Ambient air pollution and risk of congenital anomalies in England, 1991—1999

H Dolk,¹ B Armstrong,² K Lachowycz,² M Vrijheid,²,³ J Rankin,⁴ L Abramsky,⁵ P A Boyd,⁶ D Wellesley⁷

ABSTRACT

Objectives To investigate whether there is an association between risk of congenital anomaly and annual ward level exposure to air pollution in England during the 1990s.

Methods A geographical study was conducted across four regions of England using population-based congenital anomaly registers, 1991—1999. Exposure was measured as 1996 annual mean background sulphur dioxide (SO₂), nitrogen dioxide (NO₂) and particulate matter (PM₁₀) concentrations at census ward level (n=1474). Poisson regression, controlling for maternal age, area socioeconomic deprivation and hospital catchment area, was used to estimate relative risk for an increase in pollution from the 10th to the 90th centile.

Results For non-chromosomal anomalies combined, relative risks were 0.99 (95% CI 0.93 to 1.05) for SO₂, 0.97 (95% CI 0.84 to 1.11) for NO₂ and 0.89 (95% CI 0.75 to 1.07) for PM₁₀. For chromosomal anomalies, relative risks were 1.06 (95% CI 0.98 to 1.15) for SO₂, 1.11 (95% CI 0.95 to 1.30) for NO₂ and 1.18 (95% CI 0.97 to 1.42) for PM₁₀. Raised risks were found for tetralogy of Fallot and SO₂ (RR=1.38, 95% CI 1.07 to 1.79), NO₂ (RR=1.44, 95% CI 0.71 to 2.93) and PM₁₀ (RR=1.48, 95% CI 0.57 to 3.84), which is of interest in light of previously reported associations between this cardiac anomaly and other air pollutants.

Conclusions While air pollution in the 1990s did not lead to sustained geographical differences in the overall congenital anomaly rate in England, further research regarding specific anomalies is indicated.

INTRODUCTION

There is growing epidemiological evidence for adverse effects on the fetus and newborn of maternal exposure to air pollution.¹ ² The strongest evidence of a causal association relates to infant mortality, particularly postneonatal respiratory mortality, and low birth weight.¹ ² There is less evidence differentiating the two main components of low birth weight: preterm birth and intrauterine growth retardation.¹ Two recent American studies of cardiac defects and oral clefts have suggested associations between specific pollutants and specific cardiac defects,³ ⁴ and have been followed by further studies mainly concentrating on the same malformations.⁵ ⁷ Possible mechanisms of teratogenicity are at this stage speculative¹ but may include somatic effects on DNA interfering with basic processes such as programmed apoptosis (cell death), effects through early fetal growth, and indirect effects through maternal immune effects, infection, or asthma or related medication. DNA adduct levels have been found to be higher in maternal blood and placentas in areas with high pollution levels.¹ Maternal smoking is an analogous although stronger source of exposure to air pollutants for which there is some evidence of teratogenicity, particularly in relation to orofacial clefts, limb reduction defects and gastrochisis,⁸—¹¹ but as yet there is no evidence for an effect of environmental tobacco smoke.

We report the results of a study analysing a population-based database of congenital anomalies in four regions of England for 1991—1999 to investigate associations between a wide range of selected congenital anomalies and mean annual ward level exposure to sulphur dioxide (SO₂), nitrogen dioxide (NO₂) and particulate matter (PM₁₀).

METHODS

Design
This was a geographical study examining the relationship between the congenital anomaly rate in census wards for 1991—1999 and relative annual average exposure to a range of air pollutants.

