Health effects of exposure to indoor volatile organic compounds from 1980 to 2017: A systematic review and meta-analysis

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Abstract
Exposure to volatile organic compounds (VOCs) indoors is thought to be associated with several adverse health effects. However, we still lack concentration–response (C-R) relationships between VOC levels in civil buildings and various health outcomes. For this paper, we conducted a systematic review and meta-analysis of observational studies to summarize related associations and C-R relationships. Four databases were searched to collect all relevant studies published between January 1980 and December 2017. A total of 39 studies were identified in the systematic review, and 32 of these were included in the meta-analysis. We found that the pooled relative risk (RR) for leukemia was 1.03 (95% CI: 1.01–1.05) per 1 μg/m³ increase of benzene and 1.25 (95% CI: 1.14–1.37) per 0.1 μg/m³ increase of butadiene. The pooled RRs for asthma were 1.08 (95% CI: 1.02–1.14), 1.02 (95% CI: 1.00–1.04), and 1.04 (95% CI: 1.02–1.06) per 1 μg/m³ increase of benzene, toluene, and p-dichlorobenzene, respectively. The pooled RR for low birth weight was 1.12 (95% CI: 1.05–1.19) per 1 μg/m³ increase of benzene. Our findings provide robust evidence for associations between...
benzene and asthma, civil building, health outcome, leukemia, meta-analysis, volatile organic compound

1 | INTRODUCTION

With rapid urbanization and economic growth globally in recent years, severe air pollution, and especially indoor air pollution, has raised more and more concern.¹⁻⁴ Volatile organic compounds (VOCs) comprise one of the most common and important classes of indoor air pollutants. Their indoor sources are mainly various building materials (such as synthetic wooden furniture, paint, floor panels, and carpets), personal care products,⁵⁻⁸ as well as gas cooking, heating, and tobacco smoking.⁶⁻¹¹ Due to their relatively low boiling points (<250°C),¹² inhalation is the dominant pathway for personal exposure to VOCs.¹³,¹⁴

Exposure to indoor VOCs can bring many adverse health effects, ranging from allergy to serious chronic diseases including cancer. For example, formaldehyde has significant association with not only asthma,¹⁵,¹⁶ but nasopharyngeal cancer and leukemia¹⁴,¹⁷ as well. The critical health outcomes for exposure to benzene are blood dyscrasias and leukemia.¹⁴ Additionally, the International Agency for Research on Cancer (IARC) has classified 1,3-butadiene and trichloroethylene as Group 1 carcinogens.¹⁸ Because of these known risks, many countries have specified limits for VOC exposures in residences, office buildings, and other civil buildings.¹⁹⁻²⁷ Some countries, including the USA and Canada, further specify limits for both acute exposure and chronic exposure.²⁰,²²,²³ The World Health Organization (WHO)¹⁴ also suggests that benzene and trichloroethylene should be at as low as possible concentrations as they do not have a known safe level.

However, there remains a lack of quantitative associations between different diseases and VOC exposure in epidemiological studies. One reason for this is that the emphasis has been on formaldehyde exposure in recent decades,¹⁵,¹⁶,²⁸ neglecting the health impacts of other VOCs. Another reason is that most epidemiological research on VOC exposure has focused on occupational exposure for workers, where the exposure concentrations are much higher than those in residences, office buildings, or schools. For instance, the associations between benzene and leukemia,²⁹,³⁰ multiple myeloma,³¹ or non-Hodgkin lymphoma,³²⁻³⁴ and the associations between trichloroethylene and kidney or liver cancer,³⁵⁻³⁷ have been studied among workers, but whether the associations are still significant for low exposure in civil buildings remains unknown. Even though there has been some research on health effects of VOC exposure in civil buildings,³⁸⁻⁴³ these are often case-control studies or cross-sectional studies, with a small sample size, self-reported health outcomes, and non-specific exposure levels. Hence, it is worthwhile to integrate the findings from high-quality studies so as to better elucidate associations between VOC exposure and health under the low exposure circumstances in civil buildings.

In this study, we first conducted a systematic review of the associations between several common VOCs and various health outcomes, and then developed a meta-analysis for those VOC–outcome pairs using available literature. We aimed to characterize the quantitative health impacts of indoor VOC exposure, so as to pave the way for more comprehensive disease burden estimation and control of indoor VOCs.

2 | METHODS

2.1 | Selection criteria for VOCs and health outcomes

This systematic review and meta-analysis is a part of the Chinese Burden of Disease Attributable to Indoor Air Pollutants (CBD-IAP) project, whose goal is to estimate the attributable disease burden of indoor air pollution in China. In the present study, we focus on health effects of VOC exposures in indoor environments (i.e., the concentration–response (C–R) relationships for indoor VOC exposure). While exposure levels of VOCs will be detailed in another paper, the main results are shown here in the supporting information (SI) Table S1. The target indoor VOCs were chosen using the Chinese national standard for indoor air quality,¹⁹ the WHO guidelines for indoor air pollutants (IAPs),¹⁴ the ranking of cancer risk for IAPs in China,⁴⁴ and suggestions from experts in this project. Nine VOCs were finally selected: formaldehyde, benzene, toluene, xylene, acetaldehyde, p-dichlorobenzenes (p-DCB), butadiene, trichloroethylene (TCE), and tetrachloroethylene.
(also called perchloroethylene, PCE). This review focuses on eight target VOCs, excluding formaldehyde. Formaldehyde studies have generated such an abundance of data that formaldehyde will be reported in a separate paper. Health outcomes for the present study were selected using the International Program for Chemical Safety (IPCS), reviews on Web of Science and PubMed, and advice from experts in this project. A total of 31 health outcomes were finally selected and are listed in the search terms in the supporting information (SI) Table S2.

