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Pregnancy exposure to air pollution and early childhood respiratory health

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Abstract

Objectives It is unclear whether maternal air pollution exposure during pregnancy induces changes in the developing respiratory system of a child and whether it has consequences for respiratory health in early childhood. We investigated associations between exposure to moderate levels of air pollution during pregnancy and early childhood lower respiratory tract infections (LRTI) and wheezing.

Methods This study used a sub-group of 17 533 participants in the Norwegian Mother and Child Cohort Study (MoBa). Air pollution levels at residential addresses were estimated using land use regression (LUR) models, and back-extrapolated to the period of each pregnancy. Information on lower respiratory tract infections (LRTI) and wheezing, and lifestyle factors was collected from questionnaires completed by mothers during pregnancy and when the child was 6 and 18 months of age.

Results Moderate levels of NO_2 exposure during pregnancy were not statistically significant associated with LRTI before age 6 months (adjusted OR 0.99; 95% CI 0.83 to 1.19), LRTI between 6-18 months (adjusted OR 0.99; 95% CI 0.83 to 1.19) and wheezing 6-18 months (adjusted OR 0.99; 95% CI 0.98 to 1.00). Stratified analysis indicated an increased risk for LRTIs 6 to 18 months in girls only (adjusted OR 1.23; 95% CI 1.02 to 1.48).

Conclusions There were no statistically significant associations for moderate levels of pregnancy NO_2 exposure and respiratory health outcomes during early childhood in overall analysis. However, stratified analysis gave some support to the idea that girls may have higher risk for developing LRTI due to prenatal air pollution exposure.

What this paper adds

- Respiratory disorders are common chronic disease in infants and young children, and special attention should be given to modifiable factors that may influence lung development at crucial stages.
- The role of environmental exposure such as ambient air pollution in the development of childhood chronic diseases in infants is still debated.
- We used a large pregnancy cohort to analyze longitudinal, the effect of pollution on respiratory symptoms in a birth cohort, considering pregnancy NO_2 exposure.
- We found no statistically significant associations for moderate levels exposure and respiratory health at early childhood in the overall analysis.

Introduction

Lower respiratory tract infections (LRTI) are common in infants and young children.[1] They are caused primarily by viral pathogens and are clinically expressed as bronchiolitis, croup, or pneumonia.[1] Childhood wheeze is a symptom of several heterogeneous conditions, and may occur during viral respiratory infections or be associated with atopy.[2] Respiratory diseases in early childhood may have long term consequences, accounting for a significant proportion of adult lung disease.[1 3] Special attention should be given to modifiable factors that may influence lung development at crucial stages (prenatally and postnatally). Numerous epidemiologic studies have shown that children exposed to tobacco smoke or higher levels of ambient air pollution are more prone to develop respiratory disorders.[4-6] Air pollution may affect the lungs by inducing low-grade systemic inflammation and oxidative stress,[7] leading to pathological changes in the respiratory system. Children are particularly susceptible due to the continuous development of lungs that takes place from embryogenesis to early adolescence,[3 8] and continuous immune system development.[9] Of particular interest is intrauterine exposure, where air pollution may indirectly affect the developing lung tissue of the foetus.[10 11]

A number of studies have reported association of maternal smoking during pregnancy with frequent respiratory tract infections, chronic bronchitis, wheezing, and asthma in children.[12-14] In the Norwegian birth cohort, MoBa Håberg and colleagues have identified maternal smoking during pregnancy as an independent risk factor for wheeze and LRTI in the children's first 18 months of life.[15] There is an emerging interest in whether exposure to ambient air pollution during pregnancy might influence respiratory health in early childhood.[16] Some studies report associations of prenatal air pollution exposure with respiratory infections and decreased lung function.[18-20] Other studies have found no such association for LRTI and lung function in early childhood.[21 22]

In epidemiological studies investigating air pollution effects, precision of exposure estimation is an important challenge. A number of studies use data from personal monitors applied for a limited period, other studies consider residential proximity to major roads as an estimate of exposure to traffic-related air pollution. It has become increasingly common to apply modelling of air pollution exposure at individual residential addresses, such as dispersion models and land use regression (LUR) models. In this study, we used LUR modeled exposure to traffic-related pollutant NO_2 built for

specific areas of Norway: the two biggest cities in Norway (Oslo and Bergen) and their surrounding counties (Akershus and Hordaland). To our knowledge, this is the first Norwegian study to investigate air pollution exposure during pregnancy and respiratory health in early childhood. Norway is characterized by relatively low levels of air pollution, and it is of interest whether low levels might interfere with intrauterine respiratory system development and affect respiratory health later in life.

We investigated the associations between estimated exposure to traffic-related air pollution during pregnancy and early childhood respiratory health (LRTI and wheeze) in selected urban and county areas of Norway.

Methods

Study population

The Norwegian Mother and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health.[23] Pregnant women were recruited from all over Norway from 1999 to 2008. Among invited women, 41% consented to participate. Mothers could participate with more than one child, resulting in 114 500 children and 95 200 mothers included in the cohort. All participants living in our study areas (Oslo, Bergen, Akershus, and Hordaland) were eligible for our study. Only data on singleton live births were used in the analysis. Pregnancy-related information was obtained from the Medical Birth Registry of Norway (MBRN). Mothers participating in the MoBa study completed a number of questionnaires. We used data on lifestyle characteristics from the first questionnaire completed at recruitment (approximately at week 17-18 of pregnancy) and another questionnaire completed at week 30 of pregnancy. Information on the respiratory outcomes was collected from maternal questionnaires completed when the child was 6 and 18 months of age. The number of children from the studied areas with non-missing air pollution exposure data was 17 533. The children were born from 2001 to 2009, 14 386 mothers had returned the questionnaire at 6 months, and 12 231 had returned the questionnaire at 18 months (Table 1). The study was approved by the regional Ethics committee and the Norwegian Data Inspectorate. The current study is based on versions VI (pregnancy data) and VIII (respiratory outcomes) of the quality-assured data files released for research on the 15th April 2011 and on the 14th February 2014,

respectively.

2.2 Outcomes and covariates

The outcomes were based on the maternal report from questionnaires filled when children were 6 and 18 months of age. LRTI included respiratory syncytial virus infection, bronchiolitis, bronchitis, or pneumonia. Wheeze was defined as "wheezing/whistling in the chest" or "tightness in the chest" between 6 and 18 months of age.

The following characteristics were extracted from the MBRN: parity defined as number of previous deliveries (0; 1; ≥2), mother's age at birth (years), marital status (married/cohabiting; other) sex of the child (boy; girl), and year of birth. Questionnaire information was used to determine: maternal education (less than high school; high school; up to 4 years of college; more than 4 years of college (master or professional degree)), maternal smoking during pregnancy (never; any smoking during pregnancy), maternal weight at the beginning of pregnancy (kg) and maternal height (m) were used to calculate body mass index (BMI) (maternal weight divided by squared maternal height), maternal atopy (ever having hay fever, pollen allergy, atopic dermatitis, allergy to animal hair, other types of allergy, or asthma).

Adjustment variables were selected based on literature analysis and included maternal age at delivery, maternal marital status, maternal education, sex of child, maternal pre-pregnancy BMI, parity, smoking during pregnancy, maternal atopy, and area.

Air pollution exposure

Exposure to air pollution was estimated at the registered address at delivery. Women who did not change their address during pregnancy were used in a sensitivity analysis. Area variable was defined by the location of the address at delivery: Oslo, Akershus, Bergen and Hordaland.

Estimates of air pollution exposure during pregnancy were based on the methodology developed for the ESCAPE project.[24 25] LUR models for NO_2 levels were built for the studied areas in order to account for regional specifics.[26] We used air pollution measurements conducted in 2010 for Oslo and Akershus, and in 2011 for Bergen and Hordaland. Measurement campaigns included three

rounds of approximately two weeks duration with NO_2 measurements (during winter, summer and an intermediate season) within a one year period. Measurement sites were selected to represent the range of residential exposure for each study area. In analysis, we included sites with no missing data, and no geocoding mismatches.[26]

The mean exposures over the three measurement periods were averaged to obtain a yearly mean NO_2 level that was used in LUR modelling. LUR models were built separately for Oslo and Akershus. Only one model was built for the whole Hordaland County (including the city Bergen) due to a low number of valid measurement sites outside Bergen. Predictors for building the LUR model were obtained from a geographical information system (GIS) analysis of the N50 and VBASE maps (received in February 2013) providing information on land use, residential density, types of landscape and road network information. We built multiple linear regression models and performed diagnostic model tests according to the method described by Beelen and colleagues.[24]

Yearly means of air pollution levels at residential address at birth were estimated using the resulting LUR models. Variables in models were truncated in accordance to the range of corresponding variables used for LUR model building. Negative modelled values were replaced with 0.01 to avoid the unlikely scenario of negative modelled exposure and keep these in the analysis as low exposed addresses. In order to account for temporal variability, we used the ratio method of back-extrapolation to the period of each pregnancy using continuous routine monitoring station data.[25] Daily NO_2 measurements were obtained from the Norwegian Institute for Air Research database "Luftkvalitet.info" for the period 2000 - 2012 in Oslo (used for Oslo and Akershus), and for the period 2003 - 2012 in Bergen (used for Bergen and Hordaland). Daily estimates of exposure were calculated using the ratio method of back-extrapolation: the LUR-modelled yearly estimate multiplied by the ratio between daily NO_2 routine monitoring station measurement and an annual average for the year when LUR measurement campaign took place. Daily NO_2 exposure estimates were averaged separately for 1st, 2nd, and 3rd trimester, and also over the whole pregnancy. Exposures by trimester and the whole pregnancy exposure were highly correlated and we therefore decided to use only the average NO_2 exposure during the whole pregnancy as our exposure estimate.

Statistical analysis

Logistic regression models were used to evaluate associations between pregnancy NO_2 exposure and respiratory outcomes. Results are presented for crude and adjusted models. We performed stratified analysis by area, sex of child, season of birth, and maternal atopy. Multiplicative interactions were tested in the adjusted models between the continuous NO_2 pregnancy exposure variable and the following categorical variables: area, sex, parity, birth season and maternal atopy. Sensitivity analyses were performed by a) restricting the analysis to women who did not change address during pregnancy, and b) restricting the analysis to pregnancies during the last period of the MoBa recruitment. Area variable may reflect the spatial distribution of air pollution, and therefore a separate analysis was performed in adjusted model without the area variable. We used ArcGIS10.1 software (Esri, CA, USA) for GIS analyses; statistical analyses were performed using STATA 13.0 (StataCorp, Texas, USA).

Results

The study population included in this study consisting of participants from the four study areas of Norway with pregnancy air pollution exposure data had similar characteristics as the whole MoBa cohort study with information from 6 months and at 18 months (Table 1). A total of 4.5% of children had LRTI at 6 months, and 12% of children had LRTI and 40.6% had wheezing symptoms between 6 and 18 months. Mean NO_2 exposure during whole pregnancy was 13.6 ± 6.9 $\mu g/m^3$ NO_2, which is well below the European Union air quality yearly average standard of 40 $\mu g/m^3$ NO_2. The majority (86.7%) of the women did not change address during pregnancy. Maternal smoking in pregnancy was relatively uncommon (6.2%). Maternal atopy was reported in 33.1% of the women (Table 1). The distribution of the study population across birth seasons reflects the timing of recruitment into MoBa and we therefore observe slight deviation from the equal seasonal distribution.

We found no associations of NO_2 exposure during pregnancy with LRTI at 6 months, LRTI at 6-18 months, or wheeze at 6-18 months in the overall analysis (Table 2). The main covariates affecting the change in significance of odds ratio estimate from the crude to the adjusted models were parity and area. In the stratified analysis by area we observed a consistent pattern, although not statistically

significant, of positive associations for LRTI and wheeze for participants living outside big cities, in Akershus and Hordaland (Table 2). Stratified analysis by sex also showed a consistent tendency for association of pregnancy NO_2 exposure with LRTI and wheeze in girls, but not in boys (Figure 1). For instance, the risk of developing LRTI 6-18 months in girls was equal to an OR =1.23 (95% CI 1.02 to 1.48, p=0.03) per each 10μg/m^3 increase in NO_2 exposure during pregnancy. Stratified analysis by maternal atopy status and birth season did not identify any important differences between the groups. No statistically significant interactions were detected between NO_2 exposure and maternal atopy, sex of child, area, birth season, or parity. Sensitivity analyses resulted in no substantial changes compared to the reported results. This was also the case for crude analyses in a sample of children with available information on all covariates. Excluding from the adjustment set the area variable, as a factor potentially reflecting spatial distribution of air pollution, did not considerably change the results. Restricting the analysis to pregnancies during the last period of the MoBa recruitment did not result in substantial changes to the reported results.

Discussion

In this study, we found no statistically significant associations for pregnancy NO_2 exposure with LRTI or wheeze in early childhood in the overall analysis. In stratified analyses, we observed a tendency of increased risk of developing LRTI in girls, but not in boys.