Population and data
We drew on data from a database that has been previously described¹²—¹⁴ Data were contributed by four English registers of congenital anomaly (Wessex, North West Thames, Oxford, Northern) for the period 1991—1999 (1994—1999 for Wessex). These registers cover the cities of Southampton, part of London, Oxford and Newcastle, as well as surrounding areas, and all operate active ascertainment procedures.¹⁵ The study population comprised 759 995 births (live and still) in 1474 census wards, after excluding 377 wards near boundaries where more than 20% of mothers were delivering in

What this paper adds

► Some studies have found an association between risk of specific congenital cardiac defects and maternal exposure to air pollution during pregnancy.
► Whether air pollution confers a risk for other types of congenital anomaly is largely unknown.
► This study finds no association between average annual exposure to SO₂, NO₂ and PM₁₀ of the area of residence and risk of congenital anomalies in general or a wide range of specific congenital anomaly types.
► An association between risk of tetralogy of Fallot and exposure to SO₂ was found.
hospitals outside the area (where full case ascertainment was less certain). In the study area, 94.6% of mothers delivered in hospi-
tals within the register areas. Cases were geographically located
(by postcode of residence at delivery) down to census enumera-
tion district, small areas comprising about 1000 residents. In three
of the regions, a small proportion of cases could not be
geographically located (North Thames 0.8%, Wessex 6.3%,
Oxford 1.7%). Births in each enumeration district, stratified by
maternal age, were obtained from the Office for National
Statistics and adjusted down pro-rata in enumeration districts in
electoral wards in which less than 100% (ie, 80%–99%) of births
were in hospitals covered by the registry, and by the proportion of
unlocated cases in each region. Maternal age was classified into
the categories <20, 20–24, 25–29, 30–34, 35+ for non-chromosomal
and <30, 30–34, 35+ for chromosomal anomalies (large pre-specified
categories were required due to confidentiality restrictions over
release of denominator data, and thus the most relevant cate-
gories were obtained for each group). The Carstairs index of
depression16 was calculated for enumeration districts based on
1991 census data on social class of head of household, car
ownership, unemployment and overcrowding, standardised to
Great Britain. Study population enumeration districts were
divided into quintiles according to their Carstairs score. Maternal
age and socioeconomic deprivation were the only two relevant
risk factors which could be obtained for both congenital anomaly
cases (register data) and all births.

Case definition and ascertainment
We included cases of selected congenital anomalies among live
births, fetal deaths from 20 weeks gestation, and terminations
of pregnancy following prenatal diagnosis of any gestational age.12 13
Malformations were coded according to the International Clas-
sification of Diseases (ICD) version 9 or 10 (up to nine codes per
baby/foetus). We included only anomaly types that are well defined
and recorded by the agreement of participating registries. We
excluded minor anomalies according to the standard European
Surveillance of Congenital Anomalies (EUROCAT) exclusion
list,17 anomalies which are often variably recorded (eg, ventricular
septal defects (VSD)) or only recorded by one register (hypospa-
dias), and tumours and neoplasms, metabolic anomalies and
deformations. Mendelian syndromes were excluded. The range of
ICD-10 codes for inclusion was as follows: Q00–Q07, Q09, Q20,
Q05, Q110–Q112, Q160, Q172, Q20, Q211–Q219, Q22–Q23,
Q25–Q26, Q300–Q348, Q35–Q37, Q390–Q394, Q41, Q42, Q600–Q605,
Q61, Q641–Q643, Q645, Q794, Q71–Q73, Q77, Q78, Q790–Q793,
Q90–Q94 and Q96–Q99.

We classified cases into non-chromosomal and chromosomal
anomalies. A priori decisions were made to analyse in addition
the more frequent subgroups, based on EUROCAT coding
subgroups for ICD-9 and ICD-10 (14): neural tube defects,
hydrocephaly, cardiac defects, cleft lip with or without cleft
palate, cleft palate, digestive system atresias, bilateral renal
agenesis, cystic kidney disease, limb reduction, diaphragmatic
hernia, omphalocele, gastrochisis, multiple anomalies and
Down syndrome. In addition, the cardiac anomalies were split
into the following subgroups, based on EUROCAT coding
subgroups,15 due to the a priori interest in cardiac anomalies from
previous studies: anomalies of cardiac chambers (Q20), trans-
position of great vessels (Q203), malformations of cardiac septa
(excluding VSD) (Q21 excluding Q210), atrial septal defects
(Q211, if verified after 1 month of age by echocardiography,
postmortem, surgery or catheterisation), atrioventricular septal
defects (Q212), tetralogy of Fallot (Q213), malformations of
valves (Q22–Q23), hypoplastic left heart (Q234), malformations
of great arteries and veins (Q25–Q26 excluding premature patent
ductus arteriosus), coarctation of aorta (Q251) and patent ductus
arteriosus (Q250, gestational age ≥37 weeks).