2.2 Search strategy and selection criteria

We searched four databases: Web of Science, PubMed, China National Knowledge Infrastructure (CNKI), and Wan Fang Data Knowledge Service Platform. The searched studies were published between 1980 and 2017. A total of 51 search terms in Chinese and 81 search terms in English were used to conduct the literature search. These terms are listed in SI Table S2. The searched articles were international and not restricted to studies in China. The studies collected from the database search were first screened by their title and abstract. The exclusion criteria were (1) not a population-based epidemiological study (cohort study, case–control study, or cross-sectional study); (2) no reported relative risk (RR), hazard ratio (HR), or odds ratio (OR); (3) patent, standard, or report rather than a published article; and (4) not written in either Chinese or English. The studies included thus far were further screened by reviewing the full text. In addition to the criteria stated above, the exclusion criteria in this step were that (1) the article had been based on the same study as other articles, (2) the article focused on workers’ occupational exposure rather than exposure in civil buildings, (3) health outcomes were non-specific or were not objectively diagnosed. The data extracted from the final selected studies were study location, study year, study population, sample size, study design, exposure level, and RR, OR, or HR.

2.3 Quality assessment of included studies

Quality assessment was conducted for all included studies. The Newcastle–Ottawa scale (NOS) was used to assess the quality of cohort studies and case–control studies, with eight questions from the perspective of population selection, comparability, and outcome/exposure assessment. Studies with 7–9 scores, 4–6 scores, and 0–3 scores were regarded as high-quality, moderate-quality, and low-quality, respectively. Critical tools of the Joanna Briggs Institute (JBI) were employed to evaluate the quality of cross-sectional studies via a questionnaire of eight questions, each of which can be answered by “yes,” “no,” or “unclear.” Studies with 7–8 scores, 4–6 scores, and 0–3 scores were regarded as high-quality, moderate-quality, and low-quality studies, respectively. We included high- and moderate-quality studies in the meta-analysis.

2.4 Statistical analysis

Only those VOC–outcome pairs with at least one of the ratios, RR, OR, or HR, were further included in the meta-analysis. As no studies reported HR that passed the systematic review, HR is not discussed further. We transformed all ratios into relative risk per 1 μg/m³ increase in the corresponding VOC concentration (per 0.1 μg/m³ increase for butadiene). If the odds ratio (OR) was reported, it was converted to relative risk (RR) by equation (1).

\[
RR = \frac{OR}{1 - p_0 + p_0 \cdot OR}
\]

where \(p_0\) is the prevalence of the focused health outcome in the unexposed group (approximated as the prevalence in the total population in the study country in the study year if the prevalence in unexposed group was not reported). If the relative risk was reported for exposure categories instead of as per unit increase in concentration, it was transformed by equation (2).

\[
RR = (RR_{\text{reported}})^{\frac{1}{\text{CI} - \text{CI}_0}}
\]

where \(RR_{\text{reported}}\) is the reported relative risk in the literature, \(C_1\) is the mean or median concentration in the exposed group, and \(C_2\) is the mean or median concentration in the unexposed/reference group.

Meta-analysis was conducted using the R software (V 4.1.1) package “meta” (V5.1-1). The \(I^2\) statistic was used to evaluate the heterogeneity of available evidence. If \(I^2\) was smaller than 50%, the fixed effect model was applied; otherwise, the random effect model was selected. These estimates integrated the current available evidence and enhanced the strength of evidence. Analysis was performed on these subgroups: study design (cohort, case–control, or cross-sectional studies), study population (children, adults, or others), and study region (western or eastern countries), in order to identify the source of heterogeneity. Sensitivity analyses were conducted via the leave-one-out method for each included VOC–outcome pair, to see whether the results of meta-analysis were dominated by one of a few influential studies. Publication bias was assessed by Egger’s test. We rejected publications whose Egger’s test yielded a p-value less than 0.05 as indicating significant publication bias. If significant publication bias might exist after Egger’s test, the trim and fill method was applied to see whether the significance of the meta-analysis results changed. If not, publication bias was ruled out.

Finally, the meta-analysis provided the relative risk per 1 unit increase of VOC concentration, denoted as \(RR_0\). Then the C–R relationship for VOC exposure can be obtained as:

\[
RR(C) = \begin{cases} RR_0, & C \leq C_{\text{max}} \\ \frac{RR_0^C}{RR_0^0}, & C > C_{\text{max}} \end{cases}
\]

where \(C\) is the VOC concentration, \(C_0\) is the unit concentration for VOCs used in the meta-analysis result (e.g., 1 μg/m³), \(C_{\text{max}}\) is the...
maximum concentration of VOCs in the included studies in the meta-analysis for the corresponding health outcome. Given that due to lack of data it is inappropriate to use the exponential relationship to extrapolate the risk above this maximum exposure level, a conservative estimate was applied using equation (3) such that the relative risk above the maximum exposure level equals that at the maximum level.