The study of Esplugues and colleagues has reported similar results of no association of LUR-modelled prenatal NO_2 exposure (with higher than in our study whole pregnancy mean NO_2 values of 39.1μg/m^3) with LRTI or persistent cough during the 1st year of life, but they did report an association between postnatal NO_2 exposure and persistent cough.[21] In the study of Clark and colleagues exposure to a range of pollutants, including NO_2 and NO, was investigated during pregnancy and the 1st year of life and their associations with asthma up to 3 - 4 years were found for both prenatal and postnatal exposures.[27] Jedrychowski and colleagues studied prenatal exposure to another transport-related air pollutant $PM_{2.5}$, using personal monitors for short periods of time during the 2nd trimester. Exposure to $PM_{2.5}$ was associated with recurrent broncho-pulmonary infections in children of up to 7 years of age,[19] and with decrease in lung function of 5-year old children in the highest quartile of exposure.[18] In

the large international ESCAPE study, uniting cohorts from Germany, Sweden, Netherlands, and the UK, decrease in lung function parameters has been associated with exposure to LUR-modelled annual average NO_2, NO_x, $PM_{2.5}$ absorbance, and $PM_{2.5}$ at current address at 6 - 8 years of age, but not at birth address.[22] Studies that used distance to major road as a proxy for pregnancy air pollution exposure reported positive associations with respiratory infections up to 3 years of age,[20] and with doctor-diagnosed asthma and atopic eczema.[28]

In our analysis, we found a sex difference in prenatal NO_2 exposure association with LRTI: the association was present in girls, but not in boys. Male sex is a known risk factor for both respiratory infections and wheezing in childhood.[2 29 30] However, the interaction between environmental exposures and prenatal lung development in boys and girls remains uncertain,[31] and our finding was from one of several subsample analyses. There are differences in prenatal anatomic and physiological respiratory system development in sexes, as well as different sex-hormone effects on the immune system functioning.[31-33] As was reviewed by Casimir and colleagues, while boys outnumber girls in acute respiratory infections, the chronicity of inflammatory process has more adverse effects on girls than on boys.[34] Given the chronic low-grade systemic inflammation associated with air pollution exposure,[7] we might expect more adverse effect in girls. However, this issue is insufficiently studied, and the existing reports give contradictory results. For instance, there are different patterns of lung function decline in asthmatic boys and girls exposed to maternal smoking *in utero* compared to effects in children without asthma.[35] Another study found no difference between boys and girls with respect to prenatal and postnatal exposure to tobacco smoke and asthma development.[36] The international ESCAPE study reported stronger effects of air pollution exposure during the first year of life, which was LUR-modelled at birth address, on pneumonia in girls.[6]

We found some indication of different patterns for associations between prenatal air pollution exposure and early respiratory health in study participants living in cities versus counties outside cities. Living outside the city was associated with higher risk of developing LRTI and wheeze, although the estimates were not statistically significant. This might be due to a higher misclassification of exposure in cities because of higher mobility and less staying at home. On the other hand, non-city population might have more homogenous exposure and spending more time close to home. Difference

in distribution of socioeconomic factors or parity might play a role: families with several children tend to move out of large cities in Norway. Familiar predisposition to allergic disorders may be an important factor in modifying the effect of tobacco smoke exposure on wheezing.[37] Certain months of birth, due to their correlation with viral infections seasons, can be a risk factor for wheezing and LRTI.[2 30] Our study found no differences in the effect from groups divided by maternal atopy status or birth season.

Our study applied standardized individual exposure assessment for the large study population, and detailed information on potential confounders was collected from prenatal questionnaires. Estimates for prenatal exposure to NO_2 were based on LUR models and temporal back-extrapolation of exposure during entire pregnancy at the address at birth. Such estimates might be a subject to non-differential misclassification of exposure due to different mobility and lifestyle factors. However, results of the sensitivity analysis only in women who did not change address during pregnancy were similar to the overall analysis. The mean air pollution exposure levels explored in this study may be relatively low for detecting the association between prenatal exposure and postnatal respiratory health, and the reported effect estimates might be biased towards null due to non-differential misclassification of exposure. It could also be difficult to disentangle prenatal and early postnatal exposure to air pollution if family continues to live at the same address at these two periods. Prenatal exposures need to be carefully studied for identifying potential critical windows of exposure. In our data, exposures by trimester were highly correlated with whole pregnancy exposure, and therefore we only assessed the exposure during entire pregnancy. More studies are needed for exploring the causative association between prenatal air pollution exposure and respiratory health early in childhood, for characterizing critical time windows and main pollutants that are involved in pathological changes. Of interest for future research is the sex difference in prenatal exposure effect identified in our study.

In this large Norwegian pregnancy cohort we found no statistically significant associations for moderate levels of pregnancy NO_2 exposure and childhood respiratory health measured by LRTI and wheeze.

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Contribution to authorship: PN, SJL, WN, PM were involved in conception, hypothesis delineation and study design. SJL, GA, SEH, CM contributed to the exposure assessment. CM and PN drafted the manuscript. All authors were involved in data interpretation and approved the final submitted version of the manuscript.

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Details of ethics approval: The Norwegian Mother and Child Cohort Study has approvals from the Regional Ethics Committee and the Norwegian Data Inspectorate. The current study is based on version VI of the quality-assured data files released for research on the 15th April 2011.

Data sharing statement: Technical description of the MoBa data can be found at the study website (https://www.fhi.no/en/studies/moba/). Researchers can apply for access to the dataset (https://www.fhi.no/en/more/research--access-to-data/). Statistical code is available upon request from the corresponding author.

Competing interests: none declared.

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Table 1. Descriptive statistics for study participants from the MOBA cohort.

	Baseline cohort at birth with NO_2 data (N=17 533)	Questionnaire at 6 months (N=14 386)	Questionnaire at 18 months (N=12 231)
Oslo	4 669 (26.6)	3 801 (26.4)	3 320 (27.1)
Akershus	7 554 (43.1)	6 284 (43.7)	5 350 (43.7)
Bergen	3 869 (22.1)	3 135 (21.8)	2 591 (21.2)
Hordaland	1 441 (8.2)	1 166 (8.1)	970 (7.9)
LRTI0- 6 months		653 (4.5)	
Missing		500 (3.5)	
LRTI 6- 18 months			1 469 (12.0)
Missing			230 (1.9)
Wheeze 6- 18 months			4 961 (40.6)
Missing			255 (2.1)
Women who changed address during pregnancy	2 336 (13.3)	1 782 (12.4)	1 471 (12.0)
Parity			
0	8 310 (47.4)	6 973 (48.5)	6 003 (49.1)
1	6 328 (36.1)	5 138 (35.7)	4 310 (35.2)
≥2	2 895 (16.5)	2 275 (15.8)	1 918 (15.7)
Sex of child			
Boy	8 925 (50.9)	7 285 (50.6)	6 177 (50.5)
Girl	8 608 (49.1)	7 101 (49.4)	6 054 (49.5)
Maternal age at delivery, years	31.0 ± 4.5	31.1 ± 4.4	31.2 ± 4.3
Marital status			
Married/cohabiting	16 780 (95.7)	13 839 (96.2)	11 797 (96.5)
Other	753 (4.3)	547 (3.8)	434 (3.6)
Maternal education			
Less than high school	986 (5.6)	713 (5.0)	547 (4.5)
High school	4 175 (23.8)	3 465 (24.1)	2 845 (23.3)
Up to 4 years of college	6 480 (37.0)	5 677 (39.5)	4 919 (40.2)
More than 4 years of college (master or professional degree)	4 867 (27.8)	4 254 (29.6)	3 731 (30.5)
Missing	1 025 (5.9)	277 (1.9)	189 (1.6)
Maternal smoking during pregnancy	1 085 (6.2)	843 (5.9)	675 (5.5)
Missing	1 000 (5.7)	263 (1.8)	185 (1.5)
Maternal pre-pregnancy body mass index[a]	23.5 ± 3.8	23.5 ± 3.7	23.5 ± 3.7
Maternal atopy	5 802 (33.1)	4 947 (34.4)	4 276 (35.0)
Season of birth			
Winter	4 099 (23.4)	3 352 (23.3)	2 858 (23.4)
Spring	4 686 (26.7)	3 851 (26.8)	3 191 (26.1)
Summer	4 630 (26.4)	3 827 (26.6)	3 312 (27.1)
Autumn	4 118 (23.5)	3 356 (23.3)	2 870 (23.5)
LUR modelled NO_2 exposure during pregnancy, $\mu g/m^3$	13.6 ± 6.9	13.6 ± 6.9	13.7 ± 6.9

Numbers are n (%) or mean ± standard deviation
LRTI – lower respiratory tract infections; LUR – land use regression
[a]Missing data for maternal pre-pregnancy body mass index (BMI): baseline cohort 1 549 (8.8%), at 6 months 693 (4.8%), at 18 months 522 (4.3%).
European Union air quality standard for NO_2: 1-year average 40 $\mu g/m^3$

Table 2. Associations between pregnancy exposure to NO_2 and respiratory health of children by age 6 and 18 months.

	Crude			Adjusted		
	N total	N cases	OR (95% CI)	N total	N cases	OR (95% CI)
Main analysis[a]						
LRTI 0-6 months	13 886	653	0.84 (0.75 to 0.94)	13 116	616	0.99 (0.83 to 1.19)
LRTI 6-18 months	12 001	1 469	0.94 (0.86 to 1.01)	11 412	1 388	1.06 (0.94 to 1.19)
Wheeze 6-18 months	11 976	4 961	1.00 (0.95 to 1.06)	11 387	4 712	0.99 (0.98 to 1.00)
Stratified analysis[b]						
Oslo						
LRTI 0-6 months	3 695	136	0.71 (0.50 to 1.02)	3 530	128	0.75 (0.52 to 1.08)
LRTI 6-18 months	3 246	351	0.83 (0.65 to 1.07)	3 111	331	0.88 (0.68 to 1.14)
Wheeze 6-18 months	3 248	1 315	1.10 (0.94 to 1.29)	3 111	1 253	1.08 (0.92 to 1.28)
Akershus						
LRTI 0-6 months	6 014	281	1.23 (0.89 to 1.69)	5 619	263	1.35 (0.97 to 1.88)
LRTI 6-18 months	5 237	689	1.18 (0.95 to 1.45)	4 939	649	1.18 (0.95 to 1.47)
Wheeze 6-18 months	5 228	2 192	1.02 (0.88 to 1.18)	4 930	2 066	1.03 (0.88 to 1.20)
Bergen						
LRTI 0-6 months	3 045	169	0.90 (0.69 to 1.17)	2 899	161	0.98 (0.74 to 1.29)
LRTI 6-18 months	2 560	318	1.00 (0.83 to 1.20)	2 449	301	1.05 (0.86 to 1.27)
Wheeze 6-18 months	2 548	1 073	1.00 (0.88 to 1.13)	2 438	1 030	1.02 (0.89 to 1.16)
Hordaland						
LRTI 0-6 months	1 132	67	0.83 (0.47 to 1.49)	1 068	64	0.92 (0.50 to 1.70)
LRTI 6-18 months	958	111	1.36 (0.87 to 2.13)	913	107	1.40 (0.88 to 2.23)
Wheeze 6-18 months	952	381	1.35 (1.00 to 1.82)	908	363	1.31 (0.96 to 1.79)

Effect estimates per 10µg/m^3 NO_2
LRTI – lower respiratory tract infections
[a]Adjusted for maternal age at delivery, maternal marital status, maternal education, sex of child, maternal prepregnancy BMI, smoking during pregnancy, parity, maternal atopy and study area.
[b]Adjusted for maternal age at delivery, maternal marital status, maternal education, sex of child, maternal prepregnancy BMI, smoking during pregnancy, parity, maternal atopy.

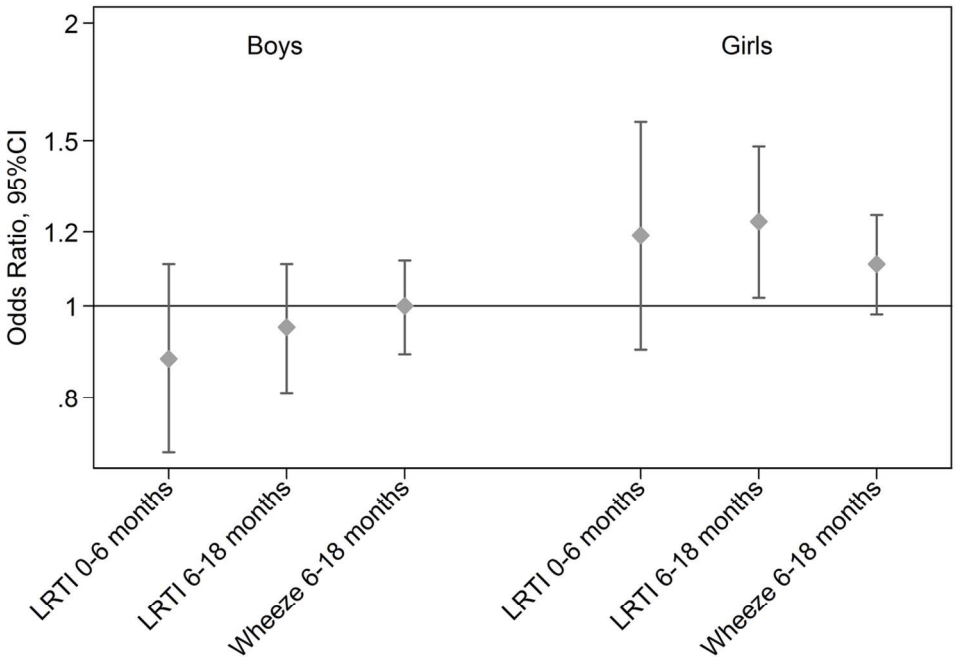

Figure 1 Stratified analysis by of the associations between pregnancy exposure to NO2 and respiratory health of children by age 6 and 18 months. Odds ratio (OR) for lower respiratory tract infections (LRTI) and wheeze, adjusted for maternal age at delivery, maternal marital status, maternal education, maternal prepregnancy BMI, smoking during pregnancy, parity, maternal atopy and study area.

60x44mm (600 x 600 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract – page 1.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found – page 2.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported – page 4.
Objectives	3	State specific objectives, including any prespecified hypotheses – page 5.
Methods		
Study design	4	Present key elements of study design early in the paper – page 5.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection – page 5.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up – page 5.
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed – N.A.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable – page 6 and 7.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group – page 6 and 7.
Bias	9	Describe any efforts to address potential sources of bias – N.A.
Study size	10	Explain how the study size was arrived at – page 5.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why – page 6.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding – page 8.
		(*b*) Describe any methods used to examine subgroups and interactions – page 8.
		(*c*) Explain how missing data were addressed – page 7.
		(*d*) If applicable, explain how loss to follow-up was addressed – N.A.
		(*e*) Describe any sensitivity analyses – page 8.
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed – page 5 and Table 1.
		(b) Give reasons for non-participation at each stage – page 5.
		(c) Consider use of a flow diagram – N.A.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders – page 8 and 9.
		(b) Indicate number of participants with missing data for each variable of interest – page 5.
		(c) Summarise follow-up time (eg, average and total amount) – page 5.
Outcome data	15*	Report numbers of outcome events or summary measures over time – page 8 and Table 1.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and

		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included – pages 8-9, Figure 1 and Tables 2-3.
		(*b*) Report category boundaries when continuous variables were categorized – page 8 and 9.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period – N.A.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses – page 9.
Discussion		
Key results	18	Summarise key results with reference to study objectives – page 9.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias – page 11.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence – page 11.
Generalisability	21	Discuss the generalisability (external validity) of the study results – page 10-11.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based – page 12.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Pregnancy exposure to air pollution and early childhood respiratory health in the Norwegian Mother and Child Cohort Study (MoBa)

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Abstract

Objectives It is unclear whether maternal air pollution exposure during pregnancy induces changes in the developing respiratory system of a child and whether it has consequences for respiratory health in early childhood. We investigated associations between exposure to moderate levels of air pollution during pregnancy and early childhood lower respiratory tract infections (LRTI) and wheezing.