Cases could belong to more than one non-chromosomal
subgroup if they had multiple congenital anomalies. In addition,
the subgroup ‘multiple anomalies’ comprised non-chromosomal
cases with more than one major anomaly not belonging to
a sequence or diagnosed syndrome18 as reviewed by two authors
(PB, DW).

Measurement of air pollution
Maps of estimated annual mean background (SO2, NO2 and PM10
concentrations at a 1 km×1 km grid resolution were obtained from
the National Environmental Technology Centre for 1996,
derived according to national methodology.19 20 Maps of carbon
monoxide, ozone and other pollutants of interest were not
available, nor were maps available for other years except 2001.
Broadly, the estimates were based on a model in which each
kilometre grid square concentration comprised two parts: a
regional background and a contribution from local emissions.
The regional background concentrations were derived from data
from monitors far from local sources, and the local contribution
from low-level emissions in the grid square and the 24
surrounding grid squares. Emissions were obtained from the UK
National Atmospheric Emissions Inventory, which includes
roads as well as stationary sources. The model parameters were
estimated using monitoring data. Correlations of modelled and
a sample of annual mean measured concentrations at monitoring
sites not included in the original model in 1996 were 0.83 and
0.75 for NO2 and SO2, respectively.19 There were insufficient
validation data to estimate such a correlation for PM10 for 1996
estimates, but a value of r=0.79 was given for 2001 estimates,
which were obtained using a similar approach.20

These maps were plotted using a geographic information
system (GIS). Census ward level pollution concentrations were
derived as population-weighted averages of pollution concen-
trations of the smallest census output areas, output area
centroids having been mapped to 1 km squares by spatial overlay.
This improved ward averaging of pollution measures in urban
areas, where a high proportion of kilometre grid squares crossed
ward boundaries. A check was made for stability of geographical
pattern by comparing 2001 data with 1996; this revealed high
inter-correlations for output areas for PM10 and NO2 (both with
correlations of 0.98), but lower correlation for SO2 (r=0.54) for
which average levels had also been declining markedly.

Correlations were examined between pollutants. PM10 and
NO2 were highly correlated (0.93) but neither was highly
 correlated with SO2 (0.54 and 0.60, respectively).

Levels of the three air pollutants in 1996 in the study area are
shown in table 1.

Statistical analysis
To simplify interpretation, cases with missing maternal age
(1.3%) and enumeration districts with deprivation index classified
as unknown (0.4%) were excluded from all analyses. Further, 0.7%
of cases were dropped from analyses because no births were reported in the enumeration district in the same age group. Because proportions of births resulting in anomaly were small, their sampling variation could be well approximated by a Poisson distribution, with the logarithm of number of births offset. We thus used a Poisson regression model of maternal age-specific enumeration district counts to adjust for maternal age, registry and area deprivation.

Earlier analysis has shown that hospital catchment was also a determinant of anomaly rate, reflecting hospital diagnostic and recording practice. We adjusted for hospital catchment with two methods: (1) by including a fixed hospital catchment effect (ie, stratifying by hospital catchment) and (2) by including a random hospital catchment effect.

The fixed effects model (which also allowed for random effects at ward level) provides the most robust control for confounding but involves substantial precision loss for pollutants for which most variation was between catchment areas. The hospital random effects model sacrifices some degree of control for confounding in order to gain some precision. It also ensures that confidence intervals are not spuriously small. The results in the tables include hospital catchment as a random effect. Tables including results using the fixed effect model are included in the online appendix.

