Particulate air pollution and panel studies in children: a systematic review

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Background: Panel studies have been used to investigate the short term effects of outdoor particulate air pollution across a wide range of environmental settings.

Aims: To systematically review the results of such studies in children, estimate summary measures of effect, and investigate potential sources of heterogeneity.

Methods: Studies were identified by searching electronic databases to June 2002, including those where outcomes and particulate level measurements were made at least daily for ≥8 weeks, and analysed using an appropriate regression model. Study results were compared using forest plots, and fixed and random effects summary effect estimates obtained. Publication bias was considered using a funnel plot.

Results: Twenty two studies were identified, all except two reporting PM10 (24 hour mean) ≥50 μg.m⁻³. Reported effects of PM10 on PEF were widely spread and smaller than those for PM2.5 (fixed effects summary: −0.012 v −0.063 l.min⁻¹ per μg.m⁻³ rise). A similar pattern was evident for symptoms. Random effects models produced larger estimates. Overall, in between-study comparisons, panels of children with diagnosed asthma or pre-existing respiratory symptoms appeared less affected by PM10 levels than those without, and effect estimates were larger where studies were conducted in higher ozone conditions. Larger PM10 effect estimates were obtained from studies using generalised estimating equations to model autocorrelation and where results were derived by pooling subject specific regression coefficients. A funnel plot of PM10 results for PEF was markedly asymmetrical.

Conclusions: The majority of identified studies indicate an adverse effect of particulate air pollution that is greater for PM2.5 than PM10. However, results show considerable heterogeneity and there is evidence consistent with publication bias, so limited confidence may be placed on summary estimates of effect. The possibility of interaction between particle and ozone effects merits further investigation, as does variability due to analytical differences that alter the interpretation of final estimates.

The short term effect of particulate air pollutants on the respiratory morbidity of children has been the subject of considerable investigation over the past decade. However, while many epidemiological studies across varied environmental conditions have indicated an acute impact of particles on lung function and reported respiratory symptoms, a recent major collaborative European study failed to show any consistent effects in asthmatic 9 and 10 year olds. An accurate measure of the environment conditions, and is necessarily subjective and may require a judgement based on study duration and environmental conditions, may be interpreted.

Epidemiological studies have commonly been of “panel” design, following a cohort prospectively with frequent observations analysed using time series methods. Air pollutant levels are expressed as a series of time averaged observations, so that the temporal relation between exposure and outcome is studied. The collection of individual level outcome data also means that hypothesis testing can provide strong evidence of associations at that level. As pollutant exposure is common to all members of the cohort, a traditional “control” group is not needed, each subject acting as his or her own control, and only covariates that vary across time within an individual need be considered by the analysis.

Subjects are followed for a predetermined period during which individuals typically record daily symptom and lung function data (for example, peak expiratory flow, PEF) in a diary. Such studies generally aim to investigate the acute effects of pollutants across a typical range of environmental conditions and may continue for many months. In this way they are distinguished from “event studies”, which seek to determine the response to pollution episodes. This distinction may require a judgement based on study duration and environmental conditions, and is necessarily subjective and open to interpretation.

The analysis of panel study data relates pollutant exposure to measures of outcome in regression models that account for time varying confounders and serial correlation in these data. Regular observations of a continuous physiological measure such as PEF (as absolute values or some metric of individual change) are commonly fitted to linear models, while logistic regression may be preferred for symptom records producing a binary series of observations, either as the simple occurrence of a symptom in an individual (prevalence) or the occurrence of new symptom episodes (incidence). Two broad analytical approaches are recognised. Either a group average outcome measure is derived for each time point and the resulting time series regressed on the predictors of interest, or the analysis is repeated for each subject with the same model predictors, and the resulting individual effect estimate pooled to derive an overall average effect. In both cases, an adequate model will consider the...
Panel studies from varied settings report an adverse effect of short term increases in particulate air pollution on children’s respiratory health. The effects of particulate air pollution on PEF appear to be greater for PM$_{2.5}$ than PM$_{10}$. Results are very heterogeneous, limiting the confidence that may be placed on summary measures of effect. Effect estimates vary according to the study population, setting, and analytical approach, and appear to be greater in conditions of high ozone and where either generalised estimating equations are used to model autocorrelation, or overall results are obtained by pooling subject specific regression coefficients.

There is evidence consistent with publication bias, at least for PM$_{10}$ and PEF.

The degree of heterogeneity evident between panel study results questions the transferability of estimated effect sizes between locations or populations, and limits the use of summary measures in quantitative risk assessment.

