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This cross-sectional study analyzed associations between urinary phthalates and behavioral outcomes among 205 teenagers from the New Bedford Cohort in Massachusetts. The cohort recruited mother-infant pairs between 1993 and 1998 after delivery at a New Bedford hospital. The original study aimed to analyze associations between prenatal exposure to organochlorines and metals and neurodevelopment among children living near the New Bedford Harbor Superfund site. Of 660 eligible members of the parent cohort, 528 (80%) participants were included in the age 15-year follow-up. Urine sample collection was initiated midway through this follow-up. 252 of these subjects had follow-up visits after urine collection was initiated, from 2011 to 2014; 205 participants provided urine samples. Urine study participants (205 of 528, 39%) were younger and more likely to be non-White but were otherwise similar to the complete age 15 follow-up study population. There was no evidence that inclusion in the original cohort study or the age 15 urine study was selective with respect to phthalates exposure and adolescent behavior.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Phthalate metabolites were measured in spot urine samples collected from adolescents during the same age 15 visit in which behavioral outcomes were assessed. Urine samples were collected and processed using sterile polypropylene cups, and frozen until analyzed at the CDC using high performance liquid chromatography-isotope dilution-tandem mass spectrometry. Quality assurance measures and that included analysis of duplicates and quality control samples indicated excellent reproducibility. Instrument reading values were used for samples with concentrations below detection limits. The proportion below LOD was 0-1% except for three of the 11 metabolites [MEHP (25%), MNP (27%), and MHBP (8%), Shoaff et al 2019, HEROID 5043592]. Specific gravity was used to account for dilution. Phthalate exposures were analyzed using individual metabolite measures and as the molar sums of DEHP metabolites, antiandrogenic metabolites and metabolites found in personal care products. There was some heterogeneity in exposure assessment. However, there was no evidence that this heterogeneity results in bias. Specifically, the 205 participants provided either one (n=61) sample, or two (n=144) urine samples about one week apart. 60 of the duplicate samples were analyzed separately and the mean of two concentrations analyzed; 84 were analyzed as a single pooled sample. In addition, urine samples were analyzed in two batches. Additional metabolites included only in the second batch (MNP, MHBP, MHiBP) were missing for 27 (13.2%) participants. Given the short half-life of phthalate metabolites, some misclassification of habitual phthalates exposure is likely, which is especially complicated by the unknown etiologically relevant time period for ADHD behaviors. The availability of two urine samples in 70% of participants may have helped to reduce misclassification.

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Study Citation:	Shoaff, J. R., Coull, B., Weuve, J., Bellinger, D. C., Calafat, A. M., Schantz, S. L., Korrick, S. A. (2020). Association of exposure to endocrine-disrupting chemicals during adolescence with attention-deficit/hyperactivity disorder-related behaviors. JAMA Network Open 3(8):e2015041.
Health Outcome(s) Assessed:	Neurological/Behavioral- Attention Deficit-Hyperactivity Disorder (ADHD) related behaviors, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	9419487

Domain	Metric	Rating	Comments
Domain 3: Outcome Assessment			
	Metric 3A: Outcome Ascertainment	Medium	Outcomes were defined as the prevalence of significant ADHD-related behaviors. Measures were characterized using two validated and widely used behavioral checklists: parent, teacher and self-reported responses to the Behavior Assessment System for Children, Second Edition (BASC-2) and parent and teacher responses using Conners Attention Deficit Scale (CADS). Parent and child scores were collected at the time of the first urine collection; teacher scores were obtained a median (SD) of 2.5 (6.6) months later. All 205 adolescents with exposure data had at least 1 outcome measure, 204 (99.5%) had parent- and self-completed checklists, and 173 (84%) had teacher ratings. Age- and sex-adjusted standardized T-scores were used to generate indices of inattention and executive function which were dichotomized at the 98th percentile to identify significant behavioral problems, consistent with checklist guidelines. Outcomes (8 BASC, 6 CADS indices) were analyzed as repeat measures, including combined ADHD-related behavior problems, attention problems, and hyperactivity problems. Sensitivity analyses evaluated the influence of excluding indices for which there were internal inconsistencies in ratings and of using the 85th percentile as a cutoff to identify possible significant behavior problems. 80% of the 56 children with a reported ADHD diagnosis were characterized as having possible or significant behavior problems on the overall CADS ADHD index. In addition, a sensitivity analysis evaluated the impact of excluding children with diagnosed ADHD on results. There was no evidence of important error or bias in outcome ascertainment.
	Metric 3B: Selective Reporting	Medium	Results were presented or described for all primary and secondary analyses included as aims.
Domain 4: Potential Confounding / Variability Control			
	Metric 4A: Potential Confounding	Medium	The authors reported using a directed acyclic graph to identify potential confounders. Models adjusted for child sex, race/ethnicity, mean test age (across teacher, parent and self-reported ratings), urine specific gravity; maternal age, income, education, marital status, and smoking during pregnancy; and a test indicator. Sensitivity analyses evaluated the influence of additionally adjusting for: early life neurotoxicants (cord serum PCBs and DDE, 12 and 36-month blood Pb), adolescent behaviors (cigarette smoking, ever alcohol or marijuana use, canned and fast food consumption, personal care product use), adolescent BMI, family history of mental illness, and diagnosed behavioral problems other than ADHD. Potential co-exposure confounding by other phthalate metabolites was considered by using indices that combined multiple phthalates based on antiandrogenic properties and personal care products as a common source. Potential confounding by other measured co-exposures (e.g., parabens, bisphenols) does not appear to have been considered. There was no evidence of any important confounding bias.

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Study Citation:	Shoaff, J. R., Coull, B., Weuve, J., Bellinger, D. C., Calafat, A. M., Schantz, S. L., Korrick, S. A. (2020). Association of exposure to endocrine-disrupting chemicals during adolescence with attention-deficit/hyperactivity disorder-related behaviors. JAMA Network Open 3(8):e2015041.
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HERO ID:	9419487

Domain	Metric	Rating	Comments
Domain 5: Analysis			
	Metric 5A: Analysis	Medium	Descriptive analyses included exposure distributions and the prevalence of significant behavior problems. Statistical analysis used modified Poisson models to analyze repeated measures of binary behavioral problems indicators within each participant as reflecting a single underlying outcome. Exposure variables were log2 transformed; the authors did not discuss formally evaluating the linearity of dose-response relationships using log2 transformed exposure variables. Results were reported as relative risks with 95% confidence intervals for each exposure variable. Models were specified using a robust error variance and independent working correlation, which accommodated missing behavioral scores and allowed inclusion of participants with at least one behavioral measure. The authors analyzed effect modification by child sex for the primary exposure indices, although not for individual metabolites. Primary results were based on complete case analysis; multiple imputation was applied in a sensitivity analysis. In addition to evaluating the influence of additional potential confounders, sensitivity analyses examined the influence of excluding participants: diagnosed with ADHD; diagnosed with other behavioral outcomes; taking prescription medication for behavioral problems; and siblings. Among others, sensitivity analyses evaluated the influence of excluding BASC measures that were overly negative or lacked internal consistency. The authors did not discuss examining evidence of any other heterogeneity in associations with outcomes that were examined as repeated measures. Though there were minor limitations, there was no evidence of important error or bias in data analyses.
	Metric 5B: Sensitivity	Medium	There was variability in each exposure variable. Analytic sample sizes ranged from 164 to 190. The prevalence of significant ADHD-related behaviors in this population (mean age at assessment 14 to 17) varied from 6% to 24% for individual indices; outcomes were analyzed using a repeated measures framework, increasing statistical power. There was no evidence of inadequate sensitivity.

Additional Comments: This cross-sectional study analyzed the association between phthalates and ADHD-related behavioral problems in 205 adolescents in the New Bedford Cohort in Massachusetts. The study began collecting urine samples about midway through the age 15-year follow-up; the urine study included about 39% of the participants in that wave. Outcomes were characterized using parent, teacher, and adolescent self-report on two validated behavioral checklists (BASC-2 and CADS), which were analyzed as repeated measures. Exposure was characterized using phthalate metabolites measured in 1 or 2 (70%) urine samples. The sum of DEHP metabolites was associated with significant increases in the risk of having significant ADHD-related behavior problems, particularly in boys. Along with DEHP metabolites, MBP, MiBP, MHBP and MBzP were also associated with significantly increased risk of behavior problems. Strengths of this study include the integrated analysis of multiple assessments from parent and teachers as well as self-report, with findings that were robust in multiple sensitivity analyses. Limitations included the cross-sectional design, and that urine samples were available for a subset of the cohort.

Overall Quality Determination — Medium

Study Citation:	Durmaz, E., Erkekoglu, P., Asci, A., Akçurin, S., Bircan, I., Kocer-Gumusel, B. (2018). Urinary phthalate metabolite concentrations in girls with premature thelarche. Environmental Toxicology and Pharmacology 59:172-181.
Health Outcome(s) Assessed:	Reproductive/Developmental- Sex hormones: serum luteinizing hormone (LH), plasma follicle stimulating hormone (FSH), serum estradiol., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5512126

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	Case-control study conducted in Antalya City, Turkey. Cases (N= 29) were girls who met the following criteria: premature thelarche (PT) was observed as isolated breast development before the age of 8 years; aged 4–8 years; not obese (BMI <95th percentile of national referent); bone age did not exceed one year above their chronological age; followed up regularly by a pediatrician for at least one year without other progression of precocious puberty (PP) besides isolated breast development. Girls with pathological conditions such as ovarian cysts (other conditions not named) identified by ultrasound were excluded. A gonadotropin releasing hormone (GnRH) stimulation test was performed to exclude girls with a diagnosis of central precocious puberty (PP) rather than PT. Controls (n=25), were healthy non-obese girls also living in Antalya City, aged 4-8 years, with no history of PT or any other endocrine disorder and no secondary sexual characteristics in their physical exam. All study subjects were examined by the same clinical pediatrician. The control group was re-monitored 12 months later "in order to evaluate their pubertal development and girls who had PT, premature pubarche, PP or any other pubertal signs in this second evaluation were excluded. " Recruitment strategies used to identify prospective participants, participation rates, and any attrition were not described. However, there was no evidence of selectivity.
Domain 2: Exposure Characterization			

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Study Citation:	Durmaz, E., Erkekoglu, P., Asci, A., Akçurin, S., Bircan, I., Kocer-Gumusel, B. (2018). Urinary phthalate metabolite concentrations in girls with premature thelarche. Environmental Toxicology and Pharmacology 59:172-181.
Health Outcome(s) Assessed:	Reproductive/Developmental- Sex hormones: serum luteinizing hormone (LH), plasma follicle stimulating hormone (FSH), serum estradiol., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5512126

Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Low	There were issues in each of three domains of exposure assessment. Together, these issues affect certainty regarding the validity of study results. 1-Sample collection and analysis: Spot urine samples were collected between 2010 and 2012; the authors did not explicitly state whether a single sample (which may misclassify habitual exposure given the short half-life) was collected per subject. Given the case control design, samples were collected after diagnosis: timing relative to diagnosis was not specified, though there was nothing to suggest systematic post-diagnosis behavior changes that would affect exposure to phthalates. Phthalate metabolites were analyzed by isotope dilution liquid chromatography with tandem mass spectrometry (LC–MS/MS) with standards and protocols to avoid contamination. Recovery rates exceeded 90%. Urinary creatinine was used to account for dilution. 2-Detection rate reporting issues. LODs (ng/mL) were: MiNP 0.61, MHiNP 0.26, MoiNP 0.25, MCiOP 0.53, MEHP 0.14, MEOHP 0.67, MECPP 0.55, MEHHP 0.91, MiBP 1.43, MnBP 1.1, MBzP 1.14. Detection rates reported in Table 1 were MiNP 24.1%, MHiNP 93.1%, MoiNP 82.8%, MCiOP 100%, MEHP 100%, MEOHP 100% MECPP 100%, MEHHP 100%, MiBP 100%, MnBP 100%, MBzP 79.3%. Handling of samples below detection was not specified. However, for MiNP, the metabolite with a substantial proportion below LOD, the minimum value was 0.00, suggested imputation as zeros vs. accepted approaches such as half the LOD. In addition, the proportions (Table 1) vs. numbers (Table 2) of samples below detection were not concordant. For example, for DiNP metabolites the proportion vs Ns reported as detectable were: (i) MiNP 24.1% of samples vs. 10/25 controls and 7 of 22 cases [i.e., 31.5% of the population]; (ii) MoiNP 0.25 82.8% vs. 25/25 controls and 24/29 cases [90.7%]; and (iii) MCiOP 100% vs. 23/25 controls and 29/29 cases [96.2%]. 3-Mean values reported with errors: The means for some metabolites were apparently reported with errors, based on the disparity between values for individual metabolites and the sum of DiNP. For example, the means (ug/g creatinine) for individual DiNP metabolites (MiNP, MHiNP, MOiNP, MCiOP) vs. the sum of metabolites (sum DiNP) were as follows in cases: 1.94, 40.02, 15.45, 86.77 vs. 287.30; and in controls 0.51, 4.97, 2.18, 8.00 vs. 284.60. The several-fold differences in means for MHiNP (15.45 vs 2.18) and MCiOP (86.77 vs 8.00) – the two metabolites reported to differ significantly in cases vs controls — along with means for MOiNP (40.02 vs 4.97) may have been calculation or conversion errors.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	The authors analyzed how phthalates correlated with several sex hormones (LSH, FSH, estradiol) among cases. Serum estradiol was measured by electrochemiluminescence immunoassay (ECLIA) using a commercial kit. Serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) in plasma were measured by enzyme linked immunosorbent assay (ELISA) (no further details). There was no description of the timing of collection of the serum measurements used to measure these hormones.

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Health Outcome(s) Assessed:	Reproductive/Developmental- Sex hormones: serum luteinizing hormone (LH), plasma follicle stimulating hormone (FSH), serum estradiol., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5512126

Domain	Metric		Rating	Comments
	Metric 3B:	Selective Reporting	Medium	Descriptive data for these sex hormone measures among cases were presented in the results text. Correlations between urinary phthalates and all three hormones (basal levels) were also presented. There was no evidence of selective reporting.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Low	There was no adjustment for confounding in the analysis correlating serum/plasma sex hormones with urinary phthalates among cases. All girls were non-obese. However, the authors did not discuss potential confounding by variability in age and BMI among cases. BMI was moderately and significantly correlated with several phthalate metabolites. Associations between BMI and sex hormones within this population were not discussed, so there is no direct evidence of important bias. Co-exposure confounding was also not evaluated.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Descriptive data for sex hormone measures was not provided. It is unclear whether there were any missing values. Correlations between phthalate metabolite levels and sex hormones were evaluated appropriately using Spearman correlation coefficients; coefficients and p-values were shown. A p value of < 0.05 was accepted as significant. Multivariate analysis of phthalate-sex hormone associations among cases were not described as an aim.
	Metric 5B:	Sensitivity	Medium	Small sample size for evaluating correlations among cases (N=29), however some strong and significant correlations were observed. There was an adequate range of and variability in metabolite exposures.

Additional Comments: This case control study in Turkey included 29 non-obese girls aged 4-8 years with premature thelarche (PT; isolated breast development) and 25 non-obese controls residing in the same city. Controls were followed for one year to confirm that they did not develop signs of precocious development. DiNP metabolites (MiNP, MHINP, MOiNP, MCiOP and their sum), DEHP metabolites (MEHP, MEHHP, MEOHP, MECPP, and their sum), MnBP, MiBP, and MBzP measured in spot urine samples were compared among cases and controls. This study had important limitations. Most importantly, there were apparent errors in the values of some metabolites (e.g., DiNP metabolites, DEHP metabolites) that were reported: values for individual metabolites vs. the sum of metabolites were not concordant. For example, values for the two DiNP metabolites reported to differ significantly in cases vs controls were implausible given that values for the sum of DiNP were roughly equivalent. Reported means (ug/g creatinine) in controls vs cases were: MHiNP (15.45 vs 2.18), MCiOP (86.77 vs 8.00) and sum DiNP (221.21 vs 220.81). The authors did not specify how values below LOD were handled, an issue for MiNP (detected in 7 of 22 cases). Additional concerns include the lack of information of the timing of diagnosis vs. recruitment into the study and urine collection, the lack of adjustments for confounding by age or BMI in within-case analyses relating phthalates to outcomes such as sex hormones, and failure to describe the methods used to assess physical markers of reproductive development such as ovarian volumes. Uncertainty regarding these issues make findings of this study uninformative.

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Study Citation:	Durmaz, E., Erkekoglu, P., Asci, A., Akçurin, S., Bircan, I., Kocer-Gumusel, B. (2018). Urinary phthalate metabolite concentrations in girls with premature thelarche. Environmental Toxicology and Pharmacology 59:172-181.
Health Outcome(s) Assessed:	Reproductive/Developmental- Sex hormones: serum luteinizing hormone (LH), plasma follicle stimulating hormone (FSH), serum estradiol., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5512126

Domain	Metric	Rating	Comments
Overall Quality Determination		**Low**	

Study Citation:	Durmaz, E., Erkekoglu, P., Asci, A., Akçurin, S., Bircan, I., Kocer-Gumusel, B. (2018). Urinary phthalate metabolite concentrations in girls with premature thelarche. Environmental Toxicology and Pharmacology 59:172-181.
Health Outcome(s) Assessed:	Reproductive/Developmental- Ovary and uterus volumes; pubic hair growth, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5512126

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	Case-control study conducted in Antalya City, Turkey. Cases (N= 29) were girls who met the following criteria: premature thelarche (PT) was observed as isolated breast development before the age of 8 years; aged 4–8 years; not obese (BMI <95th percentile of national referent); bone age did not exceed one year above their chronological age; followed up regularly by a pediatrician for at least one year without other progression of precocious puberty (PP) besides isolated breast development. Girls with pathological conditions such as ovarian cysts (other conditions not named) identified by ultrasound were excluded. A gonadotropin releasing hormone (GnRH) stimulation test was performed to exclude girls with a diagnosis of central precocious puberty (PP) rather than PT. Controls (n=25), were healthy non-obese girls also living in Antalya City, aged 4-8 years, with no history of PT or any other endocrine disorder and no secondary sexual characteristics in their physical exam. All study subjects were examined by the same clinical pediatrician. The control group was re-monitored 12 months later "in order to evaluate their pubertal development and girls who had PT, premature pubarche, PP or any other pubertal signs in this second evaluation were excluded. " Recruitment strategies used to identify prospective participants, participation rates, and any attrition were not described. However, there was no evidence of selectivity.
Domain 2: Exposure Characterization			

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Study Citation:	Durmaz, E., Erkekoglu, P., Asci, A., Akçurin, S., Bircan, I., Kocer-Gumusel, B. (2018). Urinary phthalate metabolite concentrations in girls with premature thelarche. Environmental Toxicology and Pharmacology 59:172-181.
Health Outcome(s) Assessed:	Reproductive/Developmental- Ovary and uterus volumes; pubic hair growth, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5512126

Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Low	There were issues in each of three domains of exposure assessment. Together, these issues affect certainty regarding the validity of study results. 1-Sample collection and analysis: Spot urine samples were collected between 2010 and 2012; the authors did not explicitly state whether a single sample (which may misclassify habitual exposure given the short half-life) was collected per subject. Given the case control design, samples were collected after diagnosis: timing relative to diagnosis was not specified, though there was nothing to suggest systematic post-diagnosis behavior changes that would affect exposure to phthalates. Phthalate metabolites were analyzed by isotope dilution liquid chromatography with tandem mass spectrometry (LC–MS/MS) with standards and protocols to avoid contamination. Recovery rates exceeded 90%. Urinary creatinine was used to account for dilution. 2-Detection rate reporting issues. LODs (ng/mL) were: MiNP 0.61, MHiNP 0.26, MoiNP 0.25, MCiOP 0.53, MEHP 0.14, MEOHP 0.67, MECPP 0.55, MEHHP 0.91, MiBP 1.43, MnBP 1.1, MBzP 1.14. Detection rates reported in Table 1 were MiNP 24.1%, MHiNP 93.1%, MoiNP 82.8%, MCiOP 100%, MEHP 100%, MEOHP 100% MECPP 100%, MEHHP 100%, MiBP 100%, MnBP 100%, MBzP 79.3%. Handling of samples below detection was not specified. However, for MiNP, the metabolite with a substantial proportion below LOD, the minimum value was 0.00, suggested imputation as zeros vs. accepted approaches such as half the LOD. In addition, the proportions (Table 1) vs. numbers (Table 2) of samples below detection were not concordant. For example, for DiNP metabolites the proportion vs Ns reported as detectable were: (i) MiNP 24.1% of samples vs. 10/25 controls and 7 of 22 cases [i.e., 31.5% of the population]; (ii) MoiNP 0.25 82.8% vs. 25/25 controls and 24/29 cases [90.7%]; and (iii) MCiOP 100% vs. 23/25 controls and 29/29 cases [96.2%]. 3-Mean values reported with errors: The means for some metabolites were apparently reported with errors, based on the disparity between values for individual metabolites and the sum of DiNP. For example, the means (ug/g creatinine) for individual DiNP metabolites (MiNP, MHiNP, MOiNP, MCiOP) vs. the sum of metabolites (sum DiNP) were as follows in cases: 1.94, 40.02, 15.45, 86.77 vs. 287.30; and in controls 0.51, 4.97, 2.18, 8.00 vs. 284.60. The several-fold differences in means for MHiNP (15.45 vs 2.18) and MCiOP (86.77 vs 8.00) – the two metabolites reported to differ significantly in cases vs controls — along with means for MOiNP (40.02 vs 4.97) may have been calculation or conversion errors.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Low	The authors did not describe how ovary and uterus volumes, or pubic hair development, were measured and/or scored. No descriptive data were provided for these measures.
	Metric 3B:	Selective Reporting	Medium	Correlations between urinary phthalates and each of these measures were shown in the results. There was no evidence of selective reporting.
Domain 4: Potential Confounding / Variability Control				