The association of each pollutant (singly) with anomaly rate was estimated by including in the Poisson regression model the estimated concentration of pollution as a continuous variable (ie, all data were used in the models, not just the extreme centiles). The regression coefficients were scaled and exponentiated to represent anomaly risk for exposure at the 90th centile of pollution relative to exposure at the 10th centile (ie, a relative risk comparing the 90th exposure centile to the 10th exposure centile). Only one pollutant was considered in each model, due to the high correlation between pollutants.

### RESULTS

For non-chromosomal anomalies overall, we found no evidence of an association with any of the pollution measures (table 2), and confidence intervals indicated that excess risks of an order of more than 10% were unlikely. For chromosomal anomalies (table 2) and Down syndrome specifically (table 3), there were non-significant excess risks in the order of 6%–18% for SO2, NO2 and PM10, with upper confidence limit bounds to 42% for PM10.

For the specific non-chromosomal subtypes (table 3), 42 associations were studied, with some raised risks found, generally with wide confidence intervals which included no excess risk. The association statistically least likely to be due to chance was a positive association between omphalocele and PM10 (unadjusted RR=1.53, fully adjusted RR=2.17, 95% CI 1.00 to 4.71). Omphalocele also showed a raised risk for NO2 (fully adjusted RR=1.65, 95% CI 0.94 to 3.22). In general, for SO2, results showed an excess risk of more than 50% was unlikely, while the upper confidence limits for analyses of NO2 and PM10 frequently could not exclude a twofold risk (table 3).

Of the nine cardiac anomaly subtypes studied (27 associations), the association statistically least likely to be due to chance was between tetralogy of Fallot and SO2 (unadjusted RR=1.14, fully adjusted RR=1.38, 95% CI 1.07 to 1.79) (table 4), with similarly raised risks for NO2 (adjusted RR=1.44, 95% CI 0.71 to 2.93) and PM10 (adjusted RR=1.48, 95% CI 0.57 to 3.84).

It was of note that in the unadjusted model, 10 non-chromosomal or cardiac anomaly subtypes showed statistically significant inverse associations with PM10 or NO2 or both (see online appendix), and there were two further positive statistically significant associations for SO2, showing the influence of model specification.

Results from models incorporating hospital catchment areas as fixed effects were very similar to the above random effects results (see online appendix). The positive associations between chromosomal anomalies and pollutants are reduced in size and significance, as is the association between omphalocele and PM10. The fixed effect model gives higher relative risks for tetralogy of Fallot in relation to all pollutants.

### DISCUSSION

We could find no evidence of an association between average annual ambient SO2, NO2 or PM10 air pollution of area of residence and risk of non-chromosomal congenital anomaly as a whole. For chromosomal anomalies, the data were compatible with no or a small excess risk. For congenital anomaly subtypes, the power of the analysis was much lower, and non-significant raised risks with wide confidence intervals are difficult to interpret. We found two significant positive associations—between SO2 and tetralogy of Fallot (with raised relative risks also for NO2 and PM10), and between PM10 and omphalocele (with a raised risk also for NO2). Given the multiple comparisons involved in testing a large range of congenital anomaly subtypes against three pollution measures, these could easily be chance associations. However, the tetralogy of Fallot result could also be interpreted as supporting the sensitivity of this anomaly to air pollution; a study in Texas found a positive association between tetralogy of Fallot and carbon monoxide but not SO2, and a Californian study found a positive association between ozone exposure and conotruncal defects (a group which includes tetralogy of Fallot), but not carbon monoxide and did not analyse SO2. However, three further studies reported no association between tetralogy of Fallot or conotruncal defects and black smoke, PM10, SO2, CO, NO2, CO2, NOX, and ozone.