Further research is required to characterise the sub-population of children most at risk of particulate health effects, the impact of different analytical strategies on estimated effect size, and the possibility of interaction between particulates and ozone.

Policy implications

For the purposes of this review, the term “panel study” was defined as a prospective cohort study where individual level observations of lung function or respiratory symptoms, as well as air pollutant records, were collected at least daily for not less than eight weeks. Only studies that presented results for children (under 18 years old) and particulate air pollution as PM$_{x}$ (mass concentration of particles less than $x$ μm aerodynamic diameter) derived using an appropriate regression model that controlled for the impact of trend(s), weather (or at least temperature), and autocorrelation, were considered for inclusion. Major bibliographic databases (Medline, Embase, Science Citation Index (Web of Science Interface)—the latter better representing environmental journals) were searched from 1966 (Medline) to June 2002 using a broad strategy consisting of the truncated word terms air pollu*, PM*, partic* (MESH thesaurus terms and text words) combined (“AND”) with terms for longitudinal study design or the text words “panel” or “cohort”. Results were restricted by age, but further refinement (for example, by outcome) was found to omit known studies. Consequently, this strategy resulted in a very large number of non-relevant “hits”. The search was complemented by inspecting the reference lists of the papers retrieved as well as reviews, hand searching major respiratory, epidemiological and environmental journals from 1996 onwards, and consulting books and reports known to the authors.

While checklists for the assessment of study validity are available, these concentrate on study design and are not easily applicable where studies are selected on the basis of study type. Therefore all studies that collected and analysed data in a manner consistent with the definition of a panel study offered above were given equal weight. However, information on analytical strategy (outcome measure, statistical methodology and consideration of trends, time varying confounders, and autocorrelation), population and setting were collated in a structured way. Where possible, attempts were made to express results in a uniform manner—that is, health effects were calculated per unit change (pg.m$^{-3}$) pollutant.

Study results, their relative size, precision, pattern of effects and degree of heterogeneity, were explored visually using forest plots, which display both the mean and interval effect size for a number of studies simultaneously, also indicating their relative size with a graphical marker (StatsDirect, version 2.2.0, Cambridge, UK). A statistical test of heterogeneity, Q-combinality (based on the $\chi^2$ distribution), was employed for all studies and groups based on analytical strategy, study setting, and population. However, such tests have relatively poor power to detect deviations from an assumption of homogeneity, and should not be relied on alone.

Effect estimates for all studies, or subgroups thought to explain heterogeneity in the results, were pooled to provide a weighted mean estimate of effect. The simplest approach employs a weighting relative to the inverse of the variance of each study’s estimate. This approach (precision weighting) may be straightforwardly applied to lung function results. However, techniques for pooling results for dichotomous outcomes from cohort studies are based on the difference in...
### Table 1 Main characteristics of studies identified for inclusion in the review (n = 22); pollutant levels reported as 24 average values unless specified otherwise