Methods This study used a sub-group of 17 533 participants in the Norwegian Mother and Child Cohort Study (MoBa). Air pollution levels at residential addresses were estimated using land use regression (LUR) models, and back-extrapolated to the period of each pregnancy. Information on LRTI and wheezing, and lifestyle factors was collected from questionnaires completed by mothers during pregnancy and when the child was 6 and 18 months of age.

Results Moderate levels of NO_2 (13.6 $\mu g/m^3$, range 0.01 to 60.4) exposure at residential address during pregnancy were not statistically significant associated with LRTI before age 6 months (adjusted RR 0.99; 95% CI 0.84 to 1.17), LRTI between 6-18 months (adjusted RR 1.05; 95% CI 0.94 to 1.16) and wheezing 6-18 months (adjusted RR 1.02; 95% CI 0.97 to 1.07). Exploratory post hoc analysis indicated an increased risk for LRTIs 6 to 18 months in girls only (adjusted RR 1.20; 95% CI 1.02 to 1.46).

Conclusions There were no statistically significant associations for moderate levels of pregnancy NO_2 exposure and respiratory health outcomes during early childhood in overall analysis. However, post hoc analysis gave some support to the idea that girls may have higher risk for developing LRTI due to prenatal air pollution exposure.

Strengths and limitations of this study

- Large prospective cohort with data on lower respiratory tract infections, with additional linked data from medical birth registry.
- Land use regression modelled traffic exposure assessment at residential address using both spatial and temporal adjustment.
- Not able to identify trimester-specific time windows of exposure due to correlated exposures.
- No statistically significant associations for moderate levels exposure of NO_2 and respiratory health at early childhood in the overall analysis.

Introduction

Lower respiratory tract infections (LRTI) are common in infants and young children.[1] They are caused primarily by viral pathogens and are clinically expressed as bronchiolitis, or pneumonia.[1] Childhood wheeze is a symptom of several heterogeneous conditions, and may occur during viral respiratory infections or be associated with atopy.[2] Infections and wheeze are also closely related in young children. Respiratory diseases in early childhood may have long term consequences, accounting for a significant proportion of adult lung disease.[1 3] Special attention should be given to modifiable factors that may influence lung development at crucial stages (prenatally and postnatally). Numerous epidemiologic studies have shown that children exposed to tobacco smoke or higher levels of ambient air pollution above recommended levels (e.g. standards from the EU or the WHO) are more prone to develop respiratory disorders.[4-6] Air pollution may affect the lungs by inducing low-grade systemic inflammation and oxidative stress,[7] leading to pathological changes in the respiratory system. Children are particularly susceptible due to the continuous development of lungs that takes place from embryogenesis to early adolescence,[3 8] and continuous immune system development.[9] Of particular interest is intrauterine exposure, where air pollution may indirectly affect the developing lung tissue of the foetus.[10 11]

A number of studies have reported association of maternal smoking during pregnancy with frequent respiratory tract infections, chronic bronchitis, wheezing, and asthma in children.[12-14] Maternal smoking is well-accepted as a risk factor for adverse birth outcomes and lends support for a role of outdoor air pollution on pregnancy outcomes.[15] Furthermore, maternal smoking during pregnancy has been identified as an independent risk factor for wheeze and LRTI in the children's first 18 months of life.[16] There is an emerging interest in whether exposure to ambient air pollution during pregnancy might influence respiratory health in early childhood.[17] Some studies report associations of prenatal air pollution exposure with respiratory infections and decreased lung function.[18-20] Other studies have found no such association for LRTI and lung function in early childhood.[21 22]

In this study, we investigated the associations between estimated exposure to traffic-related air pollution during pregnancy and early childhood respiratory health (LRTI and wheeze) in selected urban and county areas of Norway. Norway is characterized by relatively low levels of air pollution,[23]

and it is of interest whether low levels might interfere with intrauterine respiratory system development and affect respiratory health later in life.

Methods

Study population

The Norwegian Mother and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health.[24] Pregnant women were recruited from all over Norway from 1999 to 2008. Among invited women, 41% consented to participate. Mothers could participate with more than one child, resulting in 114 500 children and 95 200 mothers included in the cohort.

All participants living in our study areas (Oslo, Bergen, Akershus, and Hordaland) were eligible for our study (N=22 149, 23.3%). We excluded participants with missing NO_2 exposure information (N=3 876), multiple births (N=664) and non-live births (N=76). Only data on singleton live births were used in the analysis. Total number of participants from the four study areas was 17 533 (79%). Pregnancy-related information was obtained from the Medical Birth Registry of Norway (MBRN).

Mothers participating in the MoBa study completed a number of questionnaires during follow-up. We used data on lifestyle characteristics from the first questionnaire completed at recruitment (approximately at week 17-18 of pregnancy) and another questionnaire completed at week 30 of pregnancy. Information on the respiratory outcomes was collected from maternal questionnaires completed when the child was 6 and 18 months of age. The children were born from 2001 to 2009, 14 386 mothers had returned the questionnaire at 6 months, and 12 231 had returned the questionnaire at 18 months (Table 1).

The study was approved by the regional Ethics committee and the Norwegian Data Inspectorate. The current study is based on versions VI (pregnancy data) and VIII (respiratory outcomes) of the quality-assured data files released for research on the 15th April 2011 and on the 14th February 2014, respectively.

2.2 Outcomes and covariates

The outcomes were based on the maternal report from questionnaires filled when children were 6 and 18 months of age. LRTI are important health problems during early childhood, and include diagnosis of respiratory syncytial virus infection, bronchiolitis, bronchitis, or pneumonia. The outcomes were treated as dichotomous. Wheeze was defined as "wheezing/whistling in the chest" or "tightness in the chest" between 6 and 18 months of age.

The following characteristics were extracted from the MBRN: parity defined as number of previous deliveries (0; 1; ≥2), mother's age at birth (years), marital status (married/cohabiting; other) sex of the child (boy; girl), and year of birth. Questionnaire information was used to determine: maternal education (less than high school; high school; up to 4 years of college; more than 4 years of college (master or professional degree)), maternal smoking during pregnancy (never; any smoking during pregnancy), maternal weight at the beginning of pregnancy (kg) and maternal height (m) were used to calculate body mass index (BMI) (maternal weight divided by squared maternal height), maternal atopy (ever having hay fever, pollen allergy, atopic dermatitis, allergy to animal hair, other types of allergy, or asthma).

Adjustment variables were selected based on literature analysis and included maternal age at delivery, maternal marital status, maternal education, sex of child, maternal pre-pregnancy BMI, parity, year of birth, smoking during pregnancy, maternal atopy, and area.

Air pollution exposure

In this study, we used LUR modeled exposure to traffic-related pollutant NO_2 at the residential address at the time of delivery for women included in MoBa. Separate models were developed for four of the recruitment areas: the two biggest cities in Norway (Oslo and Bergen) and their surrounding counties (Akershus and Hordaland).[25]

Estimates of air pollution exposure during pregnancy were based on the methodology developed for the ESCAPE project.[26 27] Land use regression (LUR) models for NO_2 levels were built for each of the studied areas in order to account for regional specifics.[25] Sampling of air pollution is done retrospective since it was not part of the MoBa design. We measured the spatial distribution of

air pollution for Oslo and Akershus in 2010, and for Bergen and Hordaland in 2011. Measurement campaigns included three rounds of approximately two weeks duration with NO_2 measurements (during winter, summer and an intermediate season) within a one year period. Measurement sites were selected to represent the range of residential exposure for each study area. In the analysis, we included sites with no missing data, and no geocoding mismatches.[25] The models provided adjusted R^2 in the range of 55 – 85 %, and more details of these models is described elsewhere.[25]

LUR models were built separately for Oslo and Akershus. Only one model was built for the whole Hordaland County (including the city Bergen) due to a low number of valid measurement sites outside Bergen. Predictors for building the LUR model were obtained from a geographical information system (GIS) analysis of the N50 and VBASE maps (received in February 2013) providing information on land use, residential density, types of landscape and road network information. We built multiple linear regression models and performed diagnostic model tests according to the method described by Beelen and colleagues.[26]

Yearly means of air pollution levels at residential address at birth were estimated using the resulting LUR models. Variables in models were truncated in accordance to the range of corresponding variables used for LUR model building. Negative modelled values were replaced with 0.01 to avoid the unlikely scenario of negative modelled exposure and keep these in the analysis as low exposed addresses.[25] The true exposure from NO_2 at these addresses are most likely at the low end of the scale. In order to account for temporal variability, we used the ratio method of back-extrapolation to the period of each pregnancy using continuous routine monitoring station data.[27] Daily NO_2 measurements were obtained from the Norwegian Institute for Air Research database "Luftkvalitet.info" for the period 2000 - 2012 in Oslo (used for Oslo and Akershus), and for the period 2003 - 2012 in Bergen (used for Bergen and Hordaland). Daily estimates of exposure were calculated using the ratio method of back-extrapolation: the LUR-modelled yearly estimate multiplied by the ratio between daily NO_2 routine monitoring station measurement and an annual average for the year when LUR measurement campaign took place. Daily NO_2 exposure estimates were averaged separately for 1st, 2nd, and 3rd trimester, and also over the whole pregnancy. Exposures by trimester and

the whole pregnancy exposure were highly correlated and we therefore decided to use only the average NO_2 exposure during the whole pregnancy as our exposure estimate.

Statistical analysis

Generalized linear models was fitted to evaluate the associations between pregnancy NO_2 exposure and respiratory outcomes. Results are presented for crude and adjusted models as risk ratios (RR). Multiplicative interactions were tested in the adjusted models between the continuous NO_2 pregnancy exposure variable and the following categorical variables: area, sex, parity, birth season and maternal atopy.

Sensitivity analyses were performed by a) restricting the analysis to women who did not change address during pregnancy, and b) restricting the analysis to pregnancies during the last period (2006-2008) of the MoBa recruitment, thus closer in time to the exposure campaign and GIS-variables.

Area variable was defined by the location of the address at delivery: Oslo, Akershus, Bergen and Hordaland. This variable is included in the adjusted models since it previously has been reported to be a potential proxy for unmeasured factors that could vary between each study area and thus could influence the outcome variables within each separate area.[25] Still, area may also reflect the spatial distribution of air pollution, and thus result in overadjustment bias on the path between exposure and outcome.[28] We therefore performed a separate post hoc analysis by excluding the area variable from the adjusted model. In addition, we performed exploratory analyses post hoc by area, sex of child, parity, season of birth, and maternal atopy.

We used ArcGIS10.1 software (Esri, CA, USA) for GIS analyses; statistical analyses were performed using STATA 13.0 (StataCorp, Texas, USA).

Results

The study population included in this study consisting of participants from the four study areas of Norway with pregnancy air pollution exposure data had similar characteristics as the whole MoBa cohort study with information from 6 months and at 18 months (Table 1). A total of 4.5% of children

had LRTI at 6 months, and 12% of children had LRTI and 40.6% had wheezing symptoms between 6 and 18 months.

The majority (86.7%) of the women did not change address during pregnancy. Maternal smoking in pregnancy was relatively uncommon (6.2%). Maternal atopy was reported in 33.1% of the women (Table 1). The distribution of the study population across birth seasons reflects the timing of recruitment into MoBa and we therefore observe slight deviation from the equal seasonal distribution.

Mean NO_2 exposure during whole pregnancy was 13.6 ± 6.9 $\mu g/m^3$ NO_2, which is well below the European Union air quality yearly average standard of 40 $\mu g/m^3$ NO_2. The range of NO_2 spanned from 0.01 thru 60.4 $\mu g/m^3$, with a total of 27 children with concentrations equal or above 40 $\mu g/m^3$ at their residential address.

We found no associations of NO_2 exposure during pregnancy with LRTI at 6 months, LRTI at 6-18 months, or wheeze at 6-18 months in the overall analysis (Table 3). The main covariates affecting the change in significance of risk ratio estimate from the crude to the adjusted models were parity and area. In the stratified analysis by area we observed a consistent pattern, although not statistically significant, of positive associations for LRTI and wheeze for participants living outside big cities, in Akershus and Hordaland (Table 3).

A stratified analysis post hoc, showed a consistent tendency for association of pregnancy NO_2 exposure with LRTI and wheeze in girls, but not in boys. For instance, the risk of developing LRTI 6-18 months in girls was equal to an RR =1.20 (95% CI 1.02 to 1.42, p=0.03) per each 10$\mu g/m^3$ increase in NO_2 exposure during pregnancy. Stratified analysis post hoc by maternal atopy status and birth season did not identify any important differences between the groups. No statistically significant interactions were detected between NO_2 exposure and maternal atopy, sex of child, area, birth season, or parity. Sensitivity analyses resulted in no substantial changes compared to the reported results. Excluding from the adjustment set the area variable, as a factor potentially reflecting spatial distribution of air pollution, did not considerably change the results. Restricting the analysis to pregnancies during the last period of the MoBa recruitment (2006-2008) did not result in substantial changes to the reported results.

Discussion

In this study, we found no statistically significant associations for pregnancy NO_2 exposure to traffic-related air pollution exposure at residential address at birth and LRTI or wheeze in early childhood.

