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Preeclampsia and hypertension during pregnancy in areas with relatively low levels of traffic air pollution

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Abstract

Objectives—Air pollution exposure may contribute to the development of preeclampsia and hypertension during pregnancy. However, the evidence for such a relation is still limited. We investigated the associations between exposure for moderate to low levels of air pollution during pregnancy and preeclampsia and gestational hypertension in selected urban and county areas of Norway.

Methods—This study used a sub-group of 17533 women 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 preeclampsia and gestational hypertension were obtained from the Medical Birth Registry of Norway and information on lifestyle factors was collected from questionnaires completed by the women during pregnancy.

Results—Moderate mean levels of NO₂ ($13.6 \pm 6.9 \mu\text{g}/\text{m}^3$) at residential address during pregnancy were not associated with preeclampsia and pregnancy hypertension. We found no

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Compliance with Ethical Standards

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.

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statistically significant associations per 10 $\mu\text{g}/\text{m}^3$ change in NO_2 exposure and preeclampsia (adjusted OR 0.89, 95% CI 0.74, 1.08) or hypertension during pregnancy (adjusted OR 0.91, 95% CI 0.78, 1.06).

Conclusions for Practice—In this large Norwegian pregnancy cohort, we found no statistically significant associations for moderate to low levels of pregnancy NO_2 exposure and preeclampsia or hypertension during pregnancy.

Keywords

Air pollution; NO_2 ; preeclampsia; pregnancy hypertension; The Norwegian Mother and Child Cohort Study

Introduction

Preeclampsia is a serious pregnancy complication associated with morbidity and mortality in both mothers and newborns, affecting around 2-8% of pregnancies.^{1,2} The causes of this multisystem disorder are largely unknown. Pathological changes during preeclampsia involve disturbed implantation process, placental oxidative stress, increased endothelial activation, and excessive systemic inflammatory response on a later stage of the disease.¹ Exposure to air pollution is associated with low-grade systemic inflammation and oxidative stress,³ which might interact with the vascular remodeling and systemic functional changes during pregnancy. A number of epidemiological studies have shown an association of pregnancy exposure to air pollution and preeclampsia and hypertensive disorders of pregnancy.⁴⁻⁹ Recent reviews indicate that the number of studies is still relatively low, and more research is needed to address the effect of exposure at different gestational periods, the significance of exposure for different clinical manifestations, the role of individual source-specific pollutants and their composition, and applying more individualized exposure assessment methods is preferable.^{10,11} The reported odds ratios for associations of pregnancy exposure to air pollution and these outcomes have been relatively low^{10,11}, with an overall OR of 1.20 for NO_2 , 95% CI 1.00, 1.44 (N=16).¹⁰ Given the omnipresence of air pollution exposure, the effect on public health may be considerable.

In this study, we investigated the associations between estimated exposure to traffic-related air pollution during pregnancy and pregnancy preeclampsia and hypertension in selected urban and county areas of Norway. To our knowledge, this is the first Norwegian study of association of modelled air pollution exposure with preeclampsia and hypertension during pregnancy. Norway is characterized by relatively low levels of air pollution, and therefore provides a setting for analyzing whether such levels might contribute to the development of hypertensive disorders of pregnancy.

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.¹² Participants were recruited during week 17 of the pregnancy from all over Norway from

1999 to 2008. Among invited women, 41% consented to participate. Women could participate with more than one child, resulting in 114500 children and 95200 women included in the cohort.

All participants living in the study areas (Oslo, Akershus, Bergen and Hordaland) were eligible for our study (N=22149, 23.3%). We excluded women with missing exposure information at residential address (N=3876), 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 studied areas with non-missing air pollution exposure data was 17533 (79%), of which 4669 from Oslo, 7554 from Akershus, 3869 from Bergen and 1441 from Hordaland outside Bergen (Table 1). Birth records were obtained from the Medical Birth Registry of Norway (MBRN).

Women participating in the MoBa study completed a number of questionnaires during follow-up. We used data on lifestyle characteristics from questionnaire 1 filled at recruitment (approximately at week 17–18 of pregnancy) and questionnaire 3 filled at week 30 of pregnancy. The women, included in this study, gave birth during the period from 2001 to 2009.

MoBa 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.

Outcomes and covariates

The outcomes, preeclampsia and hypertension during pregnancy, were defined based on the data from the MBRN records. In Norway, information from antenatal examinations and pregnancy outcomes are transferred by midwife or obstetrician into the standardized MBRN form.^{13–15} Preeclampsia was considered present if one of the following was indicated in the MBRN form: “preeclampsia” (N=574, consisting of “preeclampsia light”, “preeclampsia serious”, and “preeclampsia unspecified”), “eclampsia” (N=12), and “HELLP syndrome” (N=19). Generally, preeclampsia was defined as persistent increase in systolic blood pressure to at least 140 mmHg and/or in diastolic blood pressure to at least 90 mmHg occurring after the 20th week of gestation, combined with proteinuria (protein excretion, at least 0.3 g per 24 h or total protein/creatinine ratio >0.3). Eclampsia was defined as convulsions occurring during pregnancy, childbirth or during the first seven days after birth, with a previously diagnosed preeclampsia or gestational hypertension, without other neurological causes of convulsions. HELLP syndrome was defined as a syndrome of Hemolysis, Elevated Liver enzymes and Low Platelets. Separate MBRN outcome indicated hypertension during pregnancy (N=941). Hypertension during pregnancy was defined as persistent increase in systolic blood pressure to at least 140 mmHg and/or in diastolic blood pressure to at least 90 mmHg occurring after the 20th week of gestation.