<table>
<thead>
<tr>
<th>Study setting</th>
<th>Population characteristics and number (n)</th>
<th>Measured particulates (PM) and peak levels</th>
<th>Measured co-pollutants (peak levels)</th>
<th>Analytical approach</th>
<th>Terms included in regression model</th>
</tr>
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<tbody>
<tr>
<td>Utah Valley, USA, Dec 1989 to Mar 1990</td>
<td>Unselected, aged 9–11 (41)</td>
<td>PM$_{10}$ 195 µg m$^{-3}$</td>
<td>NO$_2$ (note: very low ozone and undetectable PSA and H$_2$SO$_4$)</td>
<td>Regression of daily group symptom prevalence (logistic model) and mean of individuals’ daily PEF deviations (linear model)</td>
<td>Linear trend, temperature, autocorrelation (GEE approach for logistic models)</td>
</tr>
<tr>
<td>Utah Valley, USA, 1990 to 1991</td>
<td>Symptomatic or asthmatic (39) and non-symptomatic (40), aged 9–11</td>
<td>PM$_{10}$ 251 µg m$^{-3}$</td>
<td>SO$_2$ (105 µg m$^{-3}$), NO$_2$, other aerosols including HNO$_3$ (10.6 µg m$^{-3}$), SO$_4^{2-}$ (29.7 µg m$^{-3}$), NO$_3$ (36.8 µg m$^{-3}$), PSA</td>
<td>Regression of daily group symptom incidence/prevalence (logistic model) and mean of individuals’ daily PEF z-scores (linear model)</td>
<td>Linear trend, temperature, autocorrelation (1st order)</td>
</tr>
<tr>
<td>The Netherlands, winters of 1987–88 to 1989–90</td>
<td>Unselected, aged 7–11 (up to 390)</td>
<td>PM$_{10}$ 174 µg m$^{-3}$</td>
<td>Ref. (9), taking anti-asthma medication, aged 7–13 (61)</td>
<td>Regression of daily group symptom prevalence (logistic model) and mean of individuals’ daily PEF z-scores (linear model)</td>
<td>Linear trend, temperature, autocorrelation (1st order)</td>
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<tr>
<td>The Netherlands, winter 1990 to 1991</td>
<td>Unselected, aged 6–12 (73)</td>
<td>PM$_{10}$ 363 µg m$^{-3}$</td>
<td>NO$_2$, SO$_2$ (200 ppb), hourly maximum ozone (370 ppb)</td>
<td>Regression of daily group symptom prevalence/medication use (logistic model) and mean of individuals’ daily PEF z-scores (linear model)</td>
<td>Linear trend, temperature, autocorrelation (GEE approach for logistic models)</td>
</tr>
<tr>
<td>Mexico City, 1991 to 1992</td>
<td>Asthmatics, aged 5–13 (71)</td>
<td>PM$_{10}$ 171 µg m$^{-3}$</td>
<td>NO$_2$, SO$_2$ (40 ppb), NO$_x$, O$_3$ (8 hour mean 87 ppb), SO$_4^{2-}$ (15 µg m$^{-3}$), PSA (372 nmol m$^{-3}$)</td>
<td>Regression of daily group symptom incidence/prevalence (logistic model) and mean of individuals’ daily PEF z-scores (linear model)</td>
<td>Linear trend, temperature, autocorrelation (1st order)</td>
</tr>
<tr>
<td>Eastern Europe (Erfurt and Weimar), Germany and Sokolov, Czech Republic, winters 1990 to 1992</td>
<td>Unselected, aged 6–15 (up to 163)</td>
<td>PM$_{10}$ 83 µg m$^{-3}$</td>
<td>Ref. (2), taking anti-asthma medication, aged 6–15 (132)</td>
<td>Regression of daily group symptom prevalence (logistic model) and mean of individuals’ daily PEF z-scores (linear model)</td>
<td>Linear trend, temperature, autocorrelation (1st order)</td>
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<tr>
<td>Six Cities, USA, 1984 to 1988</td>
<td>Unselected, aged 6–10 (1844)</td>
<td>PM$_{10}$ 117 µg m$^{-3}$</td>
<td>SO$_2$ (8 ppb), NO$_x$, O$_3$ (hourly mean 87 ppb), SO$_4^{2-}$ (15 µg m$^{-3}$), PSA (372 nmol m$^{-3}$)</td>
<td>Regression of daily group symptom incidence/prevalence (logistic model) and mean of individuals’ daily PEF z-scores (linear model)</td>
<td>Linear trend, temperature, autocorrelation (1st order)</td>
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<tr>
<td>Uniontown, Pennsylvania, USA, summer 1990 and 1991</td>
<td>Symptomatic (71), and non-symptomatic (27), aged 9–11</td>
<td>PM$_{10}$ 83 µg m$^{-3}$</td>
<td>NO$_2$, SO$_2$ (26.5 ppb), NO$_x$, O$_3$ (92.3 ppb), SO$_4^{2-}$ (481 nmol m$^{-3}$), PSA (676 nmol m$^{-3}$)</td>
<td>Regression of daily group symptom prevalence (logistic model) and mean of individuals’ daily PEF z-scores (linear model)</td>