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Study Citation:	Durmaz, E., Erkekoglu, P., Asci, A., Akçurin, S., Bircan, I., Kocer-Gumusel, B. (2018). Urinary phthalate metabolite concentrations in girls with premature thelarche. Environmental Toxicology and Pharmacology 59:172-181.
Health Outcome(s) Assessed:	Reproductive/Developmental- Ovary and uterus volumes; pubic hair growth, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5512126

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	Low	There was no adjustment for confounding in the analysis relating these outcomes (ovary and uterine volumes, pubic hair development) and urinary phthalates among cases. The authors did not discuss potential confounding by variability in age among cases. They did not discuss potential confounding of associations with ovary/uterine volumes and public hair development by BMI, which was correlated with several phthalate metabolites. Co-exposure confounding was also not evaluated.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Descriptive data for these outcomes were not provided. It is unclear whether there were any missing values. Correlations between phthalate metabolite levels and these outcomes were evaluated appropriately using Spearman correlation coefficients; coefficients and p-values were shown. A p value of < 0.05 was accepted as significant. Multivariate analyses of associations among cases were not described as an aim.
	Metric 5B:	Sensitivity	Medium	Small sample size for evaluating correlations among cases (N=29), however some strong and significant correlations were observed. There was an adequate range of and variability in metabolite exposures.

Additional Comments: This case control study in Turkey included 29 non-obese girls aged 4-8 years with premature thelarche (PT; isolated breast development) and 25 non-obese controls residing in the same city. Controls were followed for one year to confirm that they did not develop signs of precocious development. DiNP metabolites (MiNP, MHINP, MOiNP, MCiOP and their sum), DEHP metabolites (MEHP, MEHHP, MEOHP, MECPP, and their sum), MnBP, MiBP, and MBzP measured in spot urine samples were compared among cases and controls. This study had important limitations. Most importantly, there were apparent errors in the values of some metabolites (e.g., DiNP metabolites, DEHP metabolites) that were reported: values for individual metabolites vs. the sum of metabolites were not concordant. For example, values for the two DiNP metabolites reported to differ significantly in cases vs controls were implausible given that values for the sum of DiNP were roughly equivalent. Reported means (ug/g creatinine) in controls vs cases were: MHiNP (15.45 vs 2.18), MCiOP (86.77 vs 8.00) and sum DiNP (221.21 vs 220.81). The authors did not specify how values below LOD were handled, an issue for MiNP (detected in 7 of 22 cases). Additional concerns include the lack of information of the timing of diagnosis vs. recruitment into the study and urine collection, the lack of adjustments for confounding by age or BMI in within-case analyses relating phthalates to outcomes such as sex hormones, and failure to describe the methods used to assess physical markers of reproductive development such as ovarian volumes. Uncertainty regarding these issues make findings of this study uninformative.

Overall Quality Determination — Low

Study Citation:	Durmaz, E., Erkekoglu, P., Asci, A., Akçurin, S., Bircan, I., Kocer-Gumusel, B. (2018). Urinary phthalate metabolite concentrations in girls with premature thelarche. Environmental Toxicology and Pharmacology 59:172-181.
Health Outcome(s) Assessed:	Thyroid- Serum thyroid stimulating hormone (TSH) and serum free T4 (fT4), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5512126

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	Case-control study conducted in Antalya City, Turkey. Cases (N= 29) were girls who met the following criteria: premature thelarche (PT) was observed as isolated breast development before the age of 8 years; aged 4–8 years; not obese (BMI <95th percentile of national referent); bone age did not exceed one year above their chronological age; followed up regularly by a pediatrician for at least one year without other progression of precocious puberty (PP) besides isolated breast development. Girls with pathological conditions such as ovarian cysts (other conditions not named) identified by ultrasound were excluded. A gonadotropin releasing hormone (GnRH) stimulation test was performed to exclude girls with a diagnosis of central precocious puberty (PP) rather than PT. Controls (n=25), were healthy non-obese girls also living in Antalya City, aged 4-8 years, with no history of PT or any other endocrine disorder and no secondary sexual characteristics in their physical exam. All study subjects were examined by the same clinical pediatrician. The control group was re-monitored 12 months later "in order to evaluate their pubertal development and girls who had PT, premature pubarche, PP or any other pubertal signs in this second evaluation were excluded. " Recruitment strategies used to identify prospective participants, participation rates, and any attrition were not described. However, there was no evidence of selectivity.
Domain 2: Exposure Characterization			

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Study Citation:	Durmaz, E., Erkekoglu, P., Asci, A., Akçurin, S., Bircan, I., Kocer-Gumusel, B. (2018). Urinary phthalate metabolite concentrations in girls with premature thelarche. Environmental Toxicology and Pharmacology 59:172-181.
Health Outcome(s) Assessed:	Thyroid- Serum thyroid stimulating hormone (TSH) and serum free T4 (fT4), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5512126

Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Low	There were issues in each of three domains of exposure assessment. Together, these issues affect certainty regarding the validity of study results. 1-Sample collection and analysis: Spot urine samples were collected between 2010 and 2012; the authors did not explicitly state whether a single sample (which may misclassify habitual exposure given the short half-life) was collected per subject. Given the case control design, samples were collected after diagnosis: timing relative to diagnosis was not specified, though there was nothing to suggest systematic post-diagnosis behavior changes that would affect exposure to phthalates. Phthalate metabolites were analyzed by isotope dilution liquid chromatography with tandem mass spectrometry (LC–MS/MS) with standards and protocols to avoid contamination. Recovery rates exceeded 90%. Urinary creatinine was used to account for dilution. 2-Detection rate reporting issues. LODs (ng/mL) were: MiNP 0.61, MHiNP 0.26, MoiNP 0.25, MCiOP 0.53, MEHP 0.14, MEOHP 0.67, MECPP 0.55, MEHHP 0.91, MiBP 1.43, MnBP 1.1, MBzP 1.14. Detection rates reported in Table 1 were MiNP 24.1%, MHiNP 93.1%, MoiNP 82.8%, MCiOP 100%, MEHP 100%, MEOHP 100% MECPP 100%, MEHHP 100%, MiBP 100%, MnBP 100%, MBzP 79.3%. Handling of samples below detection was not specified. However, for MiNP, the metabolite with a substantial proportion below LOD, the minimum value was 0.00, suggested imputation as zeros vs. accepted approaches such as half the LOD. In addition, the proportions (Table 1) vs. numbers (Table 2) of samples below detection were not concordant. For example, for DiNP metabolites the proportion vs Ns reported as detectable were: (i) MiNP 24.1% of samples vs. 10/25 controls and 7 of 22 cases [i.e., 31.5% of the population]; (ii) MoiNP 0.25 82.8% vs. 25/25 controls and 24/29 cases [90.7%]; and (iii) MCiOP 100% vs. 23/25 controls and 29/29 cases [96.2%]. 3-Mean values reported with errors: The means for some metabolites were apparently reported with errors, based on the disparity between values for individual metabolites and the sum of DiNP. For example, the means (ug/g creatinine) for individual DiNP metabolites (MiNP, MHiNP, MOiNP, MCiOP) vs. the sum of metabolites (sum DiNP) were as follows in cases: 1.94, 40.02, 15.45, 86.77 vs. 287.30; and in controls 0.51, 4.97, 2.18, 8.00 vs. 284.60. The several-fold differences in means for MHiNP (15.45 vs 2.18) and MCiOP (86.77 vs 8.00) – the two metabolites reported to differ significantly in cases vs controls –- along with means for MOiNP (40.02 vs 4.97) may have been calculation or conversion errors.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Serum fT4 and TSH levels were measured by chemiluminescence microparticle immunoassay using commercial kits and analyzers (DiaSorin chemiluminescence immunoassay (CLIA) kits, a Diasorin Liaison CLIA Analyzer). There was no description of the timing of collection of the serum samples used to measure these hormones.
	Metric 3B:	Selective Reporting	Medium	Correlations between urinary phthalates and thyroid hormones were presented. There was no evidence of selective reporting.

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Study Citation:	Durmaz, E., Erkekoglu, P., Asci, A., Akçurin, S., Bircan, I., Kocer-Gumusel, B. (2018). Urinary phthalate metabolite concentrations in girls with premature thelarche. Environmental Toxicology and Pharmacology 59:172-181.
Health Outcome(s) Assessed:	Thyroid- Serum thyroid stimulating hormone (TSH) and serum free T4 (fT4), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5512126

Domain	Metric	Rating	Comments
Domain 4: Potential Confounding / Variability Control			
	Metric 4A: Potential Confounding	Low	There was no adjustment for confounding in the analysis correlating thyroid hormones with urinary phthalates among cases. All girls were non-obese. However, the authors did not discuss potential confounding by variability in age and BMI among cases. BMI was moderately and significantly correlated with several phthalate metabolites. Co-exposure confounding was also not evaluated.
Domain 5: Analysis			
	Metric 5A: Analysis	Medium	Descriptive data for thyroid hormone measures was not provided. It is unclear whether there were any missing values. Correlations between phthalate metabolite levels and sex hormones were evaluated appropriately using Spearman correlation coefficients; coefficients and p-values were shown. A p value of < 0.05 was accepted as significant. Multivariate analysis of phthalate-thyroid hormone associations among cases were not described as an aim.
	Metric 5B: Sensitivity	Medium	Small sample size for evaluating correlations among cases (N=29), however some strong and significant correlations were observed. There was an adequate range of and variability in metabolite exposures.

Additional Comments: This case control study in Turkey included 29 non-obese girls aged 4-8 years with premature thelarche (PT; isolated breast development) and 25 non-obese controls residing in the same city. Controls were followed for one year to confirm that they did not develop signs of precocious development. DiNP metabolites (MiNP, MHINP, MOiNP, MCiOP and their sum), DEHP metabolites (MEHP, MEHHP, MEOHP, MECPP, and their sum), MnBP, MiBP, and MBzP measured in spot urine samples were compared among cases and controls. This study had important limitations. Most importantly, there were apparent errors in the values of some metabolites (e.g., DiNP metabolites, DEHP metabolites) that were reported: values for individual metabolites vs. the sum of metabolites were not concordant. For example, values for the two DiNP metabolites reported to differ significantly in cases vs controls were implausible given that values for the sum of DiNP were roughly equivalent. Reported means (ug/g creatinine) in controls vs cases were: MHiNP (15.45 vs 2.18), MCiOP (86.77 vs 8.00) and sum DiNP (221.21 vs 220.81). The authors did not specify how values below LOD were handled, an issue for MiNP (detected in 7 of 22 cases). Additional concerns include the lack of information of the timing of diagnosis vs. recruitment into the study and urine collection, the lack of adjustments for confounding by age or BMI in within-case analyses relating phthalates to outcomes such as sex hormones, and failure to describe the methods used to assess physical markers of reproductive development such as ovarian volumes. Uncertainty regarding these issues make findings of this study uninformative.

Overall Quality Determination — Medium

Study Citation:	Durmaz, E., Erkekoglu, P., Asci, A., Akçurin, S., Bircan, I., Kocer-Gumusel, B. (2018). Urinary phthalate metabolite concentrations in girls with premature thelarche. Environmental Toxicology and Pharmacology 59:172-181.
Health Outcome(s) Assessed:	Reproductive/Developmental- Premature thelarche (isolated breast development in girls aged 4-8 years), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5512126

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	Case-control study conducted in Antalya City, Turkey. Cases (N= 29) were girls who met the following criteria: premature thelarche (PT) was observed as isolated breast development before the age of 8 years; aged 4–8 years; not obese (BMI <95th percentile of national referent); bone age did not exceed one year above their chronological age; followed up regularly by a pediatrician for at least one year without other progression of precocious puberty (PP) besides isolated breast development. Girls with pathological conditions such as ovarian cysts (other conditions not named) identified by ultrasound were excluded. A gonadotropin releasing hormone (GnRH) stimulation test was performed to exclude girls with a diagnosis of central precocious puberty (PP) rather than PT. Controls (n=25), were healthy non-obese girls also living in Antalya City, aged 4-8 years, with no history of PT or any other endocrine disorder and no secondary sexual characteristics in their physical exam. All study subjects were examined by the same clinical pediatrician. The control group was re-monitored 12 months later "in order to evaluate their pubertal development and girls who had PT, premature pubarche, PP or any other pubertal signs in this second evaluation were excluded. " Recruitment strategies used to identify prospective participants, participation rates, and any attrition were not described. However, there was no evidence of selectivity.
Domain 2: Exposure Characterization			

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Health Outcome(s) Assessed:	Reproductive/Developmental- Premature thelarche (isolated breast development in girls aged 4-8 years), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5512126

Domain	Metric	Rating	Comments
	Metric 2A: Exposure Measurement	Low	There were issues in each of three domains of exposure assessment. Together, these issues affect certainty regarding the validity of study results. 1-Sample collection and analysis: Spot urine samples were collected between 2010 and 2012; the authors did not explicitly state whether a single sample (which may misclassify habitual exposure given the short half-life) was collected per subject. Given the case control design, samples were collected after diagnosis: timing relative to diagnosis was not specified, though there was nothing to suggest systematic post-diagnosis behavior changes that would affect exposure to phthalates. Phthalate metabolites were analyzed by isotope dilution liquid chromatography with tandem mass spectrometry (LC–MS/MS) with standards and protocols to avoid contamination. Recovery rates exceeded 90%. Urinary creatinine was used to account for dilution. 2-Detection rate reporting issues. LODs (ng/mL) were: MiNP 0.61, MHiNP 0.26, MoiNP 0.25, MCiOP 0.53, MEHP 0.14, MEOHP 0.67, MECPP 0.55, MEHHP 0.91, MiBP 1.43, MnBP 1.1, MBzP 1.14. Detection rates reported in Table 1 were MiNP 24.1%, MHiNP 93.1%, MoiNP 82.8%, MCiOP 100%, MEHP 100%, MEOHP 100% MECPP 100%, MEHHP 100%, MiBP 100%, MnBP 100%, MBzP 79.3%. Handling of samples below detection was not specified. However, for MiNP, the metabolite with a substantial proportion below LOD, the minimum value was 0.00, suggested imputation as zeros vs. accepted approaches such as half the LOD. In addition, the proportions (Table 1) vs. numbers (Table 2) of samples below detection were not concordant. For example, for DiNP metabolites the proportion vs Ns reported as detectable were: (i) MiNP 24.1% of samples vs. 10/25 controls and 7 of 22 cases [i.e., 31.5% of the population]; (ii) MoiNP 0.25 82.8% vs. 25/25 controls and 24/29 cases [90.7%]; and (iii) MCiOP 100% vs. 23/25 controls and 29/29 cases [96.2%]. 3-Mean values reported with errors: The means for some metabolites were apparently reported with errors, based on the disparity between values for individual metabolites and the sum of DiNP. For example, the means (ug/g creatinine) for individual DiNP metabolites (MiNP, MHiNP, MOiNP, MCiOP) vs. the sum of metabolites (sum DiNP) were as follows in cases: 1.94, 40.02, 15.45, 86.77 vs. 287.30; and in controls 0.51, 4.97, 2.18, 8.00 vs. 284.60. The several-fold differences in means for MHiNP (15.45 vs 2.18) and MCiOP (86.77 vs 8.00) – the two metabolites reported to differ significantly in cases vs controls — along with means for MOiNP (40.02 vs 4.97) may have been calculation or conversion errors.

Domain 3: Outcome Assessment

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Study Citation:	Durmaz, E., Erkekoglu, P., Asci, A., Akçurin, S., Bircan, I., Kocer-Gumusel, B. (2018). Urinary phthalate metabolite concentrations in girls with premature thelarche. Environmental Toxicology and Pharmacology 59:172-181.
Health Outcome(s) Assessed:	Reproductive/Developmental- Premature thelarche (isolated breast development in girls aged 4-8 years), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5512126

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	As noted above, cases were healthy non-obese girls who had isolated premature thelarche (PT) diagnosed before the age of 8 years; aged 4–8 years. All had been followed up regularly by a pediatrician for at least one year without other progression of precocious puberty. Cases were also evaluated to preclude precocious puberty due to ovarian cysts and results of a Gonadotropin releasing hormone test (cutoff criteria not specified). Variability in dates and ages of diagnoses prior to study enrollment and urinary sample collection used for phthalates measurement was not described. Any progression or regression in breast development among cases was also not discussed. Controls were healthy non-obese girls aged 4-8 years with no history of PT or any other endocrine disorder and no secondary sexual characteristics in their physical exam. Controls were monitored for 12 months to ensure that they did not develop PT or any other pubertal signs. Attrition and exclusions were not described, so it is uncertain whether the imbalanced N (29 cases, 25 controls) was due to exclusions of controls during this 12-month follow-up.
	Metric 3B:	Selective Reporting	Medium	There was no evidence of selective reporting.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	There was no adjustment for confounding. Distributions of phthalate metabolites were compared in cases and controls. Although there was no formal adjustment or pair matching, the authors reported very similar mean ages and BMI (but not BMI z-scores) among cases and controls. Co-exposure confounding was not evaluated.
Domain 5: Analysis				
	Metric 5A:	Analysis	Low	Exposure distributions were shown among both cases and controls. Arithmetic rather than geometric means were shown for cases and controls, along with medians and ranges. It is unclear whether p-values for case vs. control differences were reported using t-tests or non-parametric Mann-Whitney U tests, and whether these were based on differences in means vs. medians. Most importantly, the distributions reported for individual metabolites vs. the sum of metabolites were non-concordant, perhaps due to a conversion or other calculation error. For example, values reported for the two DiNP metabolites for which there were significant differences between cases and controls were implausibly small among cases, and not concordant with the similar concentrations in cases and controls for the sum of DiNP.
	Metric 5B:	Sensitivity	Medium	Small sample size (N=29 cases, N=25 controls), however some significant associations were observed. There was an adequate range of and variability in metabolite exposures.

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Study Citation:	Durmaz, E., Erkekoglu, P., Asci, A., Akçurin, S., Bircan, I., Kocer-Gumusel, B. (2018). Urinary phthalate metabolite concentrations in girls with premature thelarche. Environmental Toxicology and Pharmacology 59:172-181.
Health Outcome(s) Assessed:	Reproductive/Developmental- Premature thelarche (isolated breast development in girls aged 4-8 years), Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5512126

Domain	Metric	Rating	Comments
Additional Comments:	This case control study in Turkey included 29 non-obese girls aged 4-8 years with premature thelarche (PT; isolated breast development) and 25 non-obese controls residing in the same city. Controls were followed for one year to confirm that they did not develop signs of precocious development. DiNP metabolites (MiNP, MHINP, MOiNP, MCiOP and their sum), DEHP metabolites (MEHP, MEHHP, MEOHP, MECPP, and their sum), MnBP, MiBP, and MBzP measured in spot urine samples were compared among cases and controls. This study had important limitations. Most importantly, there were apparent errors in the values of some metabolites (e.g., DiNP metabolites, DEHP metabolites) that were reported: values for individual metabolites vs. the sum of metabolites were not concordant. For example, values for the two DiNP metabolites reported to differ significantly in cases vs controls were implausible given that values for the sum of DiNP were roughly equivalent. Reported means (ug/g creatinine) in controls vs cases were: MHiNP (15.45 vs 2.18), MCiOP (86.77 vs 8.00) and sum DiNP (221.21 vs 220.81). The authors did not specify how values below LOD were handled, an issue for MiNP (detected in 7 of 22 cases). Additional concerns include the lack of information of the timing of diagnosis vs. recruitment into the study and urine collection, the lack of adjustments for confounding by age or BMI in within-case analyses relating phthalates to outcomes such as sex hormones, and failure to describe the methods used to assess physical markers of reproductive development such as ovarian volumes. Uncertainty regarding these issues make findings of this study uninformative.		