Consistent with the few previous studies, we found no evidence for association between any pollutant and oral cleft anomalies or between PM10 and NO2 and cardiac anomalies as a whole. Our results do not support the association between PM10 and isolated atrial septal defects found in Texas. We excluded isolated VSD from analysis since it can be variably reported, and thus have no further evidence relating to the association found with SO2 in Texas. We also did not analyse patent ductus arteriosus in term babies, found to be associated with PM10 in Atlanta. A level of discordance between study

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**Table 2** Summary relative risks for a change in pollution from the 10th to the 90th centile for non-chromosomal and chromosomal anomalies by pollutant

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Non-chromosomal anomalies (n = 6136)</th>
<th>Chromosomal anomalies (n = 2949)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted RR (95% CI)</td>
<td>Adjusted RR (95% CI)</td>
</tr>
<tr>
<td>SO2</td>
<td>1.02 (0.98 to 1.07)</td>
<td>0.99 (0.93 to 1.05)</td>
</tr>
<tr>
<td>NO2</td>
<td>0.81 (0.75 to 0.86)</td>
<td>0.97 (0.94 to 1.11)</td>
</tr>
<tr>
<td>PM10</td>
<td>0.74 (0.69 to 0.79)</td>
<td>0.89 (0.75 to 1.07)</td>
</tr>
</tbody>
</table>
Our study has a number of strengths in relation to the very sparse existing literature. It examines a wide range of congenital anomalies. Cases include live births, late fetal deaths and terminations of pregnancy following prenatal diagnosis, the last of these being very important for some anomalies such as neural tube defects due to geographical variation in the proportion of these being very important for some anomalies such as neural tube defects. Our study results should be interpreted in the light of several sources of misclassification of exposure, which may have diluted the estimated relative risks comparing geographical areas. The use of a single year’s (1996) estimates to estimate the average for 1991–2000 would have introduced some classical error, although the high correlations for PM10 and NO2 between 1996 and 2001 estimates suggest that geographical patterns of these pollutants have not changed much over time, although for the markedly declining SO2 this would have been a bigger source of error. Even for 1996 the model estimates would be expected to have some

results must be expected due to the multiple comparisons made in each study.

Differences between countries may occur due to differences in the level and range of pollution experienced, and differences in unmeasured co-pollutants. We did not study CO, ozone or polycyclic aromatic hydrocarbons. Mean levels of air pollution for all three air pollutants studied were comparable to or lower than those reported by two of the American studies of congenital anomalies.4 6 A study of air pollution in the Czech Republic reported a higher occurrence of heart defects related to organic solvents and phosphoric acid in particular, but there was no control for socioeconomic confounding.22 Most studies of air pollution and congenital anomalies have concentrated on specific point sources and their associated emissions such as vinyl chloride plants, smelters, solvent emitters, chemical plants and waste disposal sites.23 24

Our study has a number of strengths in relation to the very sparse existing literature. It examines a wide range of congenital anomalies. Cases include live births, late fetal deaths and terminations of pregnancy following prenatal diagnosis, the last of these being very important for some anomalies such as neural tube defects due to geographical variation in the proportion of terminations of pregnancy. The population size examined was bigger than in previous studies.3–7 Geocoding was virtually complete for cases as well as all births, thus eliminating incomplete geocoding as a potential source of bias.

One of the difficult problems of environmental epidemiology using congenital anomaly registries (as opposed to investigation of other fetal effects such as birth weight) is that such data are subject to geographical ascertainment variation, mainly related to the characteristics of the registries and their data sources, and to the hospitals and their diagnostic and reporting systems. No registry can claim to be totally free from this. All four included registries follow EUROCAT guidelines, and use active case ascertainment methods.12 In order to be sure that variation in prevalence was exposure related and not ascertainment related, we incorporated registry and hospital catchment area into our statistical model. Hospital catchment area adjustment is described in a previous paper using the same dataset,14 based on area of residence rather than hospital of delivery to avoid differences between hospitals relating to selective transfers of high risk pregnancies. This is the first time this methodology has been used in the geographical analysis of a specific type of pollution. Since a substantial component of the variation in pollution was between regions rather than subregional, the statistical power of our study was reduced. However, it is notable that the unadjusted results revealed more inverse associations than positive associations, and we suggest that inadequate geographical ascertainment adjustment may also explain the high number of inverse associations found in some other studies.1 6