<td>Linear trend, temperature, autocorrelation (1st order)</td>
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<tr>
<td>State College, Pennsylvania, USA, summers 1990 and 1991</td>
<td>Symptomatic (42), and non-symptomatic (46), aged 9–11</td>
<td>PM$_{10}$ 82.7 µg m$^{-3}$</td>
<td>Ref. (4), taking anti-asthma medication, aged 9–11 (237)</td>
<td>Regression of daily group symptom prevalence (logistic model) and mean of individuals’ daily PEF z-scores (linear model)</td>
<td>Linear trend, temperature, autocorrelation (1st order)</td>
</tr>
<tr>
<td>Surrey, UK, summer 1994</td>
<td>Unselected, aged 6–10 (10)</td>
<td>PM$_{10}$ 150 µg m$^{-3}$</td>
<td>NO$_2$, SO$_2$ (8 hour mean 128 ppb)</td>
<td>Regression of daily group symptom prevalence (logistic model) and mean of individuals’ daily PEF z-scores (linear model)</td>
<td>Linear trend, temperature, autocorrelation (1st order)</td>
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<tr>
<td>The Netherlands, summer 1995</td>
<td>Chronically ill children (77% taking anti-asthma medication), aged 7–13 (61)</td>
<td>PM$_{10}$ 60.3 µg m$^{-3}$</td>
<td>Ozone (8 hour mean 111 ppb)</td>
<td>Regression of daily group symptom prevalence (logistic model) and mean of individuals’ daily PEF z-scores (linear model)</td>
<td>Linear trend, temperature, weekend indicator, autocorrelation (1st order)</td>
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<td>Vancouver, Canada, 1990 to 1992</td>
<td>Asthmatic (132) and non-asthmatic (74), aged 6–13</td>
<td>PM$_{10}$ 159 µg m$^{-3}$</td>
<td>Ref. (5), taking anti-asthma medication, aged 6–13 (237)</td>
<td>Regression of daily group symptom prevalence (logistic model) and mean of individuals’ daily PEF z-scores (linear model)</td>
<td>Linear trend, temperature, weekend indicator, autocorrelation (1st order)</td>
</tr>
<tr>
<td>The Netherlands, winters 1992–93 to 1994–95</td>
<td>Symptomatic (136), and non-symptomatic (99), aged 7–11, with and without bronchial hyperreactivity or increased IgE levels</td>
<td>PM$_{10}$ 112 µg m$^{-3}$ urban and 242 µg m$^{-3}$ rural</td>
<td>SO$_2$ (urban 152 µg m$^{-3}$, rural 43 µg m$^{-3}$), NO$_2$, SO$_2$ (urban 24 µg m$^{-3}$, rural 23 µg m$^{-3}$)</td>
<td>Regression of daily group symptom prevalence (logistic model) and mean of individuals’ daily PEF z-scores (linear model)</td>
<td>Linear trend, temperature, weekend indicator, autocorrelation (1st order)</td>
</tr>
<tr>
<td>California, USA, Autumn 1995</td>
<td>Asthmatics, aged 9–17 (25)</td>
<td>PM$_{10}$ 54 µg m$^{-3}$</td>
<td>Ozone (8 hour mean 110 ppb)</td>
<td>Regression of daily group symptom prevalence (logistic model) and mean of individuals’ daily PEF z-scores (linear model)</td>
<td>Linear trend, temperature, weekend indicator, autocorrelation (1st order)</td>
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</tbody>
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Note: PM$_{10}$ = Particulate Matter 10 micrometers or less in diameter.
outcome frequencies among exposed and non-exposed individuals, treating each study as a series of weighted 2 x 2 contingency tables. Such techniques could not be used in this case, and so where symptom results were derived from logistic regression, the log of the odds ratio (OR) was treated as a continuous outcome and precision weighting applied to studies. This method of pooling results implies a "fixed effects" model (FE)—that is, it assumes that studies are contributing data for both urban and rural panels. 3 Eleven of the identified studies were conducted in North America, with nine of the remainder from Europe (four from the Netherlands). In addition, 44 studies were retrieved for detailed review and subsequently rejected. Most of these did not present separate data for children (n = 11), did not measure PM (n = 8), or did not either (n = 18). Other studies were rejected on the basis of recording outcome data less often than daily (n = 2) or for less than five weeks (n = 4), and not presenting the analytical model (n = 1).