3 | RESULTS

3.1 | Literature search findings

Initially, 14,331 articles were identified from the database search. After title and abstract screening, 13,909 articles were excluded. After full-text screening of the remaining 422 articles, 383 articles were excluded. Finally, 39 articles were included in the systematic review. The whole procedure for the literature search is shown in Figure 1. Detailed information for each article is presented in SI Table S3. Among the included studies were 33 studies of benzene, but only 4 of butadiene. There were 9 cohort studies, 15 case-control studies, and 15 cross-sectional studies. A total of 19 health outcomes were inferred to be associated with exposures to indoor VOCs. Asthma was studied in the greatest number of articles, 16, followed by leukemia with 8 articles. The regional distribution of studies is unbalanced with respect to the size of populations studied. Nineteen studies were performed in Europe and 13 studies in North America (the USA and Canada), but only 6 studies in Asia and 1 study in Australia. No studies for South America and Africa were found. Quality assessment revealed no low-quality articles: the mean score of cohort and case-control studies reached 7.2 by NOS, and the mean score of cross-sectional studies was 7.0 by JBI. A total of 18 eligible VOC-outcome pairs from 32 studies were finally included for meta-analysis.

3.2 | Overall meta-analysis results

The overall pooled RR and 95% confidence interval (CI) of the 18 included VOC-outcome pairs are shown in Table 1. In addition, Table 1 summarizes statistics for heterogeneity, used model, and maximum concentration for each pair. The maximum concentration yields the maximum mean exposure level for each pair in all available studies. Detailed forest plots for each eligible pair are presented in Figures 2-8. For the ten eligible VOC-outcome pairs with relatively high heterogeneity, we applied random effect models for the meta-analyses. For the other 8 pairs, we used a fixed effect model.

Benzene had possible associations with 8 health outcomes: preterm birth, leukemia, cardiovascular diseases, bronchitis, asthma, dermatitis, low birth weight, and rhinitis (Figure 2). Among these, associations with leukemia, cardiovascular disease, asthma, and low birth weight are statistically significant. The pooled RR for leukemia per 1 μg/m³ increase in benzene concentration was 1.10 (95% CI = 1.05 – 1.15, I² = 22%). Indeed, leukemia was the primary reason for classifying benzene as a group 1 carcinogen. Each 1 μg/m³ increase in benzene exposure is associated with an excess 3% risk of cardiovascular diseases (pooled RR = 1.03, 95% CI = 1.01 – 1.05, I² = 25%), which have been the leading chronic disease in mortality. Additionally, an 8% increase in the risk of asthma was found for a 1 μg/m³ increase in benzene concentration (pooled RR = 1.08, 95% CI = 1.02 – 1.14, I² = 85%). Each 1 μg/m³ increase in benzene exposure was associated with 12% excess risk for low birth weight (pooled RR = 1.12, 95% CI = 1.05 – 1.19, I² = 99%), but the heterogeneity for this result was very high. Apart from these four health outcomes, the associations between benzene exposure and preterm birth, bronchitis, dermatitis, and rhinitis were not statistically significant.

The results of meta-analyses for toluene (Figure 3) and xylenes (Figure 4) were similar. Both were significantly associated with asthma, but not significantly with dermatitis or rhinitis. The pooled

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**FIGURE 1** Procedure for the literature search in the systematic review

Database: Web of Science, PubMed, CNKI (Chinese), Wanfang (Chinese)

Period: from Jan 1980 to Dec 2017

14331 articles identified by database search

13909 articles excluded:
No epidemiological studies in the population,
No specific RR, HR, OR value,
Patents, standards, reports etc.

422 articles identified by title and abstract screening

383 articles excluded:
The same criteria as those in title & abstract screening,
From the same study,
Occupational exposure (very high concentration),
No specific or diagnosed health outcomes.

39 articles identified by full-text screening
TABLE 1 Pooled RRs and 95% CIs between VOCs exposure and selected health outcomes in the meta-analyses.