Overall Quality Determination Low

Study Citation:	Durmaz, E., Erkekoglu, P., Asci, A., Akçurin, S., Bircan, I., Kocer-Gumusel, B. (2018). Urinary phthalate metabolite concentrations in girls with premature thelarche. Environmental Toxicology and Pharmacology 59:172-181.
Health Outcome(s) Assessed:	Nutritional/Metabolic- Body weight, BMI, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5512126

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	Case-control study conducted in Antalya City, Turkey. Cases (N= 29) were girls who met the following criteria: premature thelarche (PT) was observed as isolated breast development before the age of 8 years; aged 4–8 years; not obese (BMI <95th percentile of national referent); bone age did not exceed one year above their chronological age; followed up regularly by a pediatrician for at least one year without other progression of precocious puberty (PP) besides isolated breast development. Girls with pathological conditions such as ovarian cysts (other conditions not named) identified by ultrasound were excluded. A gonadotropin releasing hormone (GnRH) stimulation test was performed to exclude girls with a diagnosis of central precocious puberty (PP) rather than PT. Controls (n=25), were healthy non-obese girls also living in Antalya City, aged 4-8 years, with no history of PT or any other endocrine disorder and no secondary sexual characteristics in their physical exam. All study subjects were examined by the same clinical pediatrician. The control group was re-monitored 12 months later "in order to evaluate their pubertal development and girls who had PT, premature pubarche, PP or any other pubertal signs in this second evaluation were excluded. " Recruitment strategies used to identify prospective participants, participation rates, and any attrition were not described. However, there was no evidence of selectivity.
Domain 2: Exposure Characterization			

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Study Citation:	Durmaz, E., Erkekoglu, P., Asci, A., Akçurin, S., Bircan, I., Kocer-Gumusel, B. (2018). Urinary phthalate metabolite concentrations in girls with premature thelarche. Environmental Toxicology and Pharmacology 59:172-181.
Health Outcome(s) Assessed:	Nutritional/Metabolic- Body weight, BMI, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5512126

Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Low	There were issues in each of three domains of exposure assessment. Together, these issues affect certainty regarding the validity of study results. 1-Sample collection and analysis: Spot urine samples were collected between 2010 and 2012; the authors did not explicitly state whether a single sample (which may misclassify habitual exposure given the short half-life) was collected per subject. Given the case control design, samples were collected after diagnosis: timing relative to diagnosis was not specified, though there was nothing to suggest systematic post-diagnosis behavior changes that would affect exposure to phthalates. Phthalate metabolites were analyzed by isotope dilution liquid chromatography with tandem mass spectrometry (LC–MS/MS) with standards and protocols to avoid contamination. Recovery rates exceeded 90%. Urinary creatinine was used to account for dilution. 2-Detection rate reporting issues. LODs (ng/mL) were: MiNP 0.61, MHiNP 0.26, MoiNP 0.25, MCiOP 0.53, MEHP 0.14, MEOHP 0.67, MECPP 0.55, MEHHP 0.91, MiBP 1.43, MnBP 1.1, MBzP 1.14. Detection rates reported in Table 1 were MiNP 24.1%, MHiNP 93.1%, MoiNP 82.8%, MCiOP 100%, MEHP 100%, MEOHP 100% MECPP 100%, MEHHP 100%, MiBP 100%, MnBP 100%, MBzP 79.3%. Handling of samples below detection was not specified. However, for MiNP, the metabolite with a substantial proportion below LOD, the minimum value was 0.00, suggested imputation as zeros vs. accepted approaches such as half the LOD. In addition, the proportions (Table 1) vs. numbers (Table 2) of samples below detection were not concordant. For example, for DiNP metabolites the proportion vs Ns reported as detectable were: (i) MiNP 24.1% of samples vs. 10/25 controls and 7 of 22 cases [i.e., 31.5% of the population]; (ii) MoiNP 0.25 82.8% vs. 25/25 controls and 24/29 cases [90.7%]; and (iii) MCiOP 100% vs. 23/25 controls and 29/29 cases [96.2%]. 3-Mean values reported with errors: The means for some metabolites were apparently reported with errors, based on the disparity between values for individual metabolites and the sum of DiNP. For example, the means (ug/g creatinine) for individual DiNP metabolites (MiNP, MHiNP, MOiNP, MCiOP) vs. the sum of metabolites (sum DiNP) were as follows in cases: 1.94, 40.02, 15.45, 86.77 vs. 287.30; and in controls 0.51, 4.97, 2.18, 8.00 vs. 284.60. The several-fold differences in means for MHiNP (15.45 vs 2.18) and MCiOP (86.77 vs 8.00) – the two metabolites reported to differ significantly in cases vs controls — along with means for MOiNP (40.02 vs 4.97) may have been calculation or conversion errors.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Low	The authors analyzed how phthalates correlated with BMI and weight without accounting for age differences, e.g., by using BMI or weight z-scores standardized for age vs. a referent population. Age at measurement of height and weight, relative to age at diagnosis, was not described. The use of standardized protocols was also not specified.
	Metric 3B:	Selective Reporting	Medium	Correlations between urinary phthalates and both BMI and weight were presented. There was no evidence of selective reporting.

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Study Citation:	Durmaz, E., Erkekoglu, P., Asci, A., Akçurin, S., Bircan, I., Kocer-Gumusel, B. (2018). Urinary phthalate metabolite concentrations in girls with premature thelarche. Environmental Toxicology and Pharmacology 59:172-181.
Health Outcome(s) Assessed:	Nutritional/Metabolic- Body weight, BMI, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	5512126

Domain	Metric	Rating	Comments
Domain 4: Potential Confounding / Variability Control			
	Metric 4A: Potential Confounding	Low	There was no adjustment for confounding in the analysis correlating BMI and weight with urinary phthalates among cases. For BMI and weight, adjustment for age (range 4-8 years) was not incorporated by using standardized z-scores.
Domain 5: Analysis			
	Metric 5A: Analysis	Medium	Correlations between phthalate metabolite levels and both BMI and weight were evaluated appropriately using Spearman correlation coefficients; coefficients and p-values were shown. A p value of < 0.05 was accepted as significant. Multivariate analysis of associations with BMI and weight among cases were not described as an aim.
	Metric 5B: Sensitivity	Medium	Small sample size for evaluating correlations among cases (N=29), however some strong and significant correlations were observed. There was an adequate range of and variability in metabolite exposures.

Additional Comments: This case control study in Turkey included 29 non-obese girls aged 4-8 years with premature thelarche (PT; isolated breast development) and 25 non-obese controls residing in the same city. Controls were followed for one year to confirm that they did not develop signs of precocious development. DiNP metabolites (MiNP, MHINP, MOiNP, MCiOP and their sum), DEHP metabolites (MEHP, MEHHP, MEOHP, MECPP, and their sum), MnBP, MiBP, and MBzP measured in spot urine samples were compared among cases and controls. This study had important limitations. Most importantly, there were apparent errors in the values of some metabolites (e.g., DiNP metabolites, DEHP metabolites) that were reported: values for individual metabolites vs. the sum of metabolites were not concordant. For example, values for the two DiNP metabolites reported to differ significantly in cases vs controls were implausible given that values for the sum of DiNP were roughly equivalent. Reported means (ug/g creatinine) in controls vs cases were: MHiNP (15.45 vs 2.18), MCiOP (86.77 vs 8.00) and sum DiNP (221.21 vs 220.81). The authors did not specify how values below LOD were handled, an issue for MiNP (detected in 7 of 22 cases). Additional concerns include the lack of information of the timing of diagnosis vs. recruitment into the study and urine collection, the lack of adjustments for confounding by age or BMI in within-case analyses relating phthalates to outcomes such as sex hormones, and failure to describe the methods used to assess physical markers of reproductive development such as ovarian volumes. Uncertainty regarding these issues make findings of this study uninformative.

Overall Quality Determination — Low

Study Citation:	Dzwilewski, C., K.L., Woodbury, M. L., Aguiar, A., Shoaff, J., Merced-Nieves, F., Korrick, S. A., Schantz, S. L. (2021). Associations of prenatal exposure to phthalates with measures of cognition in 7.5-month-old infants. NeuroToxicology 84:84-95.
Health Outcome(s) Assessed:	Neurological/Behavioral- Cognition at 7-8 months as assessed by information processing speed (average run duration during familiarization trial), visual attention (time to reach familiarization criterion during familiarization trial), and visual recognition memory (novelty preference in test trial) using eye tracking within a paired comparison visual recognition memory (VRM) test., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	7978460

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Participants were a subset of pregnant women enrolled in the Illinois Kids Development Study (IKIDS) from two obstetric clinics in the Champaign-Urbana, IL area between December 2013 and August 2018. IKIDS enrolled pregnant women aged 18 and 40 years at enrollment, with singleton non-high-risk pregnancies, fluent in English, residing within a 30-minute drive of the University of Illinois at Urbana-Champaign campus. The analysis sample included 244 of 558 women enrolled: 481 (86%) had urinary phthalates data, of which 328 (68%) participated in the cognitive assessment at 7-8 months and had useable data (e.g., not too fussy or sleepy), and 244 of these (74.3%) had complete covariate data. Demographic data presented indicated that the subset was similar to the parent cohort. There was no evidence of selectivity.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Phthalates were measured via appropriate metabolites in a pooled urine sample from each mother. The sample combined aliquots of multiple first morning urines collected at about 10–14, 16–18, 22–24, 28–30, and 34–36 weeks of gestation. Pooling reduced concern for misclassification due to exposure variability and the short half-life of these metabolites. The number of samples per participant was not provided, however analysis was restricted to those infants completing all five faces trials and no missing covariate data for analyses of [sum (DEHP) and sum (DINP2), n=244] and analyses of exposure measures including MONP [sum (DINP3) and MONP, n=142]. Urinary specific gravity was used to account for differences in dilution. Phthalate metabolites were measured at the Centers for Disease Control using online solid phase extraction-high performance liquid chromatography-isotope dilution tandem mass spectrometry. Values below detection limits were imputed using machine readings. Proportions below detection were not shown; the minimum 0 for MINP and MEHP suggests some samples of this metabolite were below LOD. Where metabolite concentrations were below the limit of detection, instrument readings provided by the CDC were used in data analysis. Because urine was sent to the CDC laboratory in batches and new methods for phthalate metabolite measurement were developed between batches, MONP measures were available only for 58 % of the infants. Concern of potential bias associated with this change was mitigated by the transparent approach of analyzing DINP exposure as the molar sum of either two or three metabolites (DINP2, n=244; DINP3, n=142), as well as analyzing associations with MONP individually. This enabled comparison of associations with and without MONP. Exposure variables also included weighted molar sums of anti-androgenic metabolites, which included DINP metabolites. Distributions of phthalates for the subset of infants included vs excluded from this study were compared and were similar. There was no evidence of bias.