### Pollutants measured

Fifteen studies reported ozone measurements (including three where levels were undetectable)\(^{29-31}\). The majority of those that did not were European studies conducted in winter\(^{25-28}\) although studies from Vancouver\(^{22}\) and Bangkok\(^{33}\) also omitted ozone. Sulphur dioxide (SO\(_2\)) measures were omitted in 10 studies,\(^{19, 21, 29, 30, 32, 37}\) Measurements of sulphate (SO\(_4^{2-}\)) or particulate strong acidity (PSA) were included in 11 studies (levels were reported as undetectable in the Utah Valley studies\(^{29-32, 36-38}\) and 12 studies reported either the mass or number concentrations (PM\(_x\) analogous to PM\(_x\)) of more than one particle size fraction.\(^{20-22, 24, 32, 35, 37}\) and 19–42

### RESULTS

#### Setting and study population of included studies

The search identified 22 individual or linked panel studies of children that used daily PM measures of particulates and were analysed according to the inclusion criteria (table 1). Five were summer studies,\(^{19-24}\) while another five were conducted in winter conditions,\(^{25-28}\) including the largest study, "Pollution Effects on Asthmatic Children in Europe" (PEACE), a European collaboration involving 14 centres contributing data for both urban and rural panels.\(^{1}\) Eleven of the identified studies were conducted in North America, with nine of the remainder from Europe (four from the Netherlands). In addition, 44 studies were retrieved for detailed review and subsequently rejected. Most of these did not present separate data for children (n = 11), did not measure PM (n = 8), or did not either (n = 18). Other studies were rejected on the basis of recording outcome data less often than daily (n = 2) or for less than five weeks (n = 4), and not presenting the analytical model (n = 1).

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All except two studies\(^{35, 37}\) reported daily average PM concentrations in excess of 50 \(\mu g.m^{-3}\), although in two studies peak levels exceeded this level by 10 \(\mu g.m^{-3}\) or less.\(^{19, 34}\) Ozone levels (8 hour running mean) exceeded...
50 ppb (100 μg.m⁻³) in nine studies; six from North America¹⁰⁻¹² ³⁴ ³⁵ ³⁷ and three from elsewhere.¹⁹ ²³ ³⁶ In contrast, only four studies reported 24 hour mean SO₂ concentrations greater than 47 ppb (125 μg.m⁻³); three from Europe (including some settings within the PEACE study)³² ⁵² ⁷ and one from the USA.³⁸

Study populations

The age range of subjects typically spanned 6 to 11 years. Older children were included in nine studies; four extending the range to 13 years,¹⁹ ³² ³⁷ ⁴⁰ two to 15 years,²⁷ ³¹ and one to 17 years.³⁴ The majority of studies (15) recruited panels of children either diagnosed with asthma or with reported pre-existing respiratory symptoms (“symptomatic subjects”). In seven studies, both symptomatic and non-symptomatic subjects were recruited, although in only three were the results presented in such a way as to permit a direct comparison of effects.²⁵ ³⁰ ³⁹ Four studies presented analyses stratified by use of anti-asthma medication³ ²⁵ ²⁷ ³¹ ⁴³–⁴⁵ and two considered subgroups based on the presence of bronchial hyperreactivity and/or increased serum IgE concentrations.²⁵ ³⁶ ⁴³

Analytical approach of included studies

A two stage analytical approach was adopted by five studies,¹⁹ ²³ ³² ³⁴ the remainder employing a population daily average outcome in their analyses. Potential autocorrelation effects were modelled using GEEs in 11 studies; nine originating from North America²⁰ ²¹ ²⁹ ³⁰ ³² ³⁷ ³⁸ ⁴⁰ (of which two utilised a two stage analytical approach) and two from elsewhere.³¹ ³⁶ While all adjusted their regression models for the effects of weather, only 10 studies considered variables other than a term for temperature alone.²³ ²⁷ ³¹–³⁷ ³⁹ Dummy variables denoting weekdays or schooldays were included in the reported models from six studies,³¹ ⁶² ⁷³ ⁷³ ⁹² while three considered outdoor pollen counts,¹⁹ ²³ ³⁶ one considered “fever”,²⁷ and one time spent outdoors.³⁶

Reported effect size; peak expiratory flow

Pollutant effects on lung function were a reported outcome measure in 19 studies (table 1) and the results for 15 of these are presented in a summary forest plot (fig 1). The plots display the largest effect size observed over various pollutant lags, excluding those for multiple day averages where possible. For PM₁₀, a wide spread of results was observed (mean estimates from −0.16 to +0.01 L.min⁻¹ per μg.m⁻³), all except one in an adverse direction. Results for PM₂.⁵ showed a greater range of absolute values (mean estimates −0.05 to −0.28 L.min⁻¹ per μg.m⁻³) although their interval estimates overlapped more closely. The results of four studies could not be displayed in this manner. The first, from Surrey, UK, used spirometry and showed associations between
increased PM$_{10}$ and falls in FEV$_1$ and FVC (0.07 and 0.17 ml per g.m$^{-3}$ respectively), while results from two others (Netherlands and Paris) could not be expressed as PEF change. The Dutch study found that the odds of a significant PEF decline were increased with increased PM$_{10}$, while the French study concluded that increased PM$_{10}$ led to a PEF fall in mild, but not more severe, asthmatics (as judged by inhaled corticosteroid dose). Finally, no appropriate quantitative data could be extracted from one paper.