<table>
<thead>
<tr>
<th>VOCs</th>
<th>Health outcomes</th>
<th>RR (95% CI) per 1-unit increase</th>
<th>Unit</th>
<th>Maximum concentration</th>
<th>I²</th>
<th>p value for heterogeneity</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>Preterm birth</td>
<td>1.57 (0.50, 4.94)</td>
<td>1 μg/m³</td>
<td>3.0 μg/m³</td>
<td>72%</td>
<td>0.03</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>Leukemia</td>
<td>1.10 (1.05, 1.15)</td>
<td>1 μg/m³</td>
<td>12.0 μg/m³</td>
<td>22%</td>
<td>0.22</td>
<td>Fixed</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular diseases</td>
<td>1.03 (1.01, 1.05)</td>
<td>1 μg/m³</td>
<td>3.8 μg/m³</td>
<td>25%</td>
<td>0.27</td>
<td>Fixed</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>Asthma</td>
<td>1.58 (0.80, 3.09)</td>
<td>1 μg/m³</td>
<td>4.0 μg/m³</td>
<td>79%</td>
<td>&lt; 0.01</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>Dermatitis</td>
<td>1.08 (1.02, 1.14)</td>
<td>1 μg/m³</td>
<td>35.1 μg/m³</td>
<td>85%</td>
<td>&lt; 0.01</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>Low birth weight</td>
<td>1.12 (1.05, 1.19)</td>
<td>1 μg/m³</td>
<td>3.5 μg/m³</td>
<td>99%</td>
<td>&lt; 0.01</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>Rhinitis</td>
<td>1.04 (0.99, 1.10)</td>
<td>1 μg/m³</td>
<td>15.7 μg/m³</td>
<td>0%</td>
<td>0.47</td>
<td>Fixed</td>
</tr>
<tr>
<td>Toluene</td>
<td>Asthma</td>
<td>1.02 (1.00, 1.04)</td>
<td>1 μg/m³</td>
<td>44.5 μg/m³</td>
<td>78%</td>
<td>&lt; 0.01</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>Dermatitis</td>
<td>1.03 (0.95, 1.12)</td>
<td>1 μg/m³</td>
<td>44.5 μg/m³</td>
<td>77%</td>
<td>&lt; 0.01</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>Rhinitis</td>
<td>1.00 (0.99, 1.10)</td>
<td>1 μg/m³</td>
<td>44.5 μg/m³</td>
<td>0%</td>
<td>0.57</td>
<td>Fixed</td>
</tr>
<tr>
<td>Xylenes</td>
<td>Asthma</td>
<td>1.04 (1.01, 1.07)</td>
<td>1 μg/m³</td>
<td>30.6 μg/m³</td>
<td>68%</td>
<td>&lt; 0.01</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>Dermatitis</td>
<td>1.19 (0.96, 1.46)</td>
<td>1 μg/m³</td>
<td>22.5 μg/m³</td>
<td>86%</td>
<td>&lt; 0.01</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>Rhinitis</td>
<td>1.05 (0.98, 1.12)</td>
<td>1 μg/m³</td>
<td>22.5 μg/m³</td>
<td>57%</td>
<td>0.04</td>
<td>Random</td>
</tr>
<tr>
<td>Acetaldehyde</td>
<td>Asthma</td>
<td>1.01 (1.00, 1.02)</td>
<td>1 μg/m³</td>
<td>13.6 μg/m³</td>
<td>0%</td>
<td>0.67</td>
<td>Fixed</td>
</tr>
<tr>
<td>p-Dichlorobenzene</td>
<td>Asthma</td>
<td>1.04 (1.02, 1.06)</td>
<td>1 μg/m³</td>
<td>8.9 μg/m³</td>
<td>24%</td>
<td>0.27</td>
<td>Fixed</td>
</tr>
<tr>
<td>Butadiene</td>
<td>Leukemia</td>
<td>1.25 (1.14, 1.37)</td>
<td>0.1 μg/m³</td>
<td>0.8 μg/m³</td>
<td>0%</td>
<td>0.60</td>
<td>Fixed</td>
</tr>
<tr>
<td>Tetrachloroethylene</td>
<td>Asthma</td>
<td>1.08 (1.01, 1.16)</td>
<td>1 μg/m³</td>
<td>2.7 μg/m³</td>
<td>27%</td>
<td>0.25</td>
<td>Fixed</td>
</tr>
</tbody>
</table>

RR for asthma per 1 μg/m³ increase in toluene concentration was 1.02 (95% CI = 1.00 - 1.04, I² = 78%). Each 1 μg/m³ increase in xylene exposure was associated with 4% of excess risk for asthma (pooled RR = 1.04, 95% CI = 1.01 - 1.07, I² = 68%). In addition, we found significant associations between asthma and other VOCs. The pooled RR for asthma per 1 μg/m³ increase of acetaldehyde (Figure 5), p-dichlorobenzene (Figure 6), and tetrachloroethylene (Figure 8) were 1.01 (95% CI = 1.00 - 1.02, I² = 0%), 1.04 (95% CI = 1.02 - 1.06, I² = 24%), and 1.08 (95% CI = 1.01 - 1.16, I² = 27%), respectively. All had low heterogeneity. Finally, a 0.1 μg/m³ increase in butadiene exposure is associated with an excessive 25% risk of leukemia (pooled RR = 1.25, 95% CI = 1.14 - 1.37, I² = 0%) (Figure 7).