Adjustment variables (Table 1) were selected based on literature analyses and included diabetes mellitus, chronic hypertension, maternal age at delivery, maternal marital status, maternal education, sex of child, maternal pre-pregnancy BMI, parity, year of birth, smoking during pregnancy, and area. The following adjustment variables were extracted from the

MBRN form: diabetes mellitus (including pregestational diabetes type1, pregestational diabetes type 2, unspecified pregestational diabetes, gestational diabetes, antidiabetic medication during pregnancy registered without further information), chronic hypertension (defined as known hypertension before pregnancy or persistent increase in systolic blood pressure to at least 140 mmHg and/or in diastolic blood pressure to at least 90 mmHg occurring before 20 weeks of gestation), parity defined as number of previous deliveries (0; 1; 2), the women's age when giving birth (years), marital status (married/cohabit; other), sex of the child (boy; girl), year of birth. In addition, we used MoBa questionnaire information to determine the following adjustment variables: 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 (cm) were used to calculate body mass index (BMI) (maternal weight divided by squared maternal height). The overweight category was defined as BMI ≥ 25 .

Air pollution exposure

Sampling of air pollution was not part of the MoBa campaign, and is therefore done retrospectively. There were few available routine monitoring stations in the study areas during the observation period, and those available were situated near trafficked roads and often in a distance from populated areas. We therefore choose to use modelled air pollution exposures using non-concurrent measurements of air pollution combined with concurrent temporal variability from available monitoring stations in each study area. Estimates of air pollution exposure during pregnancy were based on the methodology developed for the European Study of Cohorts for Air Pollution Effects (ESCAPE) project.^{16,17} Land use regression (LUR) models for NO₂ levels were built for the studied areas in order to account for regional specific variation.¹⁸ We measured the spatial distribution of air pollution for Oslo and Akershus in 2010, and in Bergen and Hordaland in 2011. Measurement campaigns included three rounds of approximately two weeks duration with NO₂ measurements (during winter, summer and an intermediate season) within a one year period. The measurements were sampled using Ogawa passive diffusion badges. 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 only sites with no missing data, and with no geocoding mismatches. The models provided adjusted R^2 in the range 55 to 85%.¹⁸

LUR models were built separately for each area, three models in total (one model was built for the West Coast areas, Bergen and Hordaland, due to a low number of valid measurement sites for the latter). Predictors for building the LUR model were obtained from a GIS analysis of the N50 and VBASE maps (obtained 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 for the ESCAPE project.¹⁶

We also included an analysis of distance from residential address at birth and road proximity. This was done as a comparison for the LUR model. For the road proximity

analysis we included all categories of roads except walking and bicycling paths. The distance to the nearest road was calculated using the edge of the road for minor or major roads.

Yearly means of air pollution levels at residential address at birth were estimated using the resulting LUR models. Variables included in the 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 exposure and at the same time reflect low exposure at residential home addresses (N=112). The NO₂ exposure at these addresses are most likely in the lower end of the scale.¹⁸ 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.¹⁷ Daily NO₂ measurements from routine monitoring stations 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 NO₂ routine monitoring station measurement and an annual average for the year when the LUR measurement campaign took place. Daily NO₂ 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 NO₂ exposure and the outcomes (preeclampsia and hypertension during pregnancy). Results are presented for both crude and adjusted models as OR. Road proximity was not included in the models using NO₂ exposure. Multiplicative interactions were tested in the adjusted models between continuous air pollution exposure from NO₂ during pregnancy and the following categorical variables: maternal diabetes and chronic hypertension, smoking during pregnancy, parity, season of birth, sex and area.

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 (2005-2008) of the MoBa recruitment, and c) excluding the area of Hordaland from the models. The latter due to how this area differed from the other areas with high prevalence of preeclampsia and pregnancy hypertension, and low prevalence on several risk factors.¹⁸ Area variable may reflect the spatial distribution of air pollution, and therefore we performed a separate post hoc analysis by excluding the area variable from the adjusted model. In addition, we performed a post hoc analysis excluding all chronic hypertension cases from the adjusted model, since different etiological mechanisms may be involved for these women.

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 with included in this study (with pregnancy air pollution exposure) had similar characteristics as the whole MoBa cohort study. Preeclampsia was reported in 3.4% of the women, ranging from 2.9% in Akershus to 5.0% in Hordaland (Table 1). Hypertension during pregnancy was reported in 5.4 % of women.

The majority (86.7%) of the women did not change address during pregnancy. Parity 2 was more common in Hordaland (26%), and less common in Oslo (9.1%). Maternal smoking during pregnancy was relatively uncommon (6.2%). Diabetes was reported in 1.6% of the women (Table 1) and 27.6% were overweight (BMI>25).

The levels of modeled NO₂ exposure during pregnancy for the study population ