Evaluating the consistency of heterogeneous results: important determinants of inconsistency

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Background and Methods

Background/Aim

The analysis of study results across a set of studies is a powerful tool that can help with decisions about whether a potential bias is an important concern for an individual study, and to illuminate a pattern within apparently inconsistent effect estimates. The heterogeneity may stem from differing study designs examining varying outcome and exposure definitions and be influenced to varying degrees by sources of bias and other factors that affect the magnitude, direction, and precision of effect estimates. Influential aspects include potential bias (e.g., selection, information, confounding) and other quality aspects (e.g., sensitivity, precision). This type of analysis also can include factors, such as exposure levels, that are important for the interpretation of results. Studies of the association between indoor formaldehyde exposure and current asthma and pulmonary function were used as a case study to illustrate the impact of bias and other study attributes on the analysis of consistency across studies.

Methods:

Analyses of current asthma and pulmonary function endpoints were performed as part of a systematic evaluation of the literature database on studies examining the potential for respiratory and immune-mediated conditions in relation to formaldehyde exposure that was conducted through October 2016.

Criteria to evaluate risk of bias and sensitivity for the selected endpoints were developed using expert consultation or methodological reviews by professional organizations. The IRIS study evaluation tool included domains for participant selection, exposure, outcome, confounding, analysis, and sensitivity.

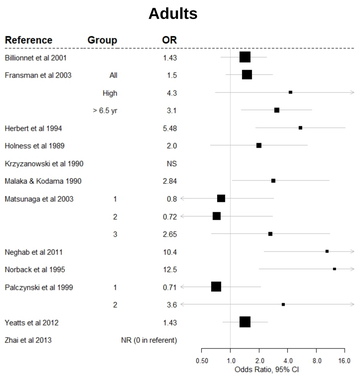
The consistency of results for current asthma was examined via forest plots presenting effect estimates (e.g., risk ratios, odds ratios) stratified by exposure levels (low vs high) and overall study confidence, and an analysis of potential confounding looking across study results was conducted for current asthma and pulmonary function endpoints.

Current Asthma in Children and Adults

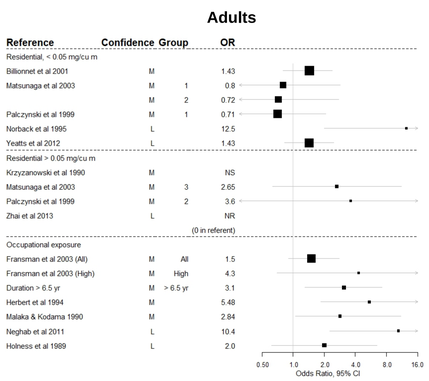
Current asthma is defined as a report of asthma symptoms during the last 12 months. Studies limited to “ever had asthma” were not included because the formaldehyde measures available did not reflect cumulative exposures that could be related to cumulative risk. The population relevant to the PECO for this analysis included children and adults in 22 studies of residential or school exposures and 5 occupational studies involving manufacture of pressed wood products, chemical production and embalming. These studies analyzed the variation in risk of prevalence of current asthma, incidence of asthma or asthma control or severity in relation to variation in formaldehyde at exposures above 0.010 mg/m^3 across a range spanning at least 0.01 mg/m^3. Of the 22 studies of residential or school settings, 4 were considered “not informative” for current asthma because the target population was under 5 years of age, an age range when asthma diagnoses are not specific. Three studies reported comparisons of mean formaldehyde concentrations in cases and controls and could not be included in the forest plots.

Sorting by Exposure Setting, Level, and Confidence for Studies of Current Asthma

Studies ordered alphabetically



Studies ordered by exposure setting, level, and confidence



Conclusion

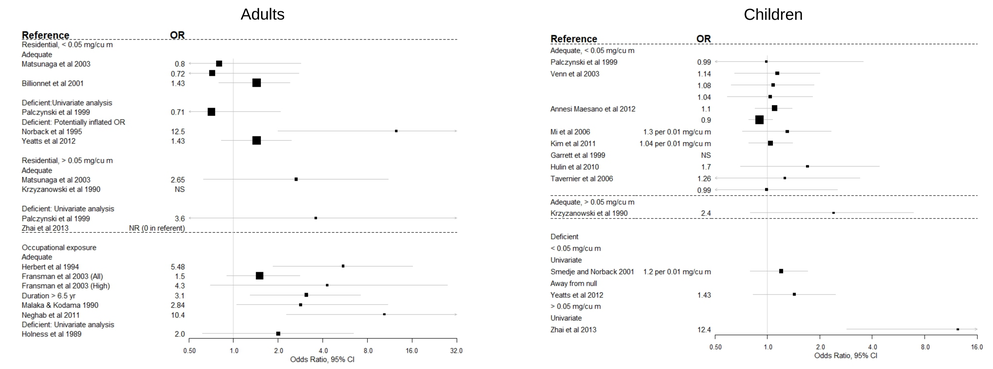
When studies are ordered alphabetically, results appear heterogenous, but when exposure levels and study confidence are considered, a pattern of increasing risk with increasing exposure levels is apparent among the high and medium confidence studies. No single domain limitation was a primary reason for the low confidence determinations, but collectively results of these studies are more variable.