### 3.3 Subgroup analyses

The results of subgroup analyses are shown in Table 2. We mainly focused on the 10 significant associations obtained in the overall meta-analysis. No subgroup analysis was conducted for leukemia and benzene because all studies were of children in Western countries, and all were case-control studies. Studies of associations between benzene and cardiovascular diseases yielded different results in different subgroups. Only one cross-sectional study of children in China showed significant associations (RR = 1.03, 95% CI = 1.01-1.05), while other two cohort studies in western countries showed insignificant associations. For the association between asthma and benzene exposure, a significant association was found within subgroups of cross-sectional studies (pooled RR = 1.07, 95% CI = 1.00-1.14), children (pooled RR = 1.09, 95% CI = 1.02-1.16), and Western countries (pooled RR = 1.08, 95% CI = 1.03-1.14). Associations between low birthweight and benzene levels were significant in subgroups of case-control studies (pooled RR = 1.11, 95% CI = 1.00-1.02) and cross-sectional studies (pooled RR = 1.16, 95% CI = 1.12-1.21). For toluene, the association with asthma showed significance in subgroups of cohort studies (RR = 1.02, 95% CI = 1.00-1.03), case-control studies (RR = 1.05, 95% CI = 1.03-1.08), and Western countries (pooled RR = 1.03, 95% CI = 1.01-1.05). Subgroups classified by study population (adults and children) showed insignificant associations. For xylene, the findings for asthma were also insignificant. However, in addition to the subgroups mentioned above with respect to toluene, associations between xylene and asthma were significant in subgroups of both adults (pooled RR = 1.14, 95% CI = 1.06-1.23) and children (pooled RR = 1.02, 95% CI = 1.00-1.05).

In addition to abundant data for the benzene series, we obtained data for four other types of VOCs in the subgroup analyses. The association between acetaldehyde and asthma was significant for subgroups in cross-sectional studies (pooled RR = 1.01, 95% CI = 1.00-1.02), children (pooled RR = 1.01, 95% CI = 1.00-1.02), and Western countries (pooled RR = 1.01, 95% CI = 1.00-1.02). The effect of p-DCB exposure on asthma prevalence was remarkably consistent; there were significant associations for all subgroups. No subgroup analysis was performed for butadiene because all studies were of children in Western countries using case-control design.
For PCE, significant association with asthma was observed in subgroup studies of cohorts (RR = 1.12, 95% CI = 1.03–1.22), children (RR = 1.12, 95% CI = 1.03–1.22), and Western countries (pooled RR = 1.08, 95% CI = 1.01–1.16).

Overall, among all 10 significant VOC–outcome pairs in the overall meta-analysis, associations between asthma and p-DCB, toluene, xylenes were more consistent in the significance and estimated RR for subgroups. Studies of associations between leukemia and benzene...
or butadiene were mainly case–control studies of children in western countries. Associations between benzene and cardiovascular diseases, PCE and asthma, yielded different results depending on the subgroups.

3.4 | Sensitivity analyses and publication bias

Sensitivity analyses were performed using the leave-one-out method in which each study is excluded, one-by-one, in turn. The results are shown in SI Figure S1–Figure S7. For all 10 significant associations, the leave-one-out test did not influence the significance and estimated RRs for benzene and leukemia, benzene and asthma, xylene and asthma, p-DCB and asthma, butadiene, and leukemia. The association between toluene and asthma is slightly affected, as omitting the study of Rumchev et al.42 changed the significance (95% lower CI = 0.9982). However, the associations between benzene and cardiovascular diseases, acetaldehyde and asthma, PCE and asthma were dramatically influenced from the perspective of significance of estimated RR.

Publication bias was assessed through Egger’s test. Seven of all 10 significant associations passed this test, with p-values ranging from 0.07 to 0.35. Associations between p-DCB and asthma (p = 0.011), butadiene and leukemia (p = 0.039), did not pass the Egger’s test directly, but after using a trim and fill method, the results of meta-analyses did not alter the significance of the association. Hence, their meta-analyses were relatively reliable. However, associations between xylenes and asthma (p = 0.032) did not pass the Egger’s test even after using the trim and fill method, suggesting potential publication bias.

4 | DISCUSSION

To our best knowledge, this is the first systematic review and meta-analysis to comprehensively summarize relationships between VOC exposure (except for formaldehyde) in civil buildings and various health outcomes. Through the overall meta-analysis, subgroup analysis, sensitivity analysis, and publication bias assessment, 6 VOC–outcome pairs were found to have relatively reliable significant associations. These are the associations between benzene and leukemia, benzene and asthma, benzene and low birthweight, toluene and asthma, p-DCB and asthma, and butadiene and leukemia.
FIGURE 4 Forest plot of the meta-analyses of associations between xylene exposure and (A) asthma, (B) dermatitis, and (C) rhinitis.

FIGURE 5 Forest plot of the meta-analyses of associations between acetaldehyde exposure and asthma.

FIGURE 6 Forest plot of the meta-analyses of associations between p-dichlorobenzene exposure and asthma.
Another 4 significant associations in the overall meta-analysis may be not so reliable. The association between benzene and cardiovascular diseases did not perform well in the subgroup analysis and sensitivity analysis. The relationship between xylenes and asthma was likely to have publication bias as shown by Egger’s test. The association between acetaldehyde and asthma was not significant in the sensitivity analysis. Additionally, the relationship between PCE and asthma was not stable enough in either the subgroup analysis or sensitivity analysis. Hence, these four associations should be viewed with caution; they require more research.