A previously study by Esplugues and colleagues has reported similar results of no association between LUR-modelled prenatal NO_2 exposure (with higher than in our study whole pregnancy mean NO_2 values of 39.1μg/m^3) with LRTI or persistent cough during the 1st year of life, but they did report an association between postnatal NO_2 exposure and persistent cough.[22] In the large international ESCAPE study, uniting cohorts from Germany, Sweden, Netherlands, and the UK, decrease in lung function parameters has been associated with exposure to LUR-modelled annual average NO_2, NO_x, $PM_{2.5}$ absorbance, and $PM_{2.5}$ at current address at 6 - 8 years of age, but not at birth address.[29]

In post hoc analysis, we found a sex difference in prenatal NO_2 exposure association with LRTI: the association was present in girls, but not in boys. Male sex is a known risk factor for both respiratory infections and wheezing in childhood.[2 30 31] However, the interaction between environmental exposures and prenatal lung development in boys and girls remains uncertain,[32] and our finding was from one of several subsample analyses. There are differences in prenatal anatomic and physiological respiratory system development in sexes, as well as different sex-hormone effects on the immune system functioning.[32-34] As was reviewed by Casimir and colleagues, while boys outnumber girls in acute respiratory infections, the chronicity of inflammatory process has more adverse effects on girls than on boys.[35] Given the chronic low-grade systemic inflammation associated with air pollution exposure,[7] we might expect more adverse effect in girls. However, this issue is insufficiently studied, and the existing reports give contradictory results. The international ESCAPE study reported stronger effects of air pollution exposure during the first year of life, which was LUR-modelled at birth address, on pneumonia in girls.[6]

We found some indication of different patterns for associations between prenatal air pollution exposure and early respiratory health in study participants living in cities versus counties outside cities. Living in non-urban areas was overall associated with higher risk of developing LRTI and wheeze, although the estimates were not statistically significant. This might be due to a higher misclassification of exposure in cities because of higher mobility (change of residential address), or

due to other types of pollutants in non-urban areas.[36] A study by Canfield and colleagues (2006) reported higher mobility for nullparious women as compared to women with several children. They explained this as related to the need for larger homes due to expecting a child (first born) and a need to live closer to health care facilities.[37] A previous study from Norway reported that half of the mothers work during pregnancy and that no difference was found when comparing using only home address to a weighted exposure of home and work address exposure.[38] On the other hand, non-city population might have more homogenous exposure and spending more time close to home. Difference in distribution of socioeconomic factors or parity might play a role: families with several children tend to move out of large cities in Norway. Familiar predisposition to allergic disorders may be an important factor in modifying the effect of tobacco smoke exposure on wheezing.[33] Certain months of birth, due to their correlation with viral infections seasons, can be a risk factor for wheezing and LRTI.[2 31] Our study found no differences in the effect from groups divided by maternal atopy status or birth season.

Our study applied standardized individual exposure assessment for the large study population, and detailed information on potential confounders was collected from prenatal questionnaires. Estimates for prenatal exposure to NO_2 were based on LUR models and temporal back-extrapolation of exposure during entire pregnancy at the address at birth. The NO_2 exposure was collected during 2010 and 2011, and the GIS-variables used in the modelling were collected in 2013. The modelled exposures at each address were back-extrapolated using fixed 24-hour monitoring data from each area in the period 1999-2009. Such estimates might be a subject to non-differential misclassification of exposure due to changes in GIS-variables, or differences in the participant's mobility and lifestyle factors. However, results of the sensitivity analysis only in women who did not change address during pregnancy were similar to the overall analysis. Likewise, restricting the analysis to pregnancies during the last period, closer in time to the collected exposure variables and GIS-variables, did not result in different associations than the overall analysis.

In epidemiological studies investigating air pollution effects, precision of exposure estimation is an important challenge. It is usually not feasible to sample personal air pollution exposure in large birth cohorts, mainly due to the amount of participants needed and due to the fact of not having information about the pregnancy before week 17. It has therefore become increasingly common to

apply modelling of air pollution exposure at individual residential addresses, such as dispersion models and LUR models. High correlations have previously been reported between indoor and outdoor concentrations of NO_2,[39] and NO_2 is also reported to display higher spatial variation as compared to other pollutants,[40] thus making it a better proxy for individual air pollution exposure.

The mean air pollution exposure levels explored in this study may be relatively low for detecting the association between prenatal exposure and postnatal respiratory health, and the reported effect estimates might be biased towards null due to non-differential misclassification of exposure. It could also be difficult to disentangle prenatal and early postnatal exposure to air pollution if family continues to live at the same address at these two periods. Prenatal exposures need to be carefully studied for identifying potential critical windows of exposure. In our data, exposures by trimester were highly correlated with whole pregnancy exposure, and therefore we only assessed the exposure during entire pregnancy. More studies are needed for exploring the causative association between prenatal air pollution exposure and respiratory health early in childhood, for characterizing critical time windows and main pollutants that are involved in pathological changes. Of interest for future research is the sex difference in prenatal exposure effect identified in our study.

In this large Norwegian pregnancy cohort we found no statistically significant associations for moderate levels of exposure to NO_2 during pregnancy and childhood respiratory health measured by LRTI and wheeze.

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Contribution to authorship: PN, SJL, WN, PM were involved in conception, hypothesis delineation and study design. SJL, GA, SEH, CM contributed to the exposure assessment. CM and PN drafted the

manuscript. All authors were involved in data interpretation and approved the final submitted version of the manuscript.

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Data sharing statement: Technical description of the MoBa data can be found at the study website (https://www.fhi.no/en/studies/moba/). Researchers can apply for access to the dataset (https://www.fhi.no/en/more/research--access-to-data/). Statistical code is available upon request from the corresponding author.

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Table 1. Descriptive statistics for study participants from the MOBA cohort.

	Baseline cohort at birth with NO_2 data (N=17 533)	Questionnaire at 6 months (N=14 386)	Questionnaire at 18 months (N=12 231)
Oslo	4 669 (26.6)	3 801 (26.4)	3 320 (27.1)
Akershus	7 554 (43.1)	6 284 (43.7)	5 350 (43.7)
Bergen	3 869 (22.1)	3 135 (21.8)	2 591 (21.2)
Hordaland	1 441 (8.2)	1 166 (8.1)	970 (7.9)
LRTI0- 6 months		653 (4.5)	
Missing		500 (3.5)	
LRTI 6- 18 months			1 469 (12.0)
Missing			230 (1.9)
Wheeze 6- 18 months			4 961 (40.6)
Missing			255 (2.1)
Women who changed address during pregnancy	2 336 (13.3)	1 782 (12.4)	1 471 (12.0)
Parity			
0	8 310 (47.4)	6 973 (48.5)	6 003 (49.1)
1	6 328 (36.1)	5 138 (35.7)	4 310 (35.2)
≥2	2 895 (16.5)	2 275 (15.8)	1 918 (15.7)
Sex of child			
Boy	8 925 (50.9)	7 285 (50.6)	6 177 (50.5)
Girl	8 608 (49.1)	7 101 (49.4)	6 054 (49.5)
Maternal age at delivery, years	31.0 ± 4.5	31.1 ± 4.4	31.2 ± 4.3
Marital status			
Married/cohabiting	16 780 (95.7)	13 839 (96.2)	11 797 (96.5)
Other	753 (4.3)	547 (3.8)	434 (3.6)
Maternal education			
Less than high school	986 (5.6)	713 (5.0)	547 (4.5)
High school	4 175 (23.8)	3 465 (24.1)	2 845 (23.3)
Up to 4 years of college	6 480 (37.0)	5 677 (39.5)	4 919 (40.2)
More than 4 years of college (master or professional degree)	4 867 (27.8)	4 254 (29.6)	3 731 (30.5)
Missing	1 025 (5.9)	277 (1.9)	189 (1.6)
Maternal smoking during pregnancy	1 085 (6.2)	843 (5.9)	675 (5.5)
Missing	1 000 (5.7)	263 (1.8)	185 (1.5)
Maternal pre-pregnancy body mass index[a]	23.5 ± 3.8	23.5 ± 3.7	23.5 ± 3.7
Maternal atopy	5 802 (33.1)	4 947 (34.4)	4 276 (35.0)
Season of birth			
Winter	4 099 (23.4)	3 352 (23.3)	2 858 (23.4)
Spring	4 686 (26.7)	3 851 (26.8)	3 191 (26.1)
Summer	4 630 (26.4)	3 827 (26.6)	3 312 (27.1)
Autumn	4 118 (23.5)	3 356 (23.3)	2 870 (23.5)

Numbers are n (%) or mean ± standard deviation.
LRTI – lower respiratory tract infections.
[a]Missing data for maternal pre-pregnancy body mass index (BMI): baseline cohort 1 549 (8.8%), at 6 months 693 (4.8%), at 18 months 522 (4.3%).

Table 2. LUR modelled air pollution exposure using residential address at time of birth. Exposure during the whole pregnancy and by trimester.

	Oslo	Akershus	Bergen	Hordaland	Total
	N=4669	N=7554	N=3869	N=1441	N=17533
Mean LUR modelled NO_2 exposure ($\mu g/m^3$)					
Whole pregnancy	21.6 ± 4.4	10.3 ± 3.8	13.2 ± 6.2	6.3 ± 4.3	13.6 ± 6.9
Trimester 1	21.7 ± 6.1	10.2 ± 4.2	13.4 ± 6.4	6.5 ± 4.4	13.7 ± 7.4
Trimester 2	22.0 ± 6.1	10.4 ± 4.3	13.3 ± 6.5	6.3 ± 4.3	13.8 ± 7.5
Trimester 3	21.5 ± 6.1	10.3 ± 4.2	13.1 ± 6.3	6.3 ± 4.3	13.6 ± 7.3

Numbers are mean ± standard deviation
LUR – land use regression
European Union air quality standard for NO_2: 1-year average 40 $\mu g/m^3$

Table 3. Associations between pregnancy exposure to NO_2 and respiratory health of children by age 6 and 18 months.

	Crude			Adjusted		
	N total	N cases	RR (95% CI)	N total	N cases	RR (95% CI)
Main analysis[a]						
LRTI 0-6 months	13 886	653	0.84 (0.76 to 0.95)	13 116	616	0.99 (0.84 to 1.17)
LRTI 6-18 months	12 001	1 469	0.94 (0.94 to 1.01)	11 412	1 388	1.05 (0.94 to 1.16)
Wheeze 6-18 months	11 976	4 961	1.00 (0.97 to 1.03)	11 387	4 712	1.02 (0.97 to 1.07)
Stratified analysis[b]						
Oslo						
LRTI 0-6 months	3 695	136	0.72 (0.51 to 1.02)	3 530	128	0.76 (0.54 to 1.06)
LRTI 6-18 months	3 246	351	0.85 (0.69 to 1.06)	3 111	331	0.89 (0.71 to 1.12)
Wheeze 6-18 months	3 248	1 315	1.05 (0.96 to 1.16)	3 111	1 253	1.04 (0.95 to 1.15)
Akershus						
LRTI 0-6 months	6 014	281	1.22 (0.90 to 1.65)	5 619	263	1.32 (0.97 to 1.80)
LRTI 6-18 months	5 237	689	1.15 (0.96 to 1.38)	4 939	649	1.15 (0.95 to 1.39)
Wheeze 6-18 months	5 228	2 192	1.01 (0.93 to 1.10)	4 930	2 066	1.12 (0.94 to 1.34)
Bergen						
LRTI 0-6 months	3 045	169	0.90 (0.71 to 1.16)	2 899	161	0.96 (0.74 to 1.25)
LRTI 6-18 months	2 560	318	1.00 (0.85 to 1.18)	2 449	301	1.04 (0.86 to 1.22)
Wheeze 6-18 months	2 548	1 073	1.00 (0.93 to 1.07)	2 438	1 030	1.00 (0.89 to 1.07)
Hordaland						
LRTI 0-6 months	1 132	67	0.84 (0.49 to 1.46)	1 068	64	0.93 (0.50 to 1.63)
LRTI 6-18 months	958	111	1.31 (0.89 to 1.93)	913	107	1.36 (0.88 to 2.03)
Wheeze 6-18 months	952	381	1.19 (1.00 to 1.42)	908	363	1.12 (0.94 to 1.34)

Effect estimates per $10\mu g/m^3$ NO_2
LRTI – lower respiratory tract infections
[a]Adjusted for maternal age at delivery, years of birth, maternal marital status, maternal education, sex of child, maternal prepregnancy BMI, smoking during pregnancy, parity, maternal atopy and study area.
[b]Adjusted for maternal age at delivery, year of birth, maternal marital status, maternal education, sex of child, maternal prepregnancy BMI, smoking during pregnancy, parity, maternal atopy.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract – page 1.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found – page 2.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported – page 4.
Objectives	3	State specific objectives, including any prespecified hypotheses – page 5.
Methods		
Study design	4	Present key elements of study design early in the paper – page 5.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection – page 5.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up – page 5.
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed – N.A.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable – page 6 and 7.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group – page 6 and 7.
Bias	9	Describe any efforts to address potential sources of bias – N.A.
Study size	10	Explain how the study size was arrived at – page 5.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why – page 6.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding – page 8.
		(*b*) Describe any methods used to examine subgroups and interactions – page 8.
		(*c*) Explain how missing data were addressed – page 7.
		(*d*) If applicable, explain how loss to follow-up was addressed – N.A.
		(*e*) Describe any sensitivity analyses – page 8.
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed – page 5 and Table 1.
		(b) Give reasons for non-participation at each stage – page 5.
		(c) Consider use of a flow diagram – N.A.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders – page 8 and 9.
		(b) Indicate number of participants with missing data for each variable of interest – page 5.
		(c) Summarise follow-up time (eg, average and total amount) – page 5.
Outcome data	15*	Report numbers of outcome events or summary measures over time – page 8 and Table 1.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and

		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included – pages 8-9, Figure 1 and Tables 2-3.
		(*b*) Report category boundaries when continuous variables were categorized – page 8 and 9.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period – N.A.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses – page 9.
Discussion		
Key results	18	Summarise key results with reference to study objectives – page 9.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias – page 11.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence – page 11.
Generalisability	21	Discuss the generalisability (external validity) of the study results – page 10-11.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based – page 12.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Pregnancy exposure to air pollution and early childhood respiratory health in the Norwegian Mother and Child Cohort Study (MoBa)

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Pregnancy exposure to air pollution and early childhood respiratory health in the Norwegian Mother and Child Cohort Study (MoBa)

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Abstract

Objectives It is unclear whether maternal air pollution exposure during pregnancy induces changes in the developing respiratory system of a child and whether it has consequences for respiratory health in early childhood. We investigated associations between exposure to moderate levels of air pollution during pregnancy and early childhood lower respiratory tract infections (LRTI) and wheezing.