Table 3 Number of cases and adjusted relative risks (95% CI) for an increase in pollution from the 10th to the 90th centile, by congenital anomaly subgroup, by pollutant

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>SO2</th>
<th>NO2</th>
<th>PM10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neural tube defects</td>
<td>1041</td>
<td>1.00 (0.88 to 1.14)</td>
<td>1.00 (0.77 to 1.31)</td>
</tr>
<tr>
<td>Hydrocephaly</td>
<td>341</td>
<td>1.22 (0.98 to 1.52)</td>
<td>1.28 (0.73 to 2.23)</td>
</tr>
<tr>
<td>Cardiac defects</td>
<td>1948</td>
<td>1.00 (0.91 to 1.10)</td>
<td>0.96 (0.78 to 1.19)</td>
</tr>
<tr>
<td>Cleft lip with or without cleft palate</td>
<td>586</td>
<td>0.92 (0.73 to 1.15)</td>
<td>0.91 (0.59 to 1.40)</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>302</td>
<td>1.09 (0.88 to 1.35)</td>
<td>0.84 (0.51 to 1.38)</td>
</tr>
<tr>
<td>Digestive system atresias</td>
<td>465</td>
<td>1.00 (0.84 to 1.20)</td>
<td>0.91 (0.62 to 1.35)</td>
</tr>
<tr>
<td>Bilateral renal agenesis</td>
<td>92</td>
<td>0.92 (0.60 to 1.42)</td>
<td>1.09 (0.45 to 2.65)</td>
</tr>
<tr>
<td>Cystic kidney disease</td>
<td>391</td>
<td>0.98 (0.79 to 1.22)</td>
<td>0.94 (0.60 to 1.46)</td>
</tr>
<tr>
<td>Limb reduction</td>
<td>295</td>
<td>1.06 (0.85 to 1.32)</td>
<td>1.40 (0.83 to 2.36)</td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
<td>203</td>
<td>1.07 (0.83 to 1.38)</td>
<td>1.06 (0.60 to 1.89)</td>
</tr>
<tr>
<td>Omphalocele</td>
<td>183</td>
<td>1.08 (0.80 to 1.45)</td>
<td>1.65 (0.84 to 3.22)</td>
</tr>
<tr>
<td>Gastrochisis</td>
<td>222</td>
<td>1.08 (0.87 to 1.33)</td>
<td>1.20 (0.69 to 2.11)</td>
</tr>
<tr>
<td>Multiple anomalies</td>
<td>689</td>
<td>1.13 (0.99 to 1.29)</td>
<td>1.30 (0.93 to 1.83)</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>1486</td>
<td>1.08 (0.96 to 1.22)</td>
<td>1.07 (0.85 to 1.34)</td>
</tr>
</tbody>
</table>

Table 4 Number of cases and adjusted relative risk (95% CI) for an increase in pollution from the 10th to the 90th centile by congenital heart disease subgroup, by pollutant