Some of the reliable significant associations are supported by toxicological research. IARC has reported that benzene can cause acute myeloid leukemia, chronic lymphoid leukemia, and chronic myeloid leukemia, likely because human exposure to benzene can induce oxidative stress and related oxidative DNA damage and even lead to chromosomal changes. Also, many studies have demonstrated the hematotoxicity of benzene exposure, including decreased leukocyte counts at lower exposures and aplastic anemia and pancytopenia at higher exposures. For butadiene, IARC reported that it can cause cancer of the hemolymphatic organs, the result of a genotoxic mechanism involving formation of reactive epoxides, their interaction with DNA, and the resulting mutagenicity. Besides the carcinogenic effect, respiratory irritation and diseases are one of the most associated outcomes with VOC exposure. Kuang et al. compared asthmatic children with healthy children and found that most VOC metabolites were correlated with N-Acetyl-S-(3,4-dihydroxybutyl)-L-cysteine (DHBMA), a biomarker that can indicate the DNA damage-mediated asthma induced by VOCs. However, it has been noted that although VOCs have irritation potency, other indoor air factors, such as humidity, noise and biological pollutants, can also contribute to these respiratory outcomes and may act as confounders. In general, the mechanism for asthma and other respiratory symptoms where VOCs were involved in remains unclear and requires further study.

Heterogeneity was evaluated by the statistic $I^2$. If the point estimate of $I^2$ was larger than 50%, it was assumed to have high heterogeneity, so the random effect model was applied. However, von Hippel suggested that if the number of studies included in the meta-analysis is small, the expectation of $I^2$ can overestimate the true heterogeneity when the true heterogeneity is relatively low, while the expectation of $I^2$ can underestimate the true heterogeneity when the true heterogeneity is relatively high. The bias of $I^2$ for small samples may influence the result of the meta-analysis through effects on model selection, which requires analysis. On the one hand, from the calculated results in the von Hippel study, when the number of studies is larger than three, the bias of $E(I^2)$ mostly did not affect whether the heterogeneity is smaller than 50% or not. Additionally, most results in the meta-analysis in this study have a lower heterogeneity than 30% or a higher heterogeneity than 70%, which is relatively far away from 50%. On the other hand, both results of fixed and random effect models have been shown in SI Table S4 to explore the sensitivity of results brought by model selection. As can be seen from SI Table S4, the difference between the results of the fixed effect model and those of the random effect model is very small for the six reliable significant associations, except for the association of benzene with low birthweight, which has an $I^2$ of 99% (extremely high heterogeneity) but the significance is not affected. Although the results of some other associations may be sensitive to model selection, these results themselves are not significant nor do they pass the sensitivity analysis and test of publication bias, which is unreliable. Therefore, we conclude that the uncertainty of $I^2$ does not have much impact on the main conclusions in this study.

Significant heterogeneity was found most especially for almost all of the associations with bronchitis, asthma, and dermatitis. From the subgroup analysis, we can infer that this heterogeneity likely comes from different study designs and different populations. Cross-sectional design and a study population of children accounts for most of the heterogeneity. This is likely because a cross-sectional design observes exposure and outcome simultaneously and cannot reflect the causal pathway from exposure to outcome. Moreover, compared with adults, children are more vulnerable and susceptible to air pollutant exposure in the surrounding environment, as exposure during children’s organogenesis may lead to permanent structural changes, while exposure after organogenesis is more likely to
### TABLE 2  The pooled RRs and 95% CIs in subgroup analyses. (*significant associations with $p < 0.05$, $+ I^2 > 50\%$ for heterogeneity).