Methods This study used a sub-group of 17 533 participants in the Norwegian Mother and Child Cohort Study (MoBa). Air pollution levels at residential addresses were estimated using land use regression (LUR) models, and back-extrapolated to the period of each pregnancy. Information on LRTI and wheezing, and lifestyle factors was collected from questionnaires completed by mothers during pregnancy and when the child was 6 and 18 months of age.

Results Moderate mean levels of NO_2 (13.6 µg/m^3, range 0.01 to 60.4) exposure at residential address during pregnancy were not statistically associated with LRTI and wheezing. No association was found per 10 µg/m^3 change in NO_2 exposure and LRTI before age 6 months (adjusted RR 0.99; 95% CI 0.84 to 1.17), or between 6-18 months of age (adjusted RR 1.05; 95% CI 0.94 to 1.16). Similar, we found no association per 10 µg/m^3 change in NO_2 exposure and wheezing between 6-18 months of age (adjusted RR 1.02; 95% CI 0.97 to 1.07). An exploratory post hoc analysis indicated an increased risk for LRTIs 6 to 18 months in girls only (adjusted RR 1.20; 95% CI 1.02 to 1.46).

Conclusions There were no statistically significant associations for moderate levels of pregnancy NO_2 exposure and respiratory health outcomes during early childhood in overall analyses. However, a post hoc analysis gave some support to the idea that girls may have higher risk for developing LRTI given prenatal air pollution exposure.

Strengths and limitations of this study

- Large prospective cohort with data on lower respiratory tract infections, with additional linked data from medical birth registry.
- Land use regression modelled traffic exposure assessment at residential address using both spatial and temporal adjustment.
- The mean air pollution exposures explored in this study are relatively low.
- Not possible to identify pregnancies where the mothers continued to live at the same address during the whole study period.

Introduction

There is increasing evidence from both experimental and epidemiologic studies that the prenatal period is a critical window for harmful effects from different types of exposures on respiratory health.[1] Lower respiratory tract infections (LRTI) are common in infants and young children.[2] They are caused primarily by viral pathogens and are clinically expressed as bronchiolitis, or pneumonia.[2] Childhood wheeze is a symptom of several heterogeneous conditions, and may occur during viral respiratory infections or be associated with atopy.[3] Infections and wheeze are also closely related in young children. Respiratory diseases in early childhood may have long term consequences, accounting for a significant proportion of adult lung disease.[2 4] Special attention should be given to modifiable factors that may influence lung development at crucial stages (prenatally and postnatally). Numerous epidemiologic studies have shown that children exposed to tobacco smoke or higher levels of ambient air pollution above recommended levels (e.g. standards from the EU or the WHO) are more prone to develop respiratory disorders.[5-7] Air pollution may affect the lungs by inducing low-grade systemic inflammation and oxidative stress,[8] leading to pathological changes in the respiratory system. Children are particularly susceptible due to the continuous development of lungs that takes place from embryogenesis to early adolescence,[4 9] and continuous immune system development.[10] Of particular interest is intrauterine exposure, where air pollution may indirectly affect the developing lung tissue of the foetus.[11 12]

A number of studies have reported association of maternal smoking during pregnancy with frequent respiratory tract infections, chronic bronchitis, wheezing, and asthma in children.[13-15] Maternal smoking is well-accepted as a risk factor for adverse birth outcomes and lends support for a role of outdoor air pollution on pregnancy outcomes.[16] Furthermore, maternal smoking during pregnancy has been identified as an independent risk factor for wheeze and LRTI in the children's first 18 months of life.[17] There is an ongoing interest in whether exposure to ambient air pollution during pregnancy might influence respiratory health in early childhood.[18] The effect of air pollution exposure during pregnancy on respiratory health and allergic responses early in life has been examined by several studies with large heterogeneity.[19-24] Some studies report associations of prenatal air pollution exposure with LRTI in early childhood.[19-22] Other studies have found no support for an association

between air pollution exposure and LRTI in early childhood.[23 24] In addition, there are animal exposure studies that have identified both anatomic/mechanical and immunological mechanisms by which air pollution exposure may increase susceptibility of the respiratory system to infections.[25 26]

In this study, we investigated the associations between estimated exposure to traffic-related air pollution during pregnancy and early childhood respiratory health (LRTI and wheeze) in selected urban and county areas of Norway. Norway is characterized by relatively low levels of air pollution,[27] and it is of interest whether low levels might interfere with intrauterine respiratory system development and affect respiratory health later in life.

Methods

Study population

The Norwegian Mother and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health.[27] Pregnant women were recruited from all over Norway from 1999 to 2008. Among invited women, 41% consented to participate. Mothers could participate with more than one child, resulting in 114 500 children and 95 200 mothers included in the cohort.

All participants living in our study areas (Oslo, Bergen, Akershus, and Hordaland) were eligible for our study (N=22 149, 23.3%). We excluded participants with missing NO_2 exposure information (N=3 876), multiple births (N=664) and non-live births (N=76). Only data on singleton live births were used in the analyses. Total number of participants from the four study areas was 17 533 (79%). Pregnancy-related information was obtained from the Medical Birth Registry of Norway (MBRN).

Mothers participating in the MoBa study completed a number of questionnaires during follow-up. We used data on lifestyle characteristics from the first questionnaire completed at recruitment (approximately at week 17-18 of pregnancy) and another questionnaire completed at week 30 of pregnancy. Information on the respiratory outcomes was collected from maternal questionnaires completed when the child was 6 and 18 months of age. The children were born from 2001 to 2009, 14 386 mothers had returned the questionnaire at 6 months, and 12 231 had returned the questionnaire at

18 months (Table 1).

The study was approved by the regional Ethics committee and the Norwegian Data Inspectorate. The current study is based on versions VI (pregnancy data) and VIII (respiratory outcomes) of the quality-assured data files released for research on the 15th April 2011 and on the 14th February 2014, respectively.

2.2 Outcomes and covariates

The outcomes, LRTI and wheeze, were based on the maternal report from questionnaires filled when children were 6 and 18 months of age. The questionnaires can be viewed at the MoBa website (https://www.fhi.no/en/studies/moba/). LRTIs included respiratory syncytial virus, bronchiolitis, bronchitis, and pneumonia. We classified hospitalization for any of these conditions as being hospitalized for LRTI at a) between 0-6 months of age, and b) between 6-18 months of age. Wheeze was defined as "wheezing/whistling in the chest" or "tightness in the chest" between 6 and 18 months of age. The outcomes were treated as dichotomous.

The following characteristics were extracted from the MBRN: parity defined as number of previous deliveries (0; 1; ≥2), mother's age at birth (years), marital status (married/cohabiting; other) sex of the child (boy; girl), and year of birth. Questionnaire information was used to determine: maternal education (less than high school; high school; up to 4 years of college; more than 4 years of college (master or professional degree)), maternal smoking during pregnancy (never; any smoking during pregnancy), maternal weight at the beginning of pregnancy (kg) and maternal height (m) were used to calculate body mass index (BMI) (maternal weight divided by squared maternal height), maternal atopy (ever having hay fever, pollen allergy, atopic dermatitis, allergy to animal hair, other types of allergy, or asthma).

Adjustment variables (Table 1) were selected based on literature analyses and included maternal age at delivery, maternal marital status, maternal education, sex of child, maternal pre-pregnancy BMI, parity, year of birth, smoking during pregnancy, maternal atopy, and area.

Air pollution exposure

In this study, we used LUR modeled exposure to traffic-related pollutant NO_2 at the residential address at the time of delivery for women included in MoBa. Separate models were developed for four of the recruitment areas: the two biggest cities in Norway (Oslo and Bergen) and their surrounding counties (Akershus and Hordaland).[28]

Estimates of air pollution exposure during pregnancy were based on the methodology developed for the ESCAPE project.[29 30] Land use regression (LUR) models for NO_2 levels were built for each of the studied areas in order to account for regional specifics.[28] Sampling of air pollution is done retrospective since it was not part of the MoBa design. We measured the spatial distribution of air pollution for Oslo and Akershus in 2010, and for Bergen and Hordaland in 2011. Measurement campaigns included three rounds of approximately two weeks duration with NO_2 measurements (during winter, summer and an intermediate season) within a one year period. Measurement sites (14 in Oslo, 36 in Akershus and 46 in Bergen/Hordaland) were selected to represent the range of residential exposure for each study area. In the analyses, we included sites with no missing data, and no geocoding mismatches. The models provided adjusted R^2 in the range of 55 – 85 %, and more details of these models is described elsewhere.[28]

LUR models were built separately for Oslo and Akershus. Only one model was built for the whole Hordaland County (including the city Bergen) due to a low number of valid measurement sites outside Bergen. Predictors for building the LUR model were obtained from a geographical information system (GIS) analyses of the N50 and VBASE maps (received in February 2013) providing information on land use, residential density, types of landscape and road network information. We built multiple linear regression models and performed diagnostic model tests according to the method described by Beelen and colleagues.[29]

Yearly means of air pollution levels at residential address at birth were estimated using the resulting LUR models. Variables in models were truncated in accordance to the range of corresponding variables used for LUR model building. Negative modelled values were replaced with 0.01 to avoid the unlikely scenario of negative modelled exposure and keep these in the analyses as low exposed addresses (N=112).[28] The true exposure from NO_2 at these addresses are most likely at the low end of the scale. In order to account for temporal variability, we used the ratio method of

back-extrapolation to the period of each pregnancy using continuous routine monitoring station data.[30] Daily NO_2 measurements were obtained from the Norwegian Institute for Air Research database "Luftkvalitet.info" for the period 2000 - 2012 in Oslo (used for Oslo and Akershus), and for the period 2003 - 2012 in Bergen (used for Bergen and Hordaland). Daily estimates of exposure were calculated using the ratio method of back-extrapolation: the LUR-modelled yearly estimate multiplied by the ratio between daily NO_2 routine monitoring station measurement and an annual average for the year when LUR measurement campaign took place. Daily NO_2 exposure estimates were averaged separately for 1st, 2nd, and 3rd trimester, and also over the whole pregnancy.

Statistical analysis

Generalized linear models was fitted to evaluate the associations between pregnancy NO_2 exposure and respiratory outcomes. Results are presented for crude and adjusted models as risk ratios (RR) with robust standard errors. Multiplicative interactions were tested in the adjusted models between the continuous NO_2 pregnancy exposure variable and the following categorical variables: area, sex, smoking during pregnancy, parity, birth season and maternal atopy.

Sensitivity analyses were performed by a) restricting the analyses to women who did not change address during pregnancy, and b) restricting the analyses to pregnancies during the last period (2006-2008) of the MoBa recruitment, thus closer in time to the exposure campaign and GIS-variables.

Area variable was defined by the location of the address at delivery: Oslo, Akershus, Bergen and Hordaland. In a previous study, the area variable was found to be an important factor in attenuating the associations between exposure and birth outcome in MoBa[28] These differences by area could be linked to more travel to and from work and to other activities, visiting central more polluted parts of the city by e.g. higher educated women and for city dwellers per se. This variable is included in the adjusted models since it previously has been reported to be a potential proxy for unmeasured factors that could vary between each study area and thus could influence the outcome variables within each separate area. Still, area may also reflect the spatial distribution of air pollution, and thus result in overadjustment bias on the path between exposure and outcome.[31] We therefore performed a separate

post hoc analysis by excluding the area variable from the adjusted model. In addition, we performed exploratory analyses post hoc by area, sex of child, parity, season of birth, and maternal atopy.

We used ArcGIS10.1 software (Esri, CA, USA) for GIS analyses; statistical analyses were performed using STATA 13.0 (StataCorp, Texas, USA).

Results

The study population included in this study consisting of participants from the four study areas of Norway with pregnancy air pollution exposure data had similar characteristics as the whole MoBa cohort study with information from 6 months and at 18 months (Table 1). A total of 4.5% of children had LRTI between 0-6 months of age, and 12% of children had LRTI between 6-18 months of age. A total of 40.6% of the children had wheezing symptoms between 6 and 18 months of age.

The majority (86.7%) of the women did not change address during pregnancy. Maternal smoking in pregnancy was relatively uncommon (6.2%). Maternal atopy was reported in 33.1% of the women (Table 1). The distribution of the study population across birth seasons reflects the timing of recruitment into MoBa and we therefore observe slight deviation from the equal seasonal distribution.

Mean NO_2 exposure during whole pregnancy was 13.6 ± 6.9 $\mu g/m^3$ NO_2, which is well below the European Union air quality yearly average standard of 40 $\mu g/m^3$ NO_2. The range of NO_2 spanned from 0.01 thru 60.4 $\mu g/m^3$, with a total of 27 children with concentrations equal or above 40 $\mu g/m^3$ at their residential address. Exposures by trimester and the whole pregnancy exposure were highly correlated (r = 0.73 to 0.85). We therefore decided to use only the average NO_2 exposure during the whole pregnancy as our exposure estimate in the analyses.

We found no associations of NO_2 exposure during pregnancy with LRTI at 0-6 months, LRTI at 6-18 months, or wheeze at 6-18 months in the overall analyses (Table 3). The main covariates affecting the change in significance of risk ratio estimate from the crude to the adjusted models were parity and area. In the stratified analyses by area we observed a consistent pattern, although not statistically significant, of positive associations for LRTI and wheeze for participants living outside big cities, in Akershus and Hordaland (Table 3). An analysis of the cumulative incidence of LRTI (0-18 months of age) was equal to an RR= 1.04 (95% CI 0.93, 1.17).

There was no evidence of effect modification by the adjustment variables. Still, there was a borderline significant interaction for child sex. A stratified analysis post hoc, showed a consistent tendency for association of pregnancy NO_2 exposure with LRTI and wheeze in girls, but not in boys. For instance, the risk of developing LRTI 6-18 months in girls was equal to an RR =1.20 (95% CI 1.02 to 1.42, p=0.03) per each 10μg/m^3 increase in NO_2 exposure during pregnancy. Stratified analyses post hoc by maternal atopy status and birth season did not identify any important differences between the groups. No statistically significant interactions were detected between NO_2 exposure and maternal atopy, sex of child, area, birth season, or parity. Sensitivity analyses resulted in no substantial changes compared to the reported results. Excluding from the adjustment set the area variable, as a factor potentially reflecting spatial distribution of air pollution, did not considerably change the results. Restricting the analyses to pregnancies during the last period of the MoBa recruitment (2006-2008) did not result in substantial changes to the reported results.