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Study Citation:	Dzwilewski, C., K.L., Woodbury, M. L., Aguiar, A., Shoaff, J., Merced-Nieves, F., Korrick, S. A., Schantz, S. L. (2021). Associations of prenatal exposure to phthalates with measures of cognition in 7.5-month-old infants. NeuroToxicology 84:84-95.
Health Outcome(s) Assessed:	Neurological/Behavioral- Cognition at 7-8 months as assessed by information processing speed (average run duration during familiarization trial), visual attention (time to reach familiarization criterion during familiarization trial), and visual recognition memory (novelty preference in test trial) using eye tracking within a paired comparison visual recognition memory (VRM) test., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	7978460

Domain	Metric		Rating	Comments
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Infant cognition was assessed at 7-8 months using a visual recognition memory (VRM) paradigm modified from prior studies (Rose et al., 1992 PMID 1446544). Outcomes were based on the duration or proportion of time infants spent looking at sets of images of faces, using automated measurement of eye movements (EyeLink 1000 Plus infrared eye tracker). The test comprised a familiarization trial (two identical photos presented side by side) followed by test phases (familiar image paired with a novel photo on either the left or right). Results were used to assess three cognitive domains: (i) information processing speed (run duration during familiarization trial); (ii) visual attention (time to familiarization); and (iii) visual recognition memory (novelty preference or attention time in test trial). The protocol was administered seated in a caregiver's lap in a booth with black curtains, with caregivers instructed to remain neutral and direct their gaze downward. Measures from the original protocol were variably predictive of subsequent IQ (e.g. Rose et al., PMIDs 12760523, 9306643 and 1446544). Infants were randomized to different image sets and sequencing. However, performance varied by testing set (Dzwilewski et al., 2020, PMID 32485220). Validity was not discussed. Information processing (run duration) and visual attention (time to familiarization) were correlated (Pearson's r = -0.49), but visual recognition memory (novelty preference) was not correlated with either outcome (r = 0.01 and -0.04). There were no clear associations between demographic factors or other potential predictors of cognitive development with outcome measures (in supplement not available at time of assessment). The sensitivity and specificity of outcomes measures within this study is uncertain. However, there was no evidence of bias, and caregivers were asked to remain neutral throughout testing and to direct their gaze downward so as not to affect the infant's behavior.
	Metric 3B:	Selective Reporting	Medium	Results were presented for all analyses described in the methods section. Additional results are included in a supplement with sex-stratified sensitivity analyses results for the entire cohort (n=244) and the subset (n=142) with additional MONP measures (and sum(DINP3) which included MONP).
Domain 4: Potential Confounding / Variability Control				

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Study Citation:	Dzwilewski, C., K.L., Woodbury, M. L., Aguiar, A., Shoaff, J., Merced-Nieves, F., Korrick, S. A., Schantz, S. L. (2021). Associations of prenatal exposure to phthalates with measures of cognition in 7.5-month-old infants. NeuroToxicology 84:84-95.
Health Outcome(s) Assessed:	Neurological/Behavioral- Cognition at 7-8 months as assessed by information processing speed (average run duration during familiarization trial), visual attention (time to reach familiarization criterion during familiarization trial), and visual recognition memory (novelty preference in test trial) using eye tracking within a paired comparison visual recognition memory (VRM) test., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	7978460

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	Medium	Potential confounders were identified based on a priori knowledge and using directed acyclic graphs (DAGs). Parental sociodemographic covariates were obtained from interviews held before or after birth. Models adjusted for maternal age, race/ethnicity (white, non-Hispanic vs. other), education (<bachelor's degree vs, bachelor's degree or higher), parity (nulliparous vs. $\geq$ 1), annual household income (<$50,000, $50,000-$99,999, $\geq$$100,000), and verbal IQ (VIQ), as well as infant sex, gestational age at birth, postnatal age at assessment, and test protocol stimulus set. Maternal smoking and alcohol intake during pregnancy were evaluated in a sensitivity analysis excluding participants with those behaviors. The authors did not discuss evaluating gestational age at birth as a potential intermediate. Co-exposure confounding was not discussed. However, there was no evidence of important residual confounding bias.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Descriptive data for the study sample as a whole were presented for exposure and outcome variables. Stratified descriptive data were not presented, and unadjusted or minimally adjusted associations were not shown. Multivariable generalized linear regression was shown to assess associations between each phthalate exposure variable and each outcome. The authors reported that unspecified regression diagnostics "generally supported" the use of continuous, untransformed biomarker measures and linear models, despite the right skewed exposure variables. Associations were presented per interquartile range increase in exposure. Models including both two-way interactions and a three-way sex-by-stimulus set-by exposure interaction were explored for every exposure-outcomerelationship. Interaction terms with p-values 0.10 were then considered as part of final model specification. Sensitivity analyses evaluated the impact of excluding influential data points identified by Cook's D values and included analyses adjusting for maternal alcohol intake, removing mothers who smoked, or removing potential high leverage observations from the analysis. Because analyses were hypothesis based, the authors did not adjust for multiple comparisons. Although the adequacy of using linear models with untransformed exposures to estimate associations is uncertain, there was no evidence that analyses were inappropriate.
	Metric 5B:	Sensitivity	Medium	There was variability in exposure and outcome variables. For ΣDINP2, for example, the median (IQR) was 0.0388 (0.0543) uumol/L. The sample size was moderate (n = 244), which may have limited statistical power particularly for sex-stratified analyses and to detect significant interactions (p<0.10 used). Sample sizes for analyses of Σ DINP3 and MONP (n=142) were less than optimal for analyses involving sex- and set-specific interaction assessment.

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Study Citation:	Dzwilewski, C., K.L., Woodbury, M. L., Aguiar, A., Shoaff, J., Merced-Nieves, F., Korrick, S. A., Schantz, S. L. (2021). Associations of prenatal exposure to phthalates with measures of cognition in 7.5-month-old infants. NeuroToxicology 84:84-95.
Health Outcome(s) Assessed:	Neurological/Behavioral- Cognition at 7-8 months as assessed by information processing speed (average run duration during familiarization trial), visual attention (time to reach familiarization criterion during familiarization trial), and visual recognition memory (novelty preference in test trial) using eye tracking within a paired comparison visual recognition memory (VRM) test., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	7978460

Domain	Metric	Rating	Comments
Additional Comments:	This study used data from a subset of 244 participants in the Illinois Kids Development Study (IKIDS) to explore associations between prenatal exposure to phthalates, including DINP, and infant cognition assessed at 7-8 months of age. Evaluating cognition in infancy is challenging. The study used a "visual recognition memory" testing protocol to assess three cognitive domains: information processing speed ('run duration'), visual attention ('time to familiarization'), and visual recognition memory ('novelty preference'), based on the duration or proportion of time infants spent looking at sets of familiar vs. novel images. Gaze was tracked and measured using an automated eye tracking system. Two DINP metabolites (MINP and MCOP) were available for the full sample. A third (MONP) became available during the study because of improvements in analytic methods and was available for 142 infants. The authors presented results of analyses using the sum of 2 (DINP2) or 3 (DINP3) metabolites, and MONP individually. Associations varied by infant sex and by the set of images used in testing. DINP2 was associated with longer processing time for image set 2, and DINP3 with longer processing time among males viewing set 2. DINP2 and DINP3 had weak negative associations with visual recognition memory (novelty preference). A strength of the study was the use of pooled aliquots from multiple maternal urine samples throughout pregnancy to estimate prenatal phthalates exposure. Sample size is a potential limitation, as the study may have had limited power to detect interactions. Specificity and sensitivity of outcome measures is uncertain and reasons for variable performance by image testing set were unclear. However, previous literature in other populations suggests these measures may predict later cognition.		

Overall Quality Determination Medium

Study Citation:	Jøhnk, C., Høst, A., Husby, S., Schoeters, G., Timmermann, G., C.A., Kyhl, H. B., Beck, I. H., Andersson, A. M., Frederiksen, H., Jensen, T. K. (2020). Maternal phthalate exposure and asthma, rhinitis and eczema in 552 children aged 5 years; a prospective cohort study. Environmental Health 19(1):32.
Health Outcome(s) Assessed:	Lung/Respiratory- Asthma, Rhinitis, Wheeze, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	7975862

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	Key elements of study design were reported within this large, population-based prospective study of prenatal third trimester urinary phthalate metabolites and age 5 offspring wheeze, self-reported and doctor diagnosed asthma and eczema, and self-reported rhinitis. All newly pregnant (gestational age (GA) 10-16 weeks) women residing in Odense 2010-2012 were invited to participate in the Odense Child Cohort (OCC) at Odense University Hospital. A total of 870 pregnant women at approximately GA 28 weeks provided a urine sample, and urine from 846 women was measured for phthalate metabolites, with reasons for the lack of urine from all 870 women not specified. A total of 1,316 parents of singleton children answered questions regarding asthma at age 5 years, and 552 mother-child pairs with phthalate metabolite measurements and information regarding asthma, eczema and rhinitis were available for inclusion. The participation rate in the OCC was 43% and participating mothers were older and more often non-smokers compared to not participating mothers. The prevalence of asthma in the current study (7.4%) was lower than the general population (12%). Authors indicated that participants did not differ in other characteristics from the rest of the OCC, however with a participation rate of 43% in the OCC it is unclear what characteristics in OCC and current study participants were compared and whether OCC non-participants might have differed from current study participants in demographic or other characteristics possibly related to exposure or the lower prevalence of asthma in the current study.
Domain 2: Exposure Characterization			

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Study Citation:	Jøhnk, C., Høst, A., Husby, S., Schoeters, G., Timmermann, G., C.A., Kyhl, H. B., Beck, I. H., Andersson, A. M., Frederiksen, H., Jensen, T. K. (2020). Maternal phthalate exposure and asthma, rhinitis and eczema in 552 children aged 5 years; a prospective cohort study. Environmental Health 19(1):32.
Health Outcome(s) Assessed:	Lung/Respiratory- Asthma, Rhinitis, Wheeze, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-isononyl phthalate (MiNP); Mono-oxo-isononyl phthalate (oxo-MiNP); Mono-hydroxy-isononyl phthalate (OH-MiNP); Mono-carboxy-isooctyl phthalate (MCOP)
HERO ID:	7975862

Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Medium	Methods used to quantify exposure to 12 prenatal third trimester urinary phthalate metabolites were well defined. Fasting spot urine samples from 552 participants were analyzed. Quantification of urinary phthalate metabolites was performed utilizing methods described within referenced sources (Frederiksen et al., 2010, HERO ID 697294) as isotope dilution liquid chromatography tandem mass spectrometry. Limits of detection (LOD) and percent greater than the LOD was reported. Percent detected for relevant DiNP metabolites were 11.6% (mono-iso-nonyl phthalate (MiNP)), 83.3% (mono-oxo-iso-nonyl phthalate (MOiNP)), 91.1% (mono-hydroxy-iso-nonyl phthalate (MHiNP)), and 100.0% (mono-carboxy-iso-octyl phthalate (MCiOP)), and 99.6% for mono-iso-butyl phthalate (MiBP), 95.3% for mono-n butyl phthalate (MnBP), 67.9% for mono-benzyl phthalate (MBzP), 90.2% for mono-2-ethylhexyl phthalate (MEHP), 89.3% for mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), 91.5% for mono-2-ethyl-5-oxohexyl phthalate (MEOHP), and 96.9% for mono-2-ethyl-5-carboxypentylphthalate (MECPP). Urinary phthalate concentrations below the LOD were replaced by LOD divided by the square root of 2 for statistical analysis. Phthalate concentrations above the LOD were osmolality adjusted. Given the short half-life of phthalates, it is unclear if a single spot urine measure adequately represents the intensity, frequency and potential peak exposures responsible for initiation and development of outcomes of interest.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Outcomes were assessed using a Danish modified version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was administered at the 5 years exam. Asthma outcomes were wheeze within the last 2 years, self-reported asthma, doctor diagnosed asthma and use of medicine to treat asthma/cold within the last 12 months. Self-reported asthma was defined as at least 3 episodes of wheeze (each lasting more than a day) within the last year. Self-reported eczema was defined as itchy symmetric eczema in the flexural folds behind the knees (possibly intermittent) within the last 6 months, while doctor-diagnosed and use of prescribed medicine included all five life years for eczema. Self-reported and doctor-diagnosed rhinitis were defined as problems with recurrent sneezing and/or runny nose without having a cold or flu and ever doctor diagnosed with hay fever. Doctor-diagnosed outcomes were all parental report of doctor diagnosis. Due to a low prevalence (1.3%) of doctor-diagnosed rhinitis, this outcome was not included for analysis. Outcomes used in final analysis were: wheeze (within the last 2 years), asthma (self-reported, doctor diagnosed, and use of medicine for asthma/cold), eczema (self-reported, doctor- diagnosed, and use of medicine for eczema) and rhinitis (self-reported). There is uncertainty as allergic disease (rhinitis, eczema) was defined by parental report of medical diagnosis/treatment and doctor prescribed medications were not defined. Information regarding age 5 rhinitis did not include parental report of doctor diagnosis and questionnaire responses for this outcome may have been less accurate than doctor diagnosis as few parents reported allergic symptoms, and few children at age 5 would be able to recall such instances of outcomes.

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HERO ID:	7975862

Domain	Metric		Rating	Comments
	Metric 3B:	Selective Reporting	Medium	There were no concerns for selective reporting.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Final models were adjusted for maternal age, maternal education, parity and family history of asthma/allergy. Information on maternal pre-pregnancy body mass index (BMI), maternal education, and maternal smoking during pregnancy was obtained through questionnaires during pregnancy. Data on birth characteristics, maternal age, parity at inclusion and gestational age was obtained from hospital records. Information on breast-feeding, smoking, pets and family history of asthma and allergy was obtained from questionnaires during the first 5 years of life. Strategy for consideration for potential confounding factors included use of directed acyclic graphs based on existing literature and a priori expectations (maternal age, educational level, parity and having a parent or sibling with allergy). Child sex was conceptualized and evaluated as an effect measure modifier. Missing data regarding confounding factors was minimal (less than 5 individuals for education and family history of asthma/allergy) and distribution of median urinary phthalate parent compounds was presented across categories of confounding factors. Although in utero exposure to maternal smoking is a well-known risk factor for development of asthma, eczema and rhinitis, smoking was not included in final models as only 3 % of mothers reported smoking during pregnancy. However, there is some uncertainty in the potential for lack of admission of smoking during pregnancy. There is additional uncertainty as other potential confounders such as season of outcome measurement and relevant co-exposures, as well as postnatal phthalate exposures were not addressed.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Logistic regression was used to examine the associations between natural log transformed urinary phthalate metabolite concentrations and outcomes of interest with results presented as adjusted odds ratios (ORs) with 95% confidence intervals. All four DiNP metabolites were summed for analysis, as were all four DEHP metabolites. MiBP and MnBP were summed for analysis. MBzP was apparently not included in analysis; reasons not stated but could plausibly be due to a lower detection rate than most other phthalate metabolites. Sensitivity analyses were not detailed. Examination of model fit, heteroscedasticity, and influence were not detailed. An interaction term of sex and phthalate metabolite was initially modeled but subsequently not utilized within final models due to non-significance of the interaction term.

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HERO ID:	7975862

Domain	Metric	Rating	Comments
	Metric 5B: Sensitivity	Medium	The analytic sample size was relatively large (n=552 mother-child pairs) and a wide variation of urinary phthalate concentrations was detected. Percent greater than the LOD was between 83.3 and 100.0 for MOiNP, MHiNP, MCiOP, however MiNP was detected in 11.6% of samples. Concerns over the low detection percentage for MiNP are mitigated as all four DiNP metabolites were summed prior to analysis. Percent greater than the LOD was between 67.9% (MBzP) and 99.6% (MiBP) for all other phthalate metabolites; MBzP was apparently not included in analysis. There is uncertainty in the lack of validation of parental report of outcomes, as well as the accuracy of recall for symptoms over the years and the use of a single spot urine for analysis of phthalate exposures in adequately representing the intensity, frequency and potential peak exposures responsible for initiation and development of outcomes of interest.

Additional Comments: This was a large, population-based prospective study of prenatal third trimester urinary phthalate metabolites in women of the Odense Child Cohort (OCC) and age 5 offspring wheeze, self-reported and doctor diagnosed asthma and eczema, and self-reported rhinitis. The prevalence of asthma in the current study (7.4%) was lower than the general population (12%). Although in utero exposure to maternal smoking is a well-known risk factor for development of asthma, eczema and rhinitis, smoking was not included in final models as only 3% of mothers reported smoking during pregnancy. There is some uncertainty in the potential for lack of admission of smoking during pregnancy. There is additional uncertainty as potential confounders such as season of outcome measurement and relevant co-exposures, as well as postnatal phthalate exposures were not addressed. Given the short half-life of phthalates, it is unclear if a single spot urine measure adequately represents the intensity, frequency and potential peak exposures responsible for initiation and development of outcomes of interest. The authors reported no significant associations between prenatal phthalate exposure and asthma, rhinitis and wheeze.

Overall Quality Determination Medium

Study Citation:	Tanner, E. M., Hallerbäck, M. U., Wikström, S., Lindh, C., Kiviranta, H., Gennings, C., Bornehag, C. G. (2020). Early prenatal exposure to suspected endocrine disruptor mixtures is associated with lower IQ at age seven. Environment International 134:105185.
Health Outcome(s) Assessed:	Neurological/Behavioral- full scale IQ, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-oxo-isononyl phthalate (oxo-MiNP)
HERO ID:	5933606

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	High	The association of prenatal urinary DiDP (MHiDP, MCNP), DiNP (MHiNP, MOiNP, MCiOP), DBP (MBP), BBP (MBzP), and DEHP (MEHP, MEHHP, MEOHP, MECPP) metabolites and child full scale IQ at age 7 was assessed in this cohort study of mother-child pairs (n = 718) from the Swedish Environmental Longitudinal Mother and Child, Asthma and Allergy (SELMA) study. 2300 pregnant women were recruited for the study from November 2007 - March 2010 in prenatal clinics in Varmland county during the first trimester. Families were invited to participate in child cognitive functioning studies consecutively based on child age. 943 were assessed, but full data were only available for 718 children. Inverse probability weights were used to incorporate baseline characteristics (child sex, maternal age, education, and smoking) with significant differences between the recruited population (n=943) and the study population. Concern for selection bias is minimal.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	MBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, MHiDP, MCNP, MHiNP, MOiNP, and MCiOP were assessed in first morning void urine samples from pregnant women during the first prenatal clinic visit (median = 10 weeks gestation). Samples were analyzed via LC-MS/MS and creatinine (measured enzymatically) was used to adjust for urine dilution. Limits of detection are reported (MBP: 0.100 ng/mL; MBzP: 0.04 ng/mL; MEHP: 0.100 ng/mL; MEHHP: 0.02 ng/mL; MEOHP: 0.03 ng/mL; MECPP: 0.02 ng/mL; MHiDP and MCNP: 0.031 ng/mL, MHiNP: 0.020 ng/mL, MOiNP: 0.010 ng/mL, MCiOP: 0.020 ng/mL) and 100% of metabolite samples were >LOD. DiNP was calculated as the molar sum of 3 metabolites (MHiNP, MOiNP, and MCiOP) and DEHP was calculated as the molar sum of 4 metabolites (MEHP, MEHHP, MEOHP, MECPP).Urinary measure during pregnancy is the etiologically window to measure exposure. However, the use of single measurements for chemicals with short half-lives to represent exposure during pregnancy may lead to misclassification. Impacts expected to be minor.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Trained psychologists evaluated full scale IQ in children at age 7 using the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV). Scores were indexed to have a mean of 100 and SD of 15. There is no discussion of validation in the study population, but the WISC-IV is a well-established tool to assess cognitive function.
	Metric 3B:	Selective Reporting	Medium	All anticipated results are reported from primary and secondary analyses.
Domain 4: Potential Confounding / Variability Control				

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Health Outcome(s) Assessed:	Neurological/Behavioral- full scale IQ, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-oxo-isononyl phthalate (oxo-MiNP)
HERO ID:	5933606