<table>
<thead>
<tr>
<th>Pollutants</th>
<th>Outcomes</th>
<th>Study design [No. of reports]</th>
<th>Population [No. of reports]</th>
<th>Region [No. of reports]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cohort studies</td>
<td>Case-control studies</td>
<td>Cross-sectional studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adults</td>
<td>Children</td>
<td>Others</td>
</tr>
<tr>
<td>Benzene</td>
<td>Preterm birth</td>
<td>1.57 $^\dagger$ (0.50, 4.94) [3]</td>
<td>NA</td>
<td>1.57 $^\dagger$ (0.50, 4.94) [3]</td>
</tr>
<tr>
<td>Leukemia</td>
<td>NA</td>
<td>1.10 $^\dagger$ (1.05, 1.15) [13]</td>
<td>NA</td>
<td>1.10 $^\dagger$ (1.05, 1.15) [13]</td>
</tr>
<tr>
<td>CVD</td>
<td>1.23 (0.98, 1.54) [2]</td>
<td>NA</td>
<td>1.03 $^\dagger$ (1.01, 1.05) [1]</td>
<td>1.16 (0.83, 1.64) [1]</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>NA</td>
<td>3.80 $^\dagger$ (1.36, 6.12) [1]</td>
<td>1.15 $^\dagger$ (1.05, 1.26) [2]</td>
<td>1.17 (0.91, 1.50) [1]</td>
</tr>
<tr>
<td>Asthma</td>
<td>1.08 $^\dagger$ (0.89, 1.30) [3]</td>
<td>1.13 $^\dagger$ (0.94, 1.36) [3]</td>
<td>1.07 $^\dagger$ (1.00, 1.14) [11]</td>
<td>1.05 $^\dagger$ (0.94, 1.17) [5]</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>1.06 (0.98, 1.15) [2]</td>
<td>NA</td>
<td>0.98 $^\dagger$ (0.85, 1.14) [6]</td>
<td>NA</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>0.96 (0.73, 1.27) [1]</td>
<td>1.01 $^\dagger$ (1.00, 1.02) [1]</td>
<td>1.16 $^\dagger$ (1.12,1.21) [4]</td>
<td>NA</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>NA</td>
<td>NA</td>
<td>1.04 (0.99, 1.10) [6]</td>
<td>1.05 (0.92, 1.21) [1]</td>
</tr>
<tr>
<td>Toluene</td>
<td>Asthma</td>
<td>1.02 $^\dagger$ (1.00, 1.03) [1]</td>
<td>1.05 $^\dagger$ (1.03, 1.08) [1]</td>
<td>1.01 $^\dagger$ (0.99, 1.04) [6]</td>
</tr>
<tr>
<td>Pollutants</td>
<td>Outcomes</td>
<td>Study design [No. of reports]</td>
<td>Population [No. of reports]</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Cohort studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis</td>
<td>NA</td>
<td>1.16 * (1.07, 1.27) [1]</td>
<td>0.98 (0.97, 0.99) [4]</td>
<td>NA</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>NA</td>
<td>NA</td>
<td>1.00 (0.99, 1.01) [5]</td>
<td>1.02 (0.99, 1.04) [1]</td>
</tr>
<tr>
<td>Xylenes</td>
<td>Asthma</td>
<td>1.04 * (1.01, 1.06) [2]</td>
<td>1.03 * (1.02, 1.05) [6]</td>
<td>1.09 * (0.89, 1.33) [5]</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>NA</td>
<td>1.19 * (1.05, 1.36) [1]</td>
<td>1.30 * (0.87, 1.93) [4]</td>
<td>NA</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>NA</td>
<td>NA</td>
<td>1.05 * (0.98, 1.12) [6]</td>
<td>1.09 * (1.03, 1.15) [2]</td>
</tr>
<tr>
<td>Acetaldehyde</td>
<td>Asthma</td>
<td>1.14 (0.92, 1.41) [1]</td>
<td>NA</td>
<td>1.01 * (1.00, 1.02) [4]</td>
</tr>
<tr>
<td>p-DCB</td>
<td>Asthma</td>
<td>NA</td>
<td>1.04 * (1.02, 1.06) [2]</td>
<td>1.15 * (1.04, 1.28) [2]</td>
</tr>
<tr>
<td>PCE</td>
<td>Asthma</td>
<td>1.12 * (1.03, 1.22) [1]</td>
<td>1.01 (0.90, 1.13) [2]</td>
<td>1.01 (0.90, 1.13) [2]</td>
</tr>
</tbody>
</table>

Note: NA, not available.
bring about functional consequences.\textsuperscript{94} However, due to a limited number of studies, we could not divide the children subgroup into more detailed age groups. Some included studies focused on infants younger than 2 years old, while some were of children from 5 to 11 years old. These are quite different developmental stages, and deserve further study.

This review also provides information about other epidemiological studies of VOCs in civil buildings in the systematic review of SI Table S3. Although evidence of associations was inadequate for this meta-analysis, these studies still offer insights into possible health effects of different VOC exposures. Except for the 8 health outcomes included in meta-analyses for benzene, there are several studies on the associations of benzene with lower respiratory infection,\textsuperscript{51} lung cancer,\textsuperscript{77,78} brain and central nervous system cancer,\textsuperscript{71} Hodgkin’s lymphoma,\textsuperscript{71} non-Hodgkin’s lymphoma,\textsuperscript{71} multiple myeloma,\textsuperscript{40} respiratory diseases;\textsuperscript{72,78} ear infections,\textsuperscript{51} and pneumonia.\textsuperscript{82} Among these, Villeneuve et al. found that the risk of lung cancer in a case–control study was significantly increased by exposure to greater than 2.7 \( \mu \text{g/m}^3 \) of benzene.\textsuperscript{77} Raaschou-Nielsen et al. reported that in a case–control study, high cumulative exposure to benzene (>1.3×10\(^3\) ppb-days) was significantly correlated with the risk of Hodgkin’s lymphoma.\textsuperscript{71} For toluene, various studies showed associations with preterm birth,\textsuperscript{70} multiple myeloma,\textsuperscript{40} leukemia,\textsuperscript{40} cardiovascular diseases,\textsuperscript{67} bronchitis,\textsuperscript{38} low birth weight,\textsuperscript{58,70} and pneumonia.\textsuperscript{82} Poirier et al.\textsuperscript{70} observed a significant association between toluene exposure and preterm birth. Mannisto et al.\textsuperscript{67} observed in a cohort study that the risk of cardiovascular diseases was significantly associated with benzene exposure among pregnant women. Exposure to benzene was also significantly related to low birth weights in Ghosh et al.’s case–control study.\textsuperscript{58} As for xylenes, studies not included in the meta-analysis showed relationships with multiple myeloma,\textsuperscript{40} leukemia,\textsuperscript{40} cardiovascular diseases,\textsuperscript{67,68} bronchitis,\textsuperscript{38} low birthweight,\textsuperscript{58} and pneumonia.\textsuperscript{82} Similar results have been seen for toluene, namely, significant associations with cardiovascular diseases and low birthweight. Available studies not included in the meta-analysis for four other indoor air pollutants are relatively fewer. Acetaldehyde and p-DCB were found to be insignificantly associated with bronchitis\textsuperscript{38} and rhinitis.\textsuperscript{39} Butadiene had insignificant associations with cardiovascular diseases\textsuperscript{57} and asthma.\textsuperscript{56} TCE and PCE were related to several health outcomes, including preterm birth,\textsuperscript{57} multiple myeloma,\textsuperscript{40} leukemia,\textsuperscript{40,41} bronchitis,\textsuperscript{38} asthma,\textsuperscript{39,53,56} low birthweight,\textsuperscript{57} and rhinitis.\textsuperscript{39} Only exposure to TCE was significantly associated with increased risk of low birth weight and rhinitis. These findings show us that further studies of associations between exposures to VOCs in civil buildings and various health outcomes warrants further study.