Results for PM$_{10}$ from fig 1 were pooled to derive a FE summary estimate (table 2). The forest plot suggested that the study results were not homogeneous, and formal testing of heterogeneity supported this view (table 2). An RE model was chosen, which produced a much greater estimated effect size, giving much greater weight to the PEACE study. and potential reasons for the large variability were therefore explored.

These results were generally the "headline" or main reported estimate for each study (typically the greatest effect size found) and most related to either the same or previous day’s pollutant levels. There were both two days’ and three day’s levels, and results for moving average (four or five day’s) levels are presented by only five studies. Their exclusion did not materially affect the pooled estimate (table 2). Only three studies employed a two stage analytical approach and their pooled effect estimate (FE) was considerably greater than that from other studies.

In addition, there was less evidence of heterogeneity between results from these studies. The majority of studies primarily considered asthmatic or symptomatic children. However, the pooled estimate (FE) for other individuals derived from five studies differed. The study conducted in the Utah Valley, USA indicated a greater effect among symptomatic children, while the study from the UK West Midlands did not. Studies with high peak ozone levels (eight hour average greater than 50 ppb) produced a pooled estimate (FE) greater than that for all studies as a whole (table 2).

Pooled results for PM$_{2.5}$ (table 2, fig 1) suggest a greater effect size per unit pollutant than for PM$_{10}$ and reduced heterogeneity among results ($0.05 > p > 0.025$), although the summary estimate derived from a RE model was still considerably greater than that from an FE approach. A direct comparison of the relative effects of these PM metrics was available from four studies; in three, the impact of PM$_{2.5}$ is (non-significantly) greater than that of PM$_{10}$ per unit pollutant, while one study reports the reverse.

Results from the remaining 14 studies investigating pollutant effects on reported symptoms are presented in two summary forest plots (figs 2 and 3). The plots for PM$_{10}$ and PM$_{2.5}$ display the largest effect size obtained over various pollutant lags excluding those for multiple day averages where possible, and exclude one study that provided insufficient data for further analysis. For PM$_{10}$, results were again widely spread (mean OR estimates range from 0.999 to 1.034 for cough and 0.998 to 1.034 for LRS) and approximately half of all reported results were not themselves statistically significant (more so in the case of LRS).

Pooling the results for PM$_{2.5}$ (FE) suggests no overall effect for cough, and a very small, but statistically significant ($p < 0.05$) effect for LRS (tables 3 and 4). In both cases, the precision weighted mean is dominated by the results from the two large multicentre studies. However, the forest plots suggest considerable heterogeneity that was statistically significant. Summary ORs from RE models show increased effect sizes, and potential sources of heterogeneity were further explored through subgroup analysis.

The pooled results for LRS include both studies reporting a composite endpoint as well as those reporting the symptom wheeze alone. Excluding the latter (five studies did not change the summary estimate (FE). For cough, eight studies analysed the symptom records as prevalent data, the remainder converting the raw data to incident episodes. For
LRS, almost all studies were analysed as prevalence. Omitting results relating to incident data did not alter either FE summary effect estimate (tables 3 and 4). As for PEF, the results presented generally reflect the pollutant lag with the greatest effect size. However, for cough, the results for only four studies relate to lags greater than two days\(^31\) \(^37\) or multiple day averages,\(^32\) \(^38\) and for LRS, all except three results relate to the same or previous day’s pollutant levels.\(^32\) \(^37\) \(^39\) The exclusion of these studies did not alter either summary effect estimate (tables 3 and 4). A two stage analytical approach was used by four studies \(^19\) \(^32\) \(^34\) \(^40\) and pooling their results (FE) suggests a greater estimated effect size among these studies than for results as a whole. Importantly, for LRS there was also less evidence of heterogeneity among these results (0.10 \(p\) > 0.05, table 4). GEEs were used to model autocorrelation effects in seven studies \(^29\) \(^2\) \(^32\) \(^37\) \(^38\) \(^40\) and again, pooled results (FE) suggest a larger overall estimated effects for these studies, although heterogeneity remained.