Discussion

In this study, we found no statistically significant associations for pregnancy NO_2 exposure to traffic-related air pollution exposure at residential address at birth and LRTI or wheeze in early childhood.

A previously study by Esplugues and colleagues has reported similar results of no association between LUR-modelled prenatal NO_2 exposure (with higher than in our study whole pregnancy mean NO_2 values of 39.1μg/m^3) with LRTI or persistent cough during the 1st year of life, but they did report an association between postnatal NO_2 exposure and persistent cough.[23] In the large international ESCAPE study, uniting cohorts from Germany, Sweden, Netherlands, and the UK, decrease in lung function parameters has been associated with exposure to LUR-modelled annual average NO_2, NO_x, $PM_{2.5}$ absorbance, and $PM_{2.5}$ at current address at 6 - 8 years of age, but not at birth address.[32]

In a post hoc analysis, we found a consistent tendency of prenatal NO_2 exposure association with LRTI: the association was present in girls, but not in boys. The tests of interaction was only borderline significant. Male sex is a known risk factor for both respiratory infections and wheezing in childhood.[3 33 34] However, the interaction between environmental exposures and prenatal lung development in boys and girls remains uncertain,[35] and our finding was from one of several subsample

analyses. There are differences in prenatal anatomic and physiological respiratory system development in sexes, as well as different sex-hormone effects on the immune system functioning.[35-37] As was reviewed by Casimir and colleagues, while boys outnumber girls in acute respiratory infections, girls had an overall enhanced inflammatory response.[38] This increased inflammatory response could have more adverse effects on girls than on boys.[38] Given the chronic low-grade systemic inflammation associated with air pollution exposure,[8] we might expect more adverse effect in girls. However, this issue is insufficiently studied, and the existing reports give contradictory results. The international ESCAPE study reported stronger effects of air pollution exposure during the first year of life, which was LUR-modelled at birth address, on pneumonia in girls.[7]

We found some indication of different patterns for associations between prenatal air pollution exposure and early respiratory health in study participants living in cities versus counties outside cities. Associations between prenatal air pollution exposure and the respiratory outcomes was overall greater in the non-urban areas, although the estimates were not statistically significant. This might be due to a higher misclassification of exposure in cities because of higher mobility (change of residential address), or due to other types of pollutants in non-urban areas.[39] A study by Canfield and colleagues (2006) reported higher mobility for nullparious women as compared to women with several children. They explained this as related to the need for larger homes due to expecting a child (first born) and a need to live closer to health care facilities.[40] A previous study from Norway reported that half of the mothers work during pregnancy and that no difference was found when comparing using only home address to a weighted exposure of home and work address exposure.[41] On the other hand, non-city population might have more homogenous exposure and spending more time close to home. Difference in distribution of socioeconomic factors or parity might play a role: families with several children tend to move out of large cities in Norway. Familiar predisposition to allergic disorders may be an important factor in modifying the effect of tobacco smoke exposure on wheezing.[36] Certain months of birth, due to their correlation with viral infections seasons, can be a risk factor for wheezing and LRTI.[3 34] Our study found no differences in the effect from groups divided by maternal atopy status or birth season.

Our study applied standardized individual exposure assessment for the large study population, and detailed information on potential confounders was collected from prenatal questionnaires. Estimates for prenatal exposure to NO_2 were based on LUR models and temporal back-extrapolation of exposure during entire pregnancy at the address at birth. The NO_2 exposure was collected during 2010 and 2011, and the GIS-variables used in the modelling were collected in 2013. The modelled exposures at each address were back-extrapolated using fixed 24-hour monitoring data from each area in the period 1999-2009. Such estimates might be a subject to non-differential misclassification of exposure due to changes in GIS-variables, or differences in the participant's mobility and lifestyle factors. However, results of the sensitivity analyses only in women who did not change address during pregnancy were similar to the overall analyses. Likewise, restricting the analyses to pregnancies during the last period, closer in time to the collected exposure variables and GIS-variables, did not result in different associations than the overall analyses.

In epidemiological studies investigating air pollution effects, precision of exposure estimation is an important challenge. It is usually not feasible to sample personal air pollution exposure in large birth cohorts, mainly due to the amount of participants needed and due to the fact of not having information about the pregnancy before week 17. It has therefore become increasingly common to apply modelling of air pollution exposure at individual residential addresses, such as dispersion models and LUR models. High correlations have previously been reported between indoor and outdoor concentrations of NO_2,[42] and NO_2 is also reported to display higher spatial variation as compared to other pollutants,[43] thus making it a better proxy for individual air pollution exposure.

The mean air pollution exposure levels explored in this study may be relatively low for detecting the association between prenatal exposure and postnatal respiratory health, and the reported effect estimates might be biased towards null due to non-differential misclassification of exposure. It could also be difficult to disentangle prenatal and early postnatal exposure to air pollution if family continues to live at the same address at these two periods. Prenatal exposures need to be carefully studied for identifying potential critical windows of exposure. In our data, exposures by trimester were highly correlated with whole pregnancy exposure, and therefore we only assessed the exposure during entire pregnancy. More studies are needed for exploring the causative association between prenatal air

pollution exposure and respiratory health early in childhood, for characterizing critical time windows and main pollutants that are involved in pathological changes. Of interest for future research is the sex difference in prenatal exposure effect identified in our study.

In this large Norwegian pregnancy cohort we found no statistically significant associations for moderate levels of exposure to NO_2 during pregnancy and childhood respiratory health measured by LRTI and wheeze.

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Details of ethics approval: The Norwegian Mother and Child Cohort Study has approvals from the Regional Ethics Committee and the Norwegian Data Inspectorate. The current study is based on version VI of the quality-assured data files released for research on the 15th April 2011.

Data sharing statement: Technical description of the MoBa data can be found at the study website (https://www.fhi.no/en/studies/moba/). Researchers can apply for access to the dataset (https://www.fhi.no/en/more/research--access-to-data/). Statistical code is available upon request from the corresponding author.

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Table 1. Descriptive statistics for study participants from the MOBA cohort.

	Baseline cohort at birth with NO_2 data (N=17 533)	Questionnaire at 6 months (N=14 386)	Questionnaire at 18 months (N=12 231)
Oslo	4 669 (26.6)	3 801 (26.4)	3 320 (27.1)
Akershus	7 554 (43.1)	6 284 (43.7)	5 350 (43.7)
Bergen	3 869 (22.1)	3 135 (21.8)	2 591 (21.2)
Hordaland	1 441 (8.2)	1 166 (8.1)	970 (7.9)
LRTI0- 6 months		653 (4.5)	
Missing		500 (3.5)	
LRTI 6- 18 months			1 469 (12.0)
Missing			230 (1.9)
Wheeze 6- 18 months			4 961 (40.6)
Missing			255 (2.1)
Women who changed address during pregnancy	2 336 (13.3)	1 782 (12.4)	1 471 (12.0)
Parity			
0	8 310 (47.4)	6 973 (48.5)	6 003 (49.1)
1	6 328 (36.1)	5 138 (35.7)	4 310 (35.2)
≥2	2 895 (16.5)	2 275 (15.8)	1 918 (15.7)
Sex of child			
Boy	8 925 (50.9)	7 285 (50.6)	6 177 (50.5)
Girl	8 608 (49.1)	7 101 (49.4)	6 054 (49.5)
Maternal age at delivery, years	31.0 ± 4.5	31.1 ± 4.4	31.2 ± 4.3
Marital status			
Married/cohabiting	16 780 (95.7)	13 839 (96.2)	11 797 (96.5)
Other	753 (4.3)	547 (3.8)	434 (3.6)
Maternal education			
Less than high school	986 (5.6)	713 (5.0)	547 (4.5)
High school	4 175 (23.8)	3 465 (24.1)	2 845 (23.3)
Up to 4 years of college	6 480 (37.0)	5 677 (39.5)	4 919 (40.2)
More than 4 years of college (master or professional degree)	4 867 (27.8)	4 254 (29.6)	3 731 (30.5)
Missing	1 025 (5.9)	277 (1.9)	189 (1.6)
Maternal smoking during pregnancy	1 085 (6.2)	843 (5.9)	675 (5.5)
Missing	1 000 (5.7)	263 (1.8)	185 (1.5)
Maternal pre-pregnancy body mass index[a]	23.5 ± 3.8	23.5 ± 3.7	23.5 ± 3.7
Maternal atopy	5 802 (33.1)	4 947 (34.4)	4 276 (35.0)
Season of birth			
Winter	4 099 (23.4)	3 352 (23.3)	2 858 (23.4)
Spring	4 686 (26.7)	3 851 (26.8)	3 191 (26.1)
Summer	4 630 (26.4)	3 827 (26.6)	3 312 (27.1)
Autumn	4 118 (23.5)	3 356 (23.3)	2 870 (23.5)

Numbers are n (%) or mean ± standard deviation.
LRTI – lower respiratory tract infections.
[a]Missing data for maternal pre-pregnancy body mass index (BMI): baseline cohort 1 549 (8.8%), at 6 months 693 (4.8%), at 18 months 522 (4.3%).

Table 2. LUR modelled air pollution exposure using residential address at time of birth. Exposure during the whole pregnancy and by trimester.

	Oslo	Akershus	Bergen	Hordaland	Total
	N=4 669	**N=7 554**	**N=3 869**	**N=1 441**	**N=17 533**
Mean LUR modelled NO_2 exposure ($\mu g/m^3$)					
Whole pregnancy	21.6 ± 4.4	10.3 ± 3.8	13.2 ± 6.2	6.3 ± 4.3	13.6 ± 6.9
Trimester 1	21.7 ± 6.1	10.2 ± 4.2	13.4 ± 6.4	6.5 ± 4.4	13.7 ± 7.4
Trimester 2	22.0 ± 6.1	10.4 ± 4.3	13.3 ± 6.5	6.3 ± 4.3	13.8 ± 7.5
Trimester 3	21.5 ± 6.1	10.3 ± 4.2	13.1 ± 6.3	6.3 ± 4.3	13.6 ± 7.3

Numbers are mean ± standard deviation
LUR – land use regression
European Union air quality standard for NO_2: 1-year average 40 $\mu g/m^3$

Table 3. Associations between pregnancy exposure to NO_2 and respiratory health of children by age 6 and 18 months.

	Crude			Adjusted		
	N total	N cases	RR (95% CI)	N total	N cases	RR (95% CI)
Main analysis[a]						
LRTI 0-6 months	13 886	653	0.84 (0.76 to 0.95)	13 116	616	0.99 (0.84 to 1.17)
LRTI 6-18 months	12 001	1 469	0.94 (0.94 to 1.01)	11 412	1 388	1.05 (0.94 to 1.16)
Wheeze 6-18 months	11 976	4 961	1.00 (0.97 to 1.03)	11 387	4 712	1.02 (0.97 to 1.07)
Stratified analysis[b]						
Oslo						
LRTI 0-6 months	3 695	136	0.72 (0.51 to 1.02)	3 530	128	0.76 (0.54 to 1.06)
LRTI 6-18 months	3 246	351	0.85 (0.69 to 1.06)	3 111	331	0.89 (0.71 to 1.12)
Wheeze 6-18 months	3 248	1 315	1.05 (0.96 to 1.16)	3 111	1 253	1.04 (0.95 to 1.15)
Akershus						
LRTI 0-6 months	6 014	281	1.22 (0.90 to 1.65)	5 619	263	1.32 (0.97 to 1.80)
LRTI 6-18 months	5 237	689	1.15 (0.96 to 1.38)	4 939	649	1.15 (0.95 to 1.39)
Wheeze 6-18 months	5 228	2 192	1.01 (0.93 to 1.10)	4 930	2 066	1.12 (0.94 to 1.34)
Bergen						
LRTI 0-6 months	3 045	169	0.90 (0.71 to 1.16)	2 899	161	0.96 (0.74 to 1.25)
LRTI 6-18 months	2 560	318	1.00 (0.85 to 1.18)	2 449	301	1.04 (0.86 to 1.22)
Wheeze 6-18 months	2 548	1 073	1.00 (0.93 to 1.07)	2 438	1 030	1.00 (0.89 to 1.07)
Hordaland						
LRTI 0-6 months	1 132	67	0.84 (0.49 to 1.46)	1 068	64	0.93 (0.50 to 1.63)
LRTI 6-18 months	958	111	1.31 (0.89 to 1.93)	913	107	1.36 (0.88 to 2.03)
Wheeze 6-18 months	952	381	1.19 (1.00 to 1.42)	908	363	1.12 (0.94 to 1.34)

Effect estimates per $10\mu g/m^3$ NO_2
LRTI – lower respiratory tract infections
[a]Adjusted for maternal age at delivery, years of birth, maternal marital status, maternal education, sex of child, maternal prepregnancy BMI, smoking during pregnancy, parity, maternal atopy and study area.
[b]Adjusted for maternal age at delivery, year of birth, maternal marital status, maternal education, sex of child, maternal prepregnancy BMI, smoking during pregnancy, parity, maternal atopy.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract – page 1.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found – page 2.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported – page 4.
Objectives	3	State specific objectives, including any prespecified hypotheses – page 5.
Methods		
Study design	4	Present key elements of study design early in the paper – page 5.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection – page 5.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up – page 5.
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed – N.A.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable – page 6 and 7.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group – page 6 and 7.
Bias	9	Describe any efforts to address potential sources of bias – N.A.
Study size	10	Explain how the study size was arrived at – page 5.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why – page 6.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding – page 8.
		(*b*) Describe any methods used to examine subgroups and interactions – page 8.
		(*c*) Explain how missing data were addressed – page 7.
		(*d*) If applicable, explain how loss to follow-up was addressed – N.A.
		(*e*) Describe any sensitivity analyses – page 8.
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed – page 5 and Table 1.
		(b) Give reasons for non-participation at each stage – page 5.
		(c) Consider use of a flow diagram – N.A.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders – page 8 and 9.
		(b) Indicate number of participants with missing data for each variable of interest – page 5.
		(c) Summarise follow-up time (eg, average and total amount) – page 5.
Outcome data	15*	Report numbers of outcome events or summary measures over time – page 8 and Table 1.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and

		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included – pages 8-9, Figure 1 and Tables 2-3.
		(*b*) Report category boundaries when continuous variables were categorized – page 8 and 9.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period – N.A.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses – page 9.
Discussion		
Key results	18	Summarise key results with reference to study objectives – page 9.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias – page 11.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence – page 11.
Generalisability	21	Discuss the generalisability (external validity) of the study results – page 10-11.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based – page 12.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Pregnancy exposure to air pollution and early childhood respiratory health in the Norwegian Mother and Child Cohort Study (MoBa)

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Pregnancy exposure to air pollution and early childhood respiratory health in the Norwegian Mother and Child Cohort Study (MoBa)

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Abstract

Objectives It is unclear whether maternal air pollution exposure during pregnancy induces changes in the developing respiratory system of a child and whether it has consequences for respiratory health in early childhood. We investigated associations between exposure to moderate levels of air pollution during pregnancy and early childhood lower respiratory tract infections (LRTI) and wheezing.