This study has some limitations. A limited number of studies of the relationships between health outcomes and VOC exposure in civil buildings were available. We found 19 health outcomes for the systematic review, and we included eight: preterm birth, asthma, dermatitis, rhinitis, cardiovascular diseases, leukemia, bronchitis, and low birthweight. Except for cardiovascular diseases, the outcomes for which there are data contribute little to the total loss of disability adjusted life years (DALYs).\textsuperscript{84} Some diseases for which strong associations with VOC exposure have been reported in occupational exposure conditions,\textsuperscript{31-34,36,37,78} have not been studied at lower exposures in civil buildings. These include such diseases as non-Hodgkin’s lymphoma, kidney cancer, and nasopharyngeal cancer. Even for significant associations between VOC exposures and health outcomes, the number of studies included was limited (as, e.g., butadiene with leukemia) and the evidence requires more research in the future. In addition, for the eight studied health outcomes, most studies were cross-sectional or case–control studies, suggesting that the evidence for causality was relatively weak. More cohort studies are needed. Another limitation is that this study only addressed 8 kinds of VOCs, omitting potential hazards brought by other kinds of VOCs. Moreover, although ten VOC–outcome pairs were found to have significant associations, their maximum concentrations were mostly very low, as these studies mainly originated in Western developed countries. Nonetheless, this shows that even very low exposure to these VOCs can bring adverse health impacts. However, using the provided RR to extrapolate the risk above this maximum exposure level may be not appropriate, suggesting that the relative risk under higher exposure levels of VOCs in developing countries remains unclear, which makes it difficult to estimate disease burden attributable to indoor VOC exposure. Last but not least, most of the available epidemiological studies only focused on health effects of exposure to a single VOC. People are often simultaneously exposed to multiple VOCs that originate from similar indoor sources. Therefore, the multicollinearity and interaction of health effects among these VOCs is neglected when studying only single VOC. In order to tackle these problems, we encourage multidisciplinary cooperation between epidemiologists and researchers in indoor air, and recommend more cohort studies on multiple VOC exposure in civil buildings. Future research can also combine the transient mass-transfer model of VOC emissions from indoor materials and the C-R relationships obtained in this study, to estimate the health impacts of VOC emissions from indoor building materials.

5 | CONCLUSIONS

In order to characterize the quantitative health effects of indoor VOC exposure, this study conducted a systematic review of associations between VOCs and related health outcomes. Through quality assessment of the included studies from the systematic review, high- and moderate-quality studies were included in the meta-analysis. Through sensitivity analysis and publication bias testing, this meta-analysis found robust and significant associations of benzene and butadiene with leukemia, of benzene with low birth weight, and of benzene, toluene, and p-DCB with asthma. These associations can provide the C-R relationships, which pave the way for estimating burden of disease attributable to indoor VOC exposure and further help to design more appropriate guidelines for VOC exposure. More cohort studies are required for VOC exposure in the future, as is further inquiry into other health outcomes.
AUTHOR CONTRIBUTION
Ningrui Liu and Zhongming Bu conducted the systematic review and extracted the data from included studies. Ningrui Liu performed the quality assessment, meta-analysis, sensitivity analysis, publication bias test, and wrote the original draft. Wei Liu, Haidong Kan, Zhuohui Zhao, Furong Deng, Chen Huang, Bin Zhao, Xiangang Zeng, Yuxinia Sun, Hua Qian, Jinhan Mo, Chanjuan Sun, Jianguo Guo, Xiaohong Zheng, and Yingping Zhang designed the framework of the whole Chinese Burden of Disease Attributable to Indoor Air Pollutants (CBD-IAP) project, including the estimation of C-R relationships focused on in this study. Louise B. Weschler revised the manuscript and polished the language. All authors involved in writing-review and editing of the manuscript.

CONFLICT OF INTERESTS
The authors declared that they have no competing interests.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available in the supplementary material of this article.

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REFERENCES


42. Delfino RJ, Gong Jr H, Linn WS, Pellizzari ED, Hy A. Asthma symptoms in Hispanic children and daily ambient exposures to toxic and criteria air pollutants. Environ Health Perspect. 2003;111(4):647-656. 10.1289/ehp.5992

43. Forand SP, Lewis-Michl EL, Gomez MI. Adverse birth outcomes and maternal exposure to trichloroethylene and tetrachloroethylene through soil vapor intrusion in New York State. Environ Health Perspect. 2012;120(4):616-621. 10.1289/ehp.1103884


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