Few studies presented results for children not selected on the basis of asthma or pre-existing respiratory symptoms. However, those that did suggested greater pollutant effects among non-symptomatic children (tables 3 and 4), particularly for LRS,\(^26\) \(^29\) \(^30\) \(^31\) \(^38\) \(^39\) and for cough, their results appeared more homogeneous than for all studies (0.025 \(p\) > 0.01).\(^26\) \(^38\) \(^39\) \(^31\) \(^38\) Of just two studies that presented direct comparisons of such children, one indicated a small increased effect of PM\(_{10}\) on symptoms in children with asthma or pre-existing symptoms,\(^41\) while the other showed no difference for cough.\(^41\) Pooled results from studies conducted in conditions of relatively high ozone suggest a greater impact of PM\(_{10}\) on both cough and LRS than for studies as a whole, although there was little evidence of homogeneity among studies reporting either outcome (tables 3 and 4).\(^19\) \(^34\) \(^37\) \(^38\) In contrast, results from panels with high SO\(_2\) levels (excluding PEACE 3) showed little if any pollutant effect.\(^27\) \(^38\) \(^43\) Pooled results for PM\(_{2.5}\) suggest a greater effect size than PM\(_{10}\), with reduced heterogeneity among results, particularly for LRS (0.05 \(p\) > 0.025, tables 3 and 4, figs 2 and 3). Results obtained from RE models remained considerably greater than those for FE models. Four studies each reporting results for cough and LRS provide a direct comparison between the effect size of PM\(_{10}\) and PM\(_{2.5}\). Results for PM\(_{2.5}\) were reported as (non-significantly) greater than for PM\(_{10}\) (per unit pollutant),\(^39\) \(^40\) approximately the same,\(^24\) \(^38\) and in one case lower (significantly so for cough).\(^17\) Again, studies were mostly derived from settings experiencing high ozone levels and environmental influences were not therefore

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Figure 2. Mean and 95% confidence interval estimates of the impact of PM\(_{10}\) and PM\(_{2.5}\) on reported cough, expressed as the multiplicative change in symptom odds per \(\mu g.m^{-2}\) rise in pollutant. “Symptomatic” indicates subjects with pre-existing respiratory symptoms or asthma and symptoms analysed as prevalence data unless indicated otherwise (incidence).
explored. Only one study considered asthmatic or symptomatic children for either outcome and its estimates were at the lower end of the range of results; one of three non-significant results for LRS.

Funnel plot for PEF results
The possibility of publication bias was considered among studies contributing to the pooled estimate for PM10 and PEF (fig 1). The resulting funnel plot is markedly asymmetrical (fig 4), showing a strong association between increasing effect size and decreasing size of the study estimate’s standard error.

DISCUSSION AND CONCLUSIONS
This review identified a large number of relevant panel studies reporting results for both PEF and symptoms, and while the majority suggest an adverse effect of outdoor particulate matter, their estimates of effect vary considerably. In general, comparisons between studies suggest a greater effect size for PM2.5 per unit pollutant compared to PM10, especially for PEF results where this pattern is mirrored in the available within-study comparisons, and while results for PM10 and cough were more often in the direction of adverse effect than those for LRS, a FE pooling of the results for cough was not statistically significantly different from zero, while that for LRS was. Effect estimates for all outcomes were small, in that the average change in lung function or increase in symptom odds per unit pollutant rise were far less than those that would be considered clinically relevant in an individual. However, pollutant levels vary by factors much greater than just unit changes and susceptibility to pollutant effects are likely to vary within the general population. For a
50 μg·m⁻³ rise in PM₁₀, the FE pooled estimate for PEF would suggest a mean fall of just 0.6 L·min⁻¹ and the RE estimate a fall of 1.7 L·min⁻¹, yet when individual level data from five panel studies of children²⁰⁻²¹, ²₈–₃₀ were re-analysed in terms of the odds of a significant PEF decline, the results indicated that a realistic rise in PM₁₀ may greatly increase the chance of a clinically significant decrement in lung function (odds of a 10% fall in PEF increased by 89% for a 100 μg·m⁻³

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Method of pooling or subgroup</th>
<th>Multiplicative change in symptom odds per unit (μg·m⁻³) increase in pollutant</th>
<th>Expected impact on symptom odds of a 50 μg·m⁻³ rise in pollutant</th>
<th>Q test</th>
<th>p value</th>
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*Number greater than the total number of studies as some studies present results separately for symptomatic and non-symptomatic/asthmatic children.