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>SO2</th>
<th>NO2</th>
<th>PM10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anomalies of cardiac chambers</td>
<td>413</td>
<td>0.99 (0.81 to 1.20)</td>
<td>1.09 (0.73 to 1.64)</td>
</tr>
<tr>
<td>Transposition of great vessels</td>
<td>251</td>
<td>0.94 (0.71 to 1.25)</td>
<td>1.15 (0.65 to 2.02)</td>
</tr>
<tr>
<td>Malformations of cardiac septa</td>
<td>596</td>
<td>1.03 (0.89 to 1.19)</td>
<td>0.94 (0.68 to 1.30)</td>
</tr>
<tr>
<td>Atrioventricular septal defects</td>
<td>109</td>
<td>0.98 (0.68 to 1.42)</td>
<td>0.62 (0.30 to 1.30)</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>146</td>
<td>1.38 (1.07 to 1.79)</td>
<td>1.44 (0.71 to 2.93)</td>
</tr>
<tr>
<td>Malformations of valves</td>
<td>802</td>
<td>1.02 (0.90 to 1.16)</td>
<td>0.95 (0.71 to 1.26)</td>
</tr>
<tr>
<td>Hypoplastic left heart syndrome</td>
<td>180</td>
<td>1.07 (0.80 to 1.44)</td>
<td>1.50 (0.77 to 2.89)</td>
</tr>
<tr>
<td>Great arteries and veins</td>
<td>580</td>
<td>0.98 (0.83 to 1.15)</td>
<td>0.96 (0.69 to 1.35)</td>
</tr>
<tr>
<td>Coarctation of aorta</td>
<td>176</td>
<td>1.15 (0.90 to 1.47)</td>
<td>1.41 (0.76 to 2.62)</td>
</tr>
</tbody>
</table>
error, as shown by the model validation results. While no air pollution estimate will be free from error, modelling such as that used here is designed to be an improvement over ‘levels at nearest monitor’ or similar approaches as used in other studies,\textsuperscript{14,19} where monitor levels are used for quite distant populations without the incorporation of further relevant information about local pollution sources. An additional source of exposure misclassification is movement and migration during pregnancy. Unpublished English data suggest that one quarter of women moved more than 2 km during pregnancy. Inevitably, studies based on residence at birth misclassify the exposure of some women who migrate. Moreover, women who stay at the same residence do not stay within the 1 km $\times$ 1 km grid squares to which they are allocated, but move more widely for work and recreation. This source of misclassification would be non-differential in the sense of being similar for cases and controls, and thus would dilute relative risk estimates, and in addition might lead us to overestimate exposure contrasts and thus underestimate risk.

We used a single estimate of average annual exposure rather than exposure in early pregnancy capturing seasonal exposure variation. To the extent that the modelled pollution values are well correlated across wards with the true annual averages, this would not lead to dilution of relative risk, as argued by Berkson,\textsuperscript{25,26} that is, our results are unbiased for the exposure contrast that we examined. Our choice of exposure model meant that we could not compare seasonal to spatial variation in exposure, although we note that our exposure contrasts (the difference between the highest and lowest levels of exposure) were similar to those in Texas averaged over only 6 weeks. On the other hand, the advantages of our approach are that we can be confident that any air pollution effects (positive or inverse) are not in fact due to uncontrolled seasonal variation\textsuperscript{2} due to other seasonally varying factors. Our results bear on the public health question of whether variation in exposure between wards leads to seasonally varying factors. Our results bear on the public health question of whether variation in exposure between wards leads to seasonally varying factors. Our results bear on the public health question of whether variation in exposure between wards leads to seasonally varying factors. Our results bear on the public health question of whether variation in exposure between wards leads to seasonally varying factors. Our results bear on the public health question of whether variation in exposure between wards leads to seasonally varying factors. Our results bear on the public health question of whether variation in exposure between wards leads to seasonally varying factors. Our results bear on the public health question of whether variation in exposure between wards leads to seasonally varying factors. 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In common with most ambient air pollution studies, we lacked data on indoor air pollution and its correlation with outdoor levels. The high correlation between PM$_{10}$ and NO$_2$ levels makes distinction of risks related to each uncertain, but as there are so few positive associations for these pollutants this has little practical consequence for interpretation.

This study found evidence that geographical variation in average exposure to the air pollutants NO$_2$, SO$_2$ and PM$_{10}$ in the 1990s did not lead to sustained geographical differences in overall congenital anomaly rate in England. This does not imply that air pollution does not raise the risk of specific congenital anomalies, and our results indicate the need for further research regarding specific anomalies, especially tetralogy of Fallot. Our results are not necessarily generalisable to other populations where the pollution contrasts are greater or the mixture different.

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**Competing interests** None.

**Ethics approval** This study was conducted with the approval of the London School of Hygiene & Tropical Medicine Ethics Committee.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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