Methods This study used a sub-group of 17 533 participants in the Norwegian Mother and Child Cohort Study (MoBa). Air pollution levels at residential addresses were estimated using land use regression (LUR) models, and back-extrapolated to the period of each pregnancy. Information on LRTI and wheezing, and lifestyle factors was collected from questionnaires completed by mothers during pregnancy and when the child was 6 and 18 months of age.

Results Moderate mean levels of NO_2 (13.6 µg/m^3, range 0.01 to 60.4) exposure at residential address during pregnancy were not statistically associated with LRTI and wheezing. No association was found per 10 µg/m^3 change in NO_2 exposure and LRTI before age 6 months (adjusted RR 0.99; 95% CI 0.84 to 1.17), or between 6-18 months of age (adjusted RR 1.05; 95% CI 0.94 to 1.16). Similarly, we found no association per 10 µg/m^3 change in NO_2 exposure and wheezing between 6-18 months of age (adjusted RR 1.02; 95% CI 0.97 to 1.07).

Conclusions There were no statistically significant associations for moderate levels of pregnancy NO_2 exposure and respiratory health outcomes during early childhood in overall analyses.

Strengths and limitations of this study

- Large prospective cohort with data on lower respiratory tract infections, with additional linked data from medical birth registry.
- Land use regression modelled traffic exposure assessment at residential address using both spatial and temporal adjustment.
- Cohort living in areas with low to moderate air pollution concentrations.
- Unable to account for any changes in address location and pollution exposure during pregnancy.

Introduction

There is increasing evidence from both experimental and epidemiologic studies that the prenatal period is a critical window for harmful effects from different types of exposures on respiratory health.[1] Lower respiratory tract infections (LRTI) are common in infants and young children.[2] They are caused primarily by viral pathogens and are clinically expressed as bronchiolitis, or pneumonia.[2] Childhood wheeze is a symptom of several heterogeneous conditions, and may occur during viral respiratory infections or be associated with atopy.[3] Infections and wheeze are also closely related in young children. Respiratory diseases in early childhood may have long term consequences, accounting for a significant proportion of adult lung disease.[2 4] Special attention should be given to modifiable factors that may influence lung development at crucial stages (prenatally and postnatally). Numerous epidemiologic studies have shown that children exposed to tobacco smoke or higher levels of ambient air pollution above recommended levels (e.g. standards from the EU or the WHO) are more prone to develop respiratory disorders.[5-7] Air pollution may affect the lungs by inducing low-grade systemic inflammation and oxidative stress,[8] leading to pathological changes in the respiratory system. Children are particularly susceptible due to the continuous development of lungs that takes place from embryogenesis to early adolescence,[4 9] and continuous immune system development.[10] Of particular interest is intrauterine exposure, where air pollution may indirectly affect the developing lung tissue of the foetus.[11 12]

There is an ongoing interest in whether exposure to ambient air pollution during pregnancy might influence respiratory health in early childhood.[13] The effect of air pollution exposure during pregnancy on respiratory health and allergic responses early in life has been examined by several studies with large heterogeneity.[14-19] Some studies report associations of prenatal air pollution exposure with LRTI in early childhood.[14-17] Other studies have found no support for an association between air pollution exposure and LRTI in early childhood.[18 19] In addition, there are animal exposure studies that have identified both anatomic/mechanical and immunological mechanisms by which air pollution exposure may increase susceptibility of the respiratory system to infections.[20 21]

In this study, we investigated the associations between estimated exposure to traffic-related air pollution during pregnancy and early childhood respiratory health (LRTI and wheeze) in selected

urban and county areas of Norway. Norway is characterized by relatively low levels of air pollution,[22] and it is of interest whether low levels might interfere with intrauterine respiratory system development and affect respiratory health later in life.

Methods

Study population

The Norwegian Mother and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health.[22] Pregnant women were recruited from all over Norway from 1999 to 2008. Among invited women, 41% consented to participate. Mothers could participate with more than one child, resulting in 114 500 children and 95 200 mothers included in the cohort.

All participants living in our study areas (Oslo, Bergen, Akershus, and Hordaland) were eligible for our study (N=22 149, 23.3%). We excluded participants with missing NO_2 exposure information (N=3 876), multiple births (N=664) and non-live births (N=76). Only data on singleton live births were used in the analyses. Total number of participants from the four study areas was 17 533 (79%). Pregnancy-related information was obtained from the Medical Birth Registry of Norway (MBRN).

Mothers participating in the MoBa study completed a number of questionnaires during follow-up. We used data on lifestyle characteristics from the first questionnaire completed at recruitment (approximately at week 17-18 of pregnancy) and another questionnaire completed at week 30 of pregnancy. Information on the respiratory outcomes was collected from maternal questionnaires completed when the child was 6 and 18 months of age. The children were born from 2001 to 2009, 14 386 mothers had returned the questionnaire at 6 months, and 12 231 had returned the questionnaire at 18 months (Table 1).

The study was approved by the regional Ethics committee and the Norwegian Data Inspectorate. The current study is based on versions VI (pregnancy data) and VIII (respiratory outcomes) of the quality-assured data files released for research on the 15th April 2011 and on the 14th February 2014, respectively.

2.2 Outcomes and covariates

The outcomes, LRTI and wheeze, were based on the maternal report from questionnaires filled when children were 6 and 18 months of age. The questionnaires can be viewed at the MoBa website (https://www.fhi.no/en/studies/moba/). LRTIs included respiratory syncytial virus, bronchiolitis, bronchitis, and pneumonia. We classified hospitalization for any of these conditions as being hospitalized for LRTI at a) between 0-6 months of age, and b) between 6-18 months of age. Wheeze was defined as "wheezing/whistling in the chest" or "tightness in the chest" between 6 and 18 months of age. The outcomes were treated as dichotomous.

The following characteristics were extracted from the MBRN: parity defined as number of previous deliveries (0; 1; ≥2), mother's age at birth (years), marital status (married/cohabiting; other) sex of the child (boy; girl), and year of birth. Questionnaire information was used to determine: maternal education (less than high school; high school; up to 4 years of college; more than 4 years of college (master or professional degree)), maternal smoking during pregnancy (never; any smoking during pregnancy), maternal weight at the beginning of pregnancy (kg) and maternal height (m) were used to calculate body mass index (BMI) (maternal weight divided by squared maternal height), maternal atopy (ever having hay fever, pollen allergy, atopic dermatitis, allergy to animal hair, other types of allergy, or asthma).

Adjustment variables (Table 1) were selected based on literature analyses and included maternal age at delivery, maternal marital status, maternal education, sex of child, maternal pre-pregnancy BMI, parity, year of birth, smoking during pregnancy, maternal atopy, and area.

Air pollution exposure

In this study, we used LUR modeled exposure to traffic-related pollutant NO_2 at the residential address at the time of delivery for women included in MoBa. Separate models were developed for four of the recruitment areas: the two biggest cities in Norway (Oslo and Bergen) and their surrounding counties (Akershus and Hordaland).[23]

Estimates of air pollution exposure during pregnancy were based on the methodology developed for the ESCAPE project.[24 25] Land use regression (LUR) models for NO_2 levels were built for each of the studied areas in order to account for regional specifics.[23] Sampling of air pollution is done retrospectively since it was not part of the MoBa design. We measured the spatial distribution of air pollution for Oslo and Akershus in 2010, and for Bergen and Hordaland in 2011. Measurement campaigns included three rounds of approximately two weeks duration with NO_2 measurements (during winter, summer and an intermediate season) within a one year period. Measurement sites (14 in Oslo, 36 in Akershus and 46 in Bergen/Hordaland) were selected to represent the range of residential exposure for each study area. In the analyses, we included sites with no missing data, and no geocoding mismatches. The models provided adjusted R^2 in the range of 55 – 85 %, and more details of these models is described elsewhere.[23]

LUR models were built separately for Oslo and Akershus. Only one model was built for the whole Hordaland County (including the city Bergen) due to a low number of valid measurement sites outside Bergen. Predictors for building the LUR model were obtained from a geographical information system (GIS) analyses of the N50 and VBASE maps (received in February 2013) providing information on land use, residential density, types of landscape and road network information. We built multiple linear regression models and performed diagnostic model tests according to the method described by Beelen and colleagues.[24]

Yearly means of air pollution levels at residential address at birth were estimated using the resulting LUR models. Variables in models were truncated in accordance to the range of corresponding variables used for LUR model building. Negative modelled values were replaced with 0.01 to avoid the unlikely scenario of negative modelled exposure and keep these in the analyses as low exposed addresses (N=112).[23] The true exposure from NO_2 at these addresses are most likely at the low end of the scale. In order to account for temporal variability, we used the ratio method of back-extrapolation to the period of each pregnancy using continuous routine monitoring station data.[25] Daily NO_2 measurements were obtained from the Norwegian Institute for Air Research database "Luftkvalitet.info" for the period 2000 - 2012 in Oslo (used for Oslo and Akershus), and for the period 2003 - 2012 in Bergen (used for Bergen and Hordaland). Daily estimates of exposure were calculated

using the ratio method of back-extrapolation: the LUR-modelled yearly estimate multiplied by the ratio between daily NO_2 routine monitoring station measurement and an annual average for the year when LUR measurement campaign took place. Daily NO_2 exposure estimates were averaged separately for 1st, 2nd, and 3rd trimester, and also over the whole pregnancy.

Statistical analysis

Generalized linear models was fitted to evaluate the associations between pregnancy NO_2 exposure and respiratory outcomes. Results are presented for crude and adjusted models as risk ratios (RR) with robust standard errors. Multiplicative interactions were tested in the adjusted models between the continuous NO_2 pregnancy exposure variable and the following categorical variables: area, sex, smoking during pregnancy, parity, birth season and maternal atopy.

Sensitivity analyses were performed by a) restricting the analyses to women who did not change address during pregnancy, and b) restricting the analyses to pregnancies during the last period (2006-2008) of the MoBa recruitment, thus closer in time to the exposure campaign and GIS-variables.

Area variable was defined by the location of the address at delivery: Oslo, Akershus, Bergen and Hordaland. In a previous study, the area variable was found to be an important factor in attenuating the associations between exposure and birth outcome in MoBa[23] These differences by area could be linked to more travel to and from work and to other activities, visiting central more polluted parts of the city by e.g. higher educated women and for city dwellers per se. This variable is included in the adjusted models since it previously has been reported to be a potential proxy for unmeasured factors that could vary between each study area and thus could influence the outcome variables within each separate area. Still, area may also reflect the spatial distribution of air pollution, and thus result in overadjustment bias on the path between exposure and outcome.[26] We therefore performed a separate post hoc analysis by excluding the area variable from the adjusted model. In addition, we performed exploratory analyses post hoc by area, sex of child, parity, season of birth, and maternal atopy.

We used ArcGIS10.1 software (Esri, CA, USA) for GIS analyses; statistical analyses were performed using STATA 13.0 (StataCorp, Texas, USA).

Results

The study population included in this study consisting of participants from the four study areas of Norway with pregnancy air pollution exposure data had similar characteristics as the whole MoBa cohort study with information from 6 months and at 18 months (Table 1). A total of 4.5% of children had LRTI between 0-6 months of age, and 12% of children had LRTI between 6-18 months of age. A total of 40.6% of the children had wheezing symptoms between 6 and 18 months of age.

The majority (86.7%) of the women did not change address during pregnancy. Maternal smoking in pregnancy was relatively uncommon (6.2%). Maternal atopy was reported in 33.1% of the women (Table 1). The distribution of the study population across birth seasons reflects the timing of recruitment into MoBa and we therefore observe slight deviation from the equal seasonal distribution.

Mean NO_2 exposure during whole pregnancy was 13.6 ± 6.9 $\mu g/m^3$ NO_2, which is well below the European Union air quality yearly average standard of 40 $\mu g/m^3$ NO_2. The range of NO_2 spanned from 0.01 thru 60.4 $\mu g/m^3$, with a total of 27 children with concentrations equal or above 40 $\mu g/m^3$ at their residential address. Exposures by trimester and the whole pregnancy exposure (Table 2) were highly correlated (r = 0.73 to 0.85). We therefore decided to use only the average NO_2 exposure during the whole pregnancy as our exposure estimate in the analyses.

We found no associations of NO_2 exposure during pregnancy with LRTI at 0-6 months, LRTI at 6-18 months, or wheeze at 6-18 months in the overall analyses (Table 3). The main covariates affecting the change in significance of risk ratio estimate from the crude to the adjusted models were parity and area. In the stratified analyses by area we observed a consistent pattern, although not statistically significant, of positive associations for LRTI and wheeze for participants living outside big cities, in Akershus and Hordaland (Table 3). An analysis of the cumulative incidence of LRTI (0-18 months of age) was equal to an RR= 1.04 (95% CI 0.93, 1.17).