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levels for the outcome of interest means that the final results (and confidence intervals) reflect only changes in those average levels. On the other hand, final results from a two stage analysis reflect the mean and spread of individual responses to pollutants. A reanalysis of the West Midlands, UK data using a two stage approach with the same terms incorporated into the regression analyses, resulted in effect estimates for PEF that were much smaller than those from the original analyses (Ward and Ayres, 2002, personal communication), the reverse of the pattern seen between studies in this review. However, the interval estimates were generally reduced even further resulting in more “statistically significant” results (for PM$_{10}$, $-0.029$ L min$^{-1}$ per µg m$^{-3}$ rise, 95% CI $-0.070$ to $0.11$; for PM$_{2.5}$, $-0.060$ L min$^{-1}$ per µg m$^{-3}$ rise, 95% CI $-0.106$ to $0.015$). The generalisability of these observations is not known and requires the reanalysis of further datasets to provide additional within-study comparisons.

Further exploration of the observed variation in study estimates also implicated aspects of the study setting and panel selection. Pooled estimates suggest that studies conducted in conditions of high peak ozone levels produced greater PM$_{10}$ estimates of effect for all outcomes than studies in other settings. This finding could arise if the effects of particulates were enhanced in such circumstances or were qualitatively different in summertime. However, confounding could equally explain these results. This might occur if studies reporting these conditions generally also recruited more susceptible children or used a different analytical approach, because children spend more time outdoors in summer and are more affected by outdoor pollutants, or because the two pollutants are closely associated and the estimate for PM$_{10}$ is not sufficiently corrected for the effects of ozone. There was no indication of a similar pattern of results for PM$_{2.5}$, although there were fewer studies to consider and virtually all estimates were derived from North American settings. Two-pollutant models are subject to problems of collinearity and may be difficult to interpret. However, several studies have presented the results of models incorporating measures of fine or secondary particulate matter and ozone: two studies from Mexico showed a persisting effect of PM$_{2.5}$ after controlling for ozone, and the effect of summertime particulate sulphate on PEF predominated over that of ozone in a study of children from Philadelphia. No similar data have been published for PM$_{10}$ although results from the Harvard Six Cities Study reveal a persisting effect of PM$_{2.5}$ on LRS, and coarse particles (PM$_{2.5–10}$) on cough, in models that include both measures.

Pooled estimates also suggested that effect estimates for PM$_{10}$ derived from panels selected on the basis of a history of asthma or asthmatic symptoms were smaller than those derived from subjects without such a history. However, there was considerable variation in the criteria used to select children, ranging from children diagnosed as asthmatic on the basis of reported wheeze, doctor diagnosed asthma, and/or chronic cough to those recruited with cough alone or with abnormal pulmonary function. In contrast, less than half of subjects from the panels in Pennsylvania 1990–91, reported no recent respiratory symptoms, although there was no apparent intention to recruit a “symptomatic” cohort of children. Thus, the great variation in criteria for panel recruitment makes the relative susceptibility of various groups hard to determine from between-study comparisons and may contribute to the heterogeneity among results.

The pooled estimates presented in this review should be considered in the light of the markedly asymmetrical funnel plot obtained for the PM$_{10}$ and PEF results. This raises the possibility of publication bias, whereby small studies are less likely to be published if they have “negative” findings. Ideas

**Figure 4** Funnel plot illustrating the relation between the size of either single study or pooled effect estimates, and the precision (inverse of standard error, SE) of those estimates, for results contributing to the pooled estimates of the effect of PM$_{10}$ on PEF (fig 1 and table 1).
regarding the relation between study size and validity have been developed in the context of clinical trials, and it may be that for observational studies, a small study that characterises exposure and confounding factors well may be more valid than a large one that does not or that the precision of an effect estimate is determined by the variability in exposure, and this could plausibly be related to the reported effect size. In addition, asymmetry may also arise where any principal cause of heterogeneity is distributed non-randomly across studies of different sizes. These include those considered here such as study population, setting, study design, and analysis.

In summary, this review of panel studies in children has shown a small overall effect of particles, especially for PEF where the effects of PM$_2.5$ appear to be greater than for PM$_{10}$. However, there is evidence of considerable heterogeneity among results and this prevents too much confidence being placed on the summary measures of effect. This may be a reflection of factors such as susceptible sub-populations or differing analytical approaches, but it does have implications when considering transferability of effect size or when considering use of the summary estimates in quantitative risk assessment. There is a suggestion that the effects of particles are greater when ozone levels are higher, similar to the finding in some studies for hospital admissions. However, this finding could be due to confounding, either in the selection of studies or because of inadequate allowance for interaction between ozone and particle effects. Furthermore, there is evidence that could suggest publication bias and the authors believe that the magnitude of particle effects on children’s health at lower levels of morbidity and exposure remains to be clearly defined.

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