Limitations of Low Confidence Studies

	Adults
Norback et al, 1995	Information bias: Most values < LOQ for formaldehyde Confounding: Unable to distinguish RR for VOCs with formaldehyde
Yeatts et al, 2012	Information bias: Analyses combined children and adults; mothers responded for children Confounding: Unable to distinguish RR for SO_2 with formaldehyde
Zhai et al, 2013	Selection bias: Participation rates not reported, but selection criteria were reported Information bias: Sampling period and protocol details not reported Confounding: Univariate, but magnitude of OR not likely explained by confounding Analysis: Small number of cases for analysis
Neghab et al, 2011	Selection bias: Lead time bias, Left truncation Information bias: Short formaldehyde sampling period; Asthma definition imprecise Confounding: Possible residual confounding for smoking
Holness et al, 1989	Selection bias: Lead time bias, Left truncation Information bias: Asthma definition imprecise Confounding: Univariate analysis
	Children
Smedje and Norback, 2001	Information bias: Exposure, uncertain concentration distribution, high proportion < LOD Confounding: No adjustment for coexposures, but results varied among exposures
Garrett et al, 1999	Selection bias: Potential household correlation of cases and controls Information bias: Asthma definition imprecise Analysis: Adjusted results reported as not signif
Hulin et al, 2010	Analysis: Small sample size; uncertain interpretation of urban/ rural stratified analyses
Tavernier et al, 2006	Selection bias: Missing data for 50% cases; not reported for controls Exposure: Distribution not reported Information bias: Asthma definition included questions not specific to asthma Analysis: Exposure levels by tertile not reported
Yeatts et al, 2012	Information bias: Analyses combined children and adults Confounding: Unable to distinguish RR for SO_2 with formaldehyde
Hsu et al, 2012	Not plotted. Selection bias: Low, differential participation rate Information bias: Short formaldehyde sampling period and protocol not reported Confounding: Univariate analysis Analysis: Limited
Hwang et al, 2011	Not plotted. Selection bias: High prevalence family history asthma in both groups Information bias: Asthma definition imprecise Analysis: Questions about analysis and distribution

Analysis of Confounding

Current Asthma: Sorting by Rating for Confounding



Conclusion

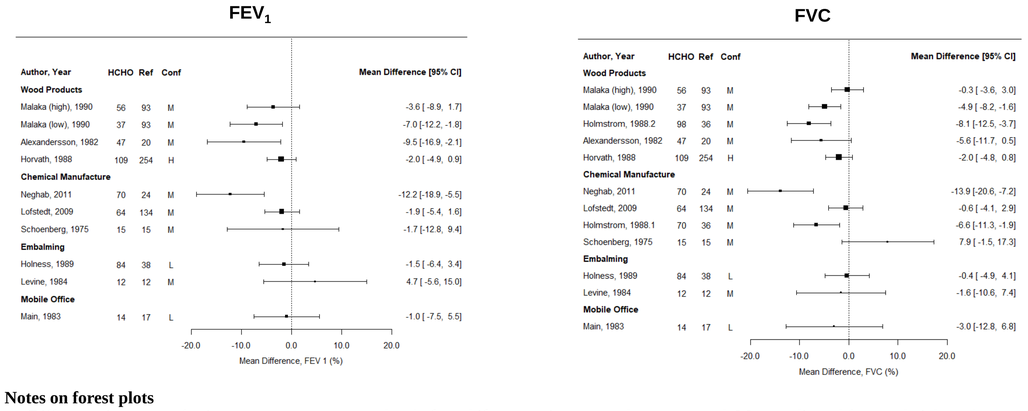
For studies in residential or school settings with lower exposure levels, a deficient rating for confounding with a predicted direction away from the null provides a potential explanation for some of the heterogeneity in odds ratios.

Occupational Studies of Pulmonary Function: Confounding

Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were the most common measures analyzed by the studies of formaldehyde exposure. The population relevant to the PECO for this analysis included workers with occupational exposure to formaldehyde in studies where exposure was confirmed by air measurements, or involved professional categories of embalmers and anatomists/pathologists. A total of 21 studies involving manufacture of wood products, chemical production, embalming or offices in mobile trailers were identified, which analyzed variation in pulmonary function values in relation to variation in formaldehyde at exposures above 0.010 mg/m^3 across a range spanning at least 0.01 mg/m^3. Of the 21 studies, 5 were determined “not informative” because of one or more critical deficiencies; one reported additional analyses in the same cohort, and three presented longitudinal analyses or cross-shift changes, which are not shown in this example.

The occupational studies were limited by low sensitivity due to healthy worker survivor bias resulting from the cross-sectional analyses and loss of sensitive individuals before the studies began. Different analytic approaches were used making it challenging to examine results across studies in a graph using a single metric. However, most of the studies provided a mean value for exposed and referent groups as a percent of predicted adjusting for age, sex and height, and some expression of error. For these studies, forest plots were constructed using the mean difference of percent of predicted FEV_1 or FVC and confidence intervals. The mean difference is adjusted for smoking in these graphs only for three of the studies (Malaka et al., 1999; Holmstrom et al., 1988; Levine et al., 1984). However, most of the studies addressed smoking either in their designs or analyses, and the plotted results are in the same direction as the reported study results.

Cross-sectional analyses of pulmonary function endpoints in relation to occupational exposure



Notes on forest plots

- Difference in means of spirometry measurements taken before shift comparing exposed to unexposed. Means adjusted for age, height and sex.
- Study regression analyses also adjusted for smoking, and coefficients were in the same direction as those in forest plot.
- Two studies were not plotted because the studies reported only means of the unadjusted absolute values. Herbert et al. (1984) found a statistically significant decrease in FEV_1/FVC in analyses adjusted for age, height, sex and smoking, and Khamgaonkar et al. (1991) found a statistically significant decrease in FEV_1 and FVC in analyses adjusted for age, height, weight and sex.

Conclusion

Overall, mean values of pulmonary function among exposed workers were lower than those of unexposed comparison groups. The difference is not large, but is consistently observed in most of the studies, which were limited by a healthy worker survival bias, which may have attenuated the size of the observed difference. Concern for residual confounding is lessened because findings were consistent between the wood products and chemical manufacturing industries, which involve different coexposures.

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