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	Medium	Covariates were selected for inclusion through examination of the literature and bivariate associations with study data. Child sex and the maternal characteristics (parity, age, weight, education, IQ (RAVEN), and smoking) were included as confounders in final models. Maternal fish consumption and breast feeding were also considered as confounders. Additionally, child sex, maternal age, maternal education, maternal smoking, and prenatal creatinine-corrected MEP and MBzP, trans-nonachlor, and PCBs were included via inverse probability weights to adjust for potential selection bias. These variables were summarized in a directed acyclic graph. Analyses were also stratified by child sex. Information on potential confounders was collected from mothers during visits via questionnaire. Subsequent information was collected via follow-up questionnaires (i.e., information on breast feeding). Gestational age, birth weight, and maternal weight data were obtained from the Swedish Medical birth register.
Domain 5: Analysis				
	Metric 5A:	Analysis	High	Weighted quantile sum (WQS) regression was used to examine the association between exposure to mixtures of EDC chemicals (natural log-transformed), including the phthalate metabolites of interest, and child full scale IQ. For these regressions, a WQS index (of all chemicals) is included in a multivariable linear model to assess the effects on the outcome. Effect estimates and 95% CI are reported from WQS regression. Construction of the WQS used negative weights from 100 bootstrap samples for each chemical, anchored by an assumption that IQ would decrease with increasing exposure. Chemicals with weights >3.8% were considered chemicals of concern. Authors deemed this an explanatory approach.A repeated holdout validation was conducted to simulate a distribution of validated results from the underlying population. The resulting mean estimate is reported along with the range of values representing the uncertainty in a weight uncertainty plot.Additional sensitivity analyses were conducted with the population stratified by child sex, with the addition of covariates (maternal fish consumption, breastfeeding). The WQS regression was conducted with 40% of the data to assess the origin of differences between the explanatory approach and repeated holdout validation. Additional analyses were conducted without the highest weight chemical and with an assumption of a positive association between exposure and outcome (i.e., using positive weights instead of negative).Analyses were conducted on individuals with complete data; thus, treatment of missing values was not necessary.
	Metric 5B:	Sensitivity	Low	Study had adequate sample size (n = 718 mother-child pairs) and exposure distribution to detect an effect. Importantly, the study analyzes the effect of EDC mixtures on child cognitive functioning (IQ). As a result, single chemical effects cannot be gleaned from the findings.

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Health Outcome(s) Assessed:	Neurological/Behavioral- full scale IQ, Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-oxo-isononyl phthalate (oxo-MiNP)
HERO ID:	5933606

Domain	Metric	Rating	Comments
Additional Comments:	This cohort study examined mother-child pairs (n=718) from the SELMA study and the association between prenatal urinary phthalate exposure (MBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, MHiDP, MCNP, MHiNP, MOiNP, MCiOP) and child IQ at age 7. The study used a robust analysis and appropriate recruiting, outcome, and exposure assessment methods. However, the results are reported for mixtures of EDCs only, limiting the study's sensitivity to determine single-pollutant effects. DEHP (calculated as the molar sum of MEHP, MEHHP, MEOHP, and MECPP), DiNP (calculated as the molar sum of MHiNP, MOiNP, and MCiOP), MBP, MHiDP, and MCiNP were below the threshold of concern, however, in some analyses with positive weights, DiNP was above the threshold. MBzP was above the threshold of concern in the full sample explanatory approach (weight: 6%).		

Overall Quality Determination Medium

Study Citation:	Zettergren, A., Andersson, N., Larsson, K., Kull, I., Melen, E., Georgelis, A., Berglund, M., Lindh, C., Bergstrom, A. (2021). Exposure to environmental phthalates during preschool age and obesity from childhood to young adulthood. Environmental Research 192:10249-10249.
Health Outcome(s) Assessed:	Nutritional/Metabolic- Obesity: overweight/obesity, body mass index (BMI), waist circumference (WC), body fat %, and trunk fat %., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-oxo-isononyl phthalate (oxo-MiNP)
HERO ID:	7978414

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Participants in this longitudinal study are a sub-sample of the Swedish birth cohort, BAMSE (Swedish abbreviation for Children, Allergy, Milieu, Stockholm, Epidemiology) which enrolled 4,089 participants born in Stockholm in 1994-1996. Follow-up occurred at 2 months, and at 1, 4, 8, 12, 16, and 24 years of age. This analysis includes a sub-sample of 100 participants selected for a time trend analysis of preschool phthalates exposure. Eligible BAMSE participants had questionnaires at baseline, 4 and 16 years, and urine samples at age 4y (n=720); selection for urine sampling at age 4 was based on allergy prevalence (n=933, 684 with symptoms). The sub-sample of 50 girls and 50 boys was selected to have an equal number of each sex with/without symptoms. The sample was similar to the parent cohort in terms of parental occupation, breastfeeding duration, and maternal smoking in pregnancy. Attrition was modest (n=100 at 4 and 16y, n=91 at 8y, n=71 at 24y). There was no evidence of biased selection (i.e., associated with both phthalates and obesity). The authors stated there was no significant difference in phthalate concentrations for participants with vs without allergy symptoms (data not shown). The authors did not discuss whether there was an association between allergy prevalence and obesity measures within the sub-sample, as observed in some childhood studies.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	DiNP metabolites mono(hydroxy-isononyl) phthalate (MHiNP), mono(oxo-isononyl) phthalate (MOiNP) and mono(carboxy-isooctyl) phthalate (MCiOP) were measured in a single urine sample collected at age 4 years. The molar sum of the three metabolites was used as a measure of DiNP; this measure was converted back to ng/ml multiplying by the average molar mass of each metabolite. Liquid chromatography tandem mass spectrometry (LC-MS/MS) was used to analyze the samples. The laboratory conducting analyses participates in a European QA/QC and is certified as qualified for analysis of these phthalate metabolites. The authors stated that 100% of samples were above detection limits. Specific gravity was used to correct for urine dilution. The authors acknowledged that due to high within-person variability and short half-lives, use of a single spot urine sample collected at random times of day may to some extent misclassify habitual DiNP exposure. However, there was no evidence of differential misclassification.
Domain 3: Outcome Assessment				

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Health Outcome(s) Assessed:	Nutritional/Metabolic- Obesity: overweight/obesity, body mass index (BMI), waist circumference (WC), body fat %, and trunk fat %., Non-cancer
Chemical:	Diisononyl Phthalate- Metabolite: Mono-oxo-isononyl phthalate (oxo-MiNP)
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Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Outcomes of overweight/obesity at ages 4-24 and body mass index (BMI), waist circumference (WC), body fat % and trunk fat % at age 24 years were assessed for analysis with age 4 urinary phthalate metabolite concentrations. Overweight/ obesity ages 4-24 based on BMI was assessed using repeated measures over time; at age 24 y additional measures were obtained. Height and weight measures were obtained at ages 4, 8, 16, and 24. The International Obesity Task Force (childhood) and WHO standards (age 24y) were used to classify participants as overweight and obese. Height was measured to the nearest 0.1 cm, and weight to the nearest 0.1 kg. At age 24y, waist circumference was measured (nearest 0.1cm) and body fat percentages (total and trunk fat) were estimated using bioelectrical impedance analysis (BIA, Tanita MC-708 MA P). The use of multiple. longitudinal BMI measures, and of more direct measures of body fat amounts and distribution at age 24y, are an important strength. However, BIA based estimates of body fat are not a gold standard; estimates are based on prediction equations that may have substantial error.
	Metric 3B:	Selective Reporting	Medium	The authors presented all analyses reported in the methods and results sections adequately.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Covariates were identified based on previous literature. Models exploring the association between phthalate metabolite levels at age 4 years with repeated measures of BMI category outcomes of overweight/obesity versus thin/normal were adjusted for gender, baseline parental socioeconomic status (SES) based on parental education and occupation, maternal smoking during pregnancy, exclusive breastfeeding duration, total energy intake at 8 years, participation in organized physical activity at 8, 16 and 24 years, puberty stage at 16 years, smoking at 16 and 24 years and urinary cotinine. Associations between urinary phthalate concentrations and BMI, WC, body fat % and trunk fat % at age 24 years were adjusted for gender, parental socioeconomic status, maternal smoking during pregnancy, duration of exclusive breastfeeding, physical activity and smoking at age 24 years and urinary cotinine. Information on potential confounders came from questionnaires completed by both parents and participants. Models did not adjust for allergy, which may be a downstream effect of obesity. The authors noted residual confounding by dietary factors at age 4 (the time of exposure assessment) as a limitation. Other potential sources of residual confounding include changes in SES over time and measures of diet quality at age 8y beyond energy intake (measured with error in food frequency questionnaires). Co-exposure confounding by other phthalates was not evaluated, however, the authors analyzed both individual DiNP metabolites and their sum.
Domain 5: Analysis				

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Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Medium	Descriptive data on participant characteristics, outcome measures, and phthalates exposures were presented. Analysis methods were appropriate. Phthalate metabolite measures were log-transformed for analyses. Associations between phthalates exposures at age 4y and repeated measures of overweight/obesity status were analyzed using generalized estimating equations with a logit link. Exposure by age interaction terms were used to estimate age-specific associations. Associations between phthalates and measures of BMI, waist circumference, body fat percentage and trunk fat percentage at age 24 years were estimated using multiple linear regression. Effect estimates were reported as odds ratios or beta coefficients with 95% confidence intervals. Stratified analyses (e.g., by gender) were not discussed. The authors did not mention conducting sensitivity analyses to assess the robustness of findings. However, robustness was observed in terms of consistent associations for associations at multiple ages and multiple outcome measures.
	Metric 5B:	Sensitivity	Medium	There was substantial variability in both individual DiNP metabolites and their sum (DINP mean $\pm$ sd =34.5 $\pm$ 47.4 ng/mL). The prevalence of overweight was adequate for analysis: 20% at age 4y and 23.9% at age 24y. Statistical power was increased by the availability of repeated measures for some outcomes. However, the relatively small sample size (n=71 to 100) means that power was likely limited for stratified analyses.

Additional Comments: This longitudinal cohort study analyzed associations between phthalates exposure at age 4 and obesity measures through age 24y in a subset of 100 participants in the Swedish BAMSE cohort. Cohort members were born in 1994-1996. DiNP metabolites mono(hydroxy-isononyl) phthalate (MHiNP), mono(oxo-isononyl) phthalate (MOiNP), and mono(carboxy-isooctyl) phthalate (MCiOP), along with DEHP metabolites, were measured in urine samples at 4 years of age. Overweight status was measured at ages 4, 8, 12, 16, and 24 years. In addition, waist circumference, and BIA based body fat percentage and trunk fat percentage were analyzed at age 24y. The study found significant associations between increases in DiNP metabolites at age 4y and obesity measures obtained at ages 8 and above. The cross-sectional association between DiNP and obesity at age 4, as well as associations between DEHP metabolites and obesity at all ages, were null. The long follow-up and multiple obesity measures are strengths of this study. However, sample size was small. An additional potential limitation is residual confounding, in particular by dietary factors, which were not assessed at age 4y.

Overall Quality Determination Medium