There was no evidence of effect modification by the adjustment variables. Stratified analyses post hoc by maternal atopy status and birth season did not identify any important differences between the groups. No statistically significant interactions were detected between NO_2 exposure and maternal atopy, sex of child, area, birth season, or parity. Sensitivity analyses resulted in no substantial changes

compared to the reported results. Excluding from the adjustment set the area variable, as a factor potentially reflecting spatial distribution of air pollution, did not considerably change the results. Restricting the analyses to pregnancies during the last period of the MoBa recruitment (2006-2008) did not result in substantial changes to the reported results.

Discussion

In this study, we found no statistically significant associations for pregnancy NO_2 exposure to traffic-related air pollution exposure at residential address at birth and LRTI or wheeze in early childhood.

A previously study by Esplugues and colleagues has reported similar results of no association between LUR-modelled prenatal NO_2 exposure (with higher than in our study whole pregnancy mean NO_2 values of 39.1$\mu g/m^3$) with LRTI or persistent cough during the 1st year of life, but they did report an association between postnatal NO_2 exposure and persistent cough.[18] In the large international ESCAPE study, uniting cohorts from Germany, Sweden, Netherlands, and the UK, decrease in lung function parameters has been associated with exposure to LUR-modelled annual average NO_2, NO_x, $PM_{2.5}$ absorbance, and $PM_{2.5}$ at current address at 6 - 8 years of age, but not at birth address.[27]

We found some indication of different patterns for associations between prenatal air pollution exposure and early respiratory health in study participants living in cities versus counties outside cities. Associations between prenatal air pollution exposure and the respiratory outcomes was overall greater in the non-urban areas, although the estimates were not statistically significant. This might be due to a higher misclassification of exposure in cities because of higher mobility (change of residential address), or due to other types of pollutants in non-urban areas.[28] A study by Canfield and colleagues (2006) reported higher mobility for nullparious women as compared to women with several children. They explained this as related to the need for larger homes due to expecting a child (first born) and a need to live closer to health care facilities.[29] A previous study from Norway reported that half of the mothers work during pregnancy and that no difference was found when comparing using only home address to a weighted exposure of home and work address exposure.[30] On the other hand, non-city population might have more homogenous exposure and spending more time close to home. Difference

in distribution of socioeconomic factors or parity might play a role: families with several children tend to move out of large cities in Norway. Familiar predisposition to allergic disorders may be an important factor in modifying the effect of tobacco smoke exposure on wheezing.[31] Certain months of birth, due to their correlation with viral infections seasons, can be a risk factor for wheezing and LRTI.[3 32] Our study found no differences in the effect from groups divided by maternal atopy status or birth season.

Our study applied standardized individual exposure assessment for the large study population, and detailed information on potential confounders was collected from prenatal questionnaires. Estimates for prenatal exposure to NO_2 were based on LUR models and temporal back-extrapolation of exposure during entire pregnancy at the address at birth. The NO_2 exposure was collected during 2010 and 2011, and the GIS-variables used in the modelling were collected in 2013. The modelled exposures at each address were back-extrapolated using fixed 24-hour monitoring data from each area in the period 1999-2009. Such estimates might be a subject to non-differential misclassification of exposure due to changes in GIS-variables, or differences in the participant's mobility and lifestyle factors. However, results of the sensitivity analyses only in women who did not change address during pregnancy were similar to the overall analyses. Likewise, restricting the analyses to pregnancies during the last period, closer in time to the collected exposure variables and GIS-variables, did not result in different associations than the overall analyses.

In epidemiological studies investigating air pollution effects, precision of exposure estimation is an important challenge. It is usually not feasible to sample personal air pollution exposure in large birth cohorts, mainly due to the amount of participants needed and due to the fact of not having information about the pregnancy before week 17. It has therefore become increasingly common to apply modelling of air pollution exposure at individual residential addresses, such as dispersion models and LUR models. High correlations have previously been reported between indoor and outdoor concentrations of NO_2,[33] and NO_2 is also reported to display higher spatial variation as compared to other pollutants,[34] thus making it a better proxy for individual air pollution exposure.

The mean air pollution exposure levels explored in this study may be relatively low for detecting the association between prenatal exposure and postnatal respiratory health, and the reported

effect estimates might be biased towards null due to non-differential misclassification of exposure. It could also be difficult to disentangle prenatal and early postnatal exposure to air pollution if family continues to live at the same address at these two periods. Prenatal exposures need to be carefully studied for identifying potential critical windows of exposure. In our data, exposures by trimester were highly correlated with whole pregnancy exposure, and therefore we only assessed the exposure during entire pregnancy. More studies are needed for exploring the causative association between prenatal air pollution exposure and respiratory health early in childhood, for characterizing critical time windows and main pollutants that are involved in pathological changes. Of interest for future research is the sex difference in prenatal exposure effect identified in our study.

In this large Norwegian pregnancy cohort we found no statistically significant associations for moderate levels of exposure to NO_2 during pregnancy and childhood respiratory health measured by LRTI and wheeze.

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Contribution to authorship: PN, SJL, WN, PM were involved in conception, hypothesis delineation and study design. SJL, GA, SEH, CM contributed to the exposure assessment. CM and PN drafted the manuscript. All authors were involved in data interpretation and approved the final submitted version of the manuscript.

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Program of the NIH, National Institute of Environmental Health Sciences (project number Z01 ES49019).

Details of ethics approval: The Norwegian Mother and Child Cohort Study has approvals from the Regional Ethics Committee and the Norwegian Data Inspectorate. The current study is based on version VI of the quality-assured data files released for research on the 15th April 2011.

Data sharing statement: Technical description of the MoBa data can be found at the study website (https://www.fhi.no/en/studies/moba/). Researchers can apply for access to the dataset (https://www.fhi.no/en/more/research--access-to-data/). Statistical code is available upon request from the corresponding author.

Competing interests: none declared.

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Table 1. Descriptive statistics for study participants from the MOBA cohort.

	Baseline cohort at birth with NO_2 data (N=17 533)	**Questionnaire at 6 months (N=14 386)**	**Questionnaire at 18 months (N=12 231)**
Oslo	4 669 (26.6)	3 801 (26.4)	3 320 (27.1)
Akershus	7 554 (43.1)	6 284 (43.7)	5 350 (43.7)
Bergen	3 869 (22.1)	3 135 (21.8)	2 591 (21.2)
Hordaland	1 441 (8.2)	1 166 (8.1)	970 (7.9)
LRTI0- 6 months		653 (4.5)	
Missing		500 (3.5)	
LRTI 6- 18 months			1 469 (12.0)
Missing			230 (1.9)
Wheeze 6- 18 months			4 961 (40.6)
Missing			255 (2.1)
Women who changed address during pregnancy	2 336 (13.3)	1 782 (12.4)	1 471 (12.0)
Parity			
0	8 310 (47.4)	6 973 (48.5)	6 003 (49.1)
1	6 328 (36.1)	5 138 (35.7)	4 310 (35.2)
≥2	2 895 (16.5)	2 275 (15.8)	1 918 (15.7)
Sex of child			
Boy	8 925 (50.9)	7 285 (50.6)	6 177 (50.5)
Girl	8 608 (49.1)	7 101 (49.4)	6 054 (49.5)
Maternal age at delivery, years	31.0 ± 4.5	31.1 ± 4.4	31.2 ± 4.3
Marital status			
Married/cohabiting	16 780 (95.7)	13 839 (96.2)	11 797 (96.5)
Other	753 (4.3)	547 (3.8)	434 (3.6)
Maternal education			
Less than high school	986 (5.6)	713 (5.0)	547 (4.5)
High school	4 175 (23.8)	3 465 (24.1)	2 845 (23.3)
Up to 4 years of college	6 480 (37.0)	5 677 (39.5)	4 919 (40.2)
More than 4 years of college (master or professional degree)	4 867 (27.8)	4 254 (29.6)	3 731 (30.5)
Missing	1 025 (5.9)	277 (1.9)	189 (1.6)
Maternal smoking during pregnancy	1 085 (6.2)	843 (5.9)	675 (5.5)
Missing	1 000 (5.7)	263 (1.8)	185 (1.5)
Maternal pre-pregnancy body mass index[a]	23.5 ± 3.8	23.5 ± 3.7	23.5 ± 3.7
Maternal atopy	5 802 (33.1)	4 947 (34.4)	4 276 (35.0)
Season of birth			
Winter	4 099 (23.4)	3 352 (23.3)	2 858 (23.4)
Spring	4 686 (26.7)	3 851 (26.8)	3 191 (26.1)
Summer	4 630 (26.4)	3 827 (26.6)	3 312 (27.1)
Autumn	4 118 (23.5)	3 356 (23.3)	2 870 (23.5)

Numbers are n (%) or mean ± standard deviation.
LRTI – lower respiratory tract infections.
[a]Missing data for maternal pre-pregnancy body mass index (BMI): baseline cohort 1 549 (8.8%), at 6 months 693 (4.8%), at 18 months 522 (4.3%).

Table 2. LUR modelled air pollution exposure using residential address at time of birth. Exposure during the whole pregnancy and by trimester.

	Oslo	Akershus	Bergen	Hordaland	Total
	N=4 669	**N=7 554**	**N=3 869**	**N=1 441**	**N=17 533**
Mean LUR modelled NO_2 exposure ($\mu g/m^3$)					
Whole pregnancy	21.6 ± 4.4	10.3 ± 3.8	13.2 ± 6.2	6.3 ± 4.3	13.6 ± 6.9
Trimester 1	21.7 ± 6.1	10.2 ± 4.2	13.4 ± 6.4	6.5 ± 4.4	13.7 ± 7.4
Trimester 2	22.0 ± 6.1	10.4 ± 4.3	13.3 ± 6.5	6.3 ± 4.3	13.8 ± 7.5
Trimester 3	21.5 ± 6.1	10.3 ± 4.2	13.1 ± 6.3	6.3 ± 4.3	13.6 ± 7.3

Numbers are mean ± standard deviation
LUR – land use regression
European Union air quality standard for NO_2: 1-year average 40 $\mu g/m^3$

Table 3. Associations between pregnancy exposure to NO_2 and respiratory health of children by age 6 and 18 months.

	Crude			Adjusted		
	N total	N cases	RR (95% CI)	N total	N cases	RR (95% CI)
Main analysis[a]						
LRTI 0-6 months	13 886	653	0.84 (0.76 to 0.95)	13 116	616	0.99 (0.84 to 1.17)
LRTI 6-18 months	12 001	1 469	0.94 (0.94 to 1.01)	11 412	1 388	1.05 (0.94 to 1.16)
Wheeze 6-18 months	11 976	4 961	1.00 (0.97 to 1.03)	11 387	4 712	1.02 (0.97 to 1.07)
Stratified analysis[b]						
Oslo						
LRTI 0-6 months	3 695	136	0.72 (0.51 to 1.02)	3 530	128	0.76 (0.54 to 1.06)
LRTI 6-18 months	3 246	351	0.85 (0.69 to 1.06)	3 111	331	0.89 (0.71 to 1.12)
Wheeze 6-18 months	3 248	1 315	1.05 (0.96 to 1.16)	3 111	1 253	1.04 (0.95 to 1.15)
Akershus						
LRTI 0-6 months	6 014	281	1.22 (0.90 to 1.65)	5 619	263	1.32 (0.97 to 1.80)
LRTI 6-18 months	5 237	689	1.15 (0.96 to 1.38)	4 939	649	1.15 (0.95 to 1.39)
Wheeze 6-18 months	5 228	2 192	1.01 (0.93 to 1.10)	4 930	2 066	1.12 (0.94 to 1.34)
Bergen						
LRTI 0-6 months	3 045	169	0.90 (0.71 to 1.16)	2 899	161	0.96 (0.74 to 1.25)
LRTI 6-18 months	2 560	318	1.00 (0.85 to 1.18)	2 449	301	1.04 (0.86 to 1.22)
Wheeze 6-18 months	2 548	1 073	1.00 (0.93 to 1.07)	2 438	1 030	1.00 (0.89 to 1.07)
Hordaland						
LRTI 0-6 months	1 132	67	0.84 (0.49 to 1.46)	1 068	64	0.93 (0.50 to 1.63)
LRTI 6-18 months	958	111	1.31 (0.89 to 1.93)	913	107	1.36 (0.88 to 2.03)
Wheeze 6-18 months	952	381	1.19 (1.00 to 1.42)	908	363	1.12 (0.94 to 1.34)

Effect estimates per $10\mu g/m^3$ NO_2
LRTI – lower respiratory tract infections
[a]Adjusted for maternal age at delivery, years of birth, maternal marital status, maternal education, sex of child, maternal prepregnancy BMI, smoking during pregnancy, parity, maternal atopy and study area.
[b]Adjusted for maternal age at delivery, year of birth, maternal marital status, maternal education, sex of child, maternal prepregnancy BMI, smoking during pregnancy, parity, maternal atopy.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract – page 1.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found – page 2.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported – page 4.
Objectives	3	State specific objectives, including any prespecified hypotheses – page 5.
Methods		
Study design	4	Present key elements of study design early in the paper – page 5.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection – page 5.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up – page 5.
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed – N.A.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable – page 6 and 7.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group – page 6 and 7.
Bias	9	Describe any efforts to address potential sources of bias – N.A.
Study size	10	Explain how the study size was arrived at – page 5.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why – page 6.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding – page 8.
		(*b*) Describe any methods used to examine subgroups and interactions – page 8.
		(*c*) Explain how missing data were addressed – page 7.
		(*d*) If applicable, explain how loss to follow-up was addressed – N.A.
		(*e*) Describe any sensitivity analyses – page 8.
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed – page 5 and Table 1.
		(b) Give reasons for non-participation at each stage – page 5.
		(c) Consider use of a flow diagram – N.A.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders – page 8 and 9.
		(b) Indicate number of participants with missing data for each variable of interest – page 5.
		(c) Summarise follow-up time (eg, average and total amount) – page 5.
Outcome data	15*	Report numbers of outcome events or summary measures over time – page 8 and Table 1.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and

		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included – pages 8-9, Figure 1 and Tables 2-3.
		(*b*) Report category boundaries when continuous variables were categorized – page 8 and 9.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period – N.A.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses – page 9.
Discussion		
Key results	18	Summarise key results with reference to study objectives – page 9.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias – page 11.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence – page 11.
Generalisability	21	Discuss the generalisability (external validity) of the study results – page 10-11.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based – page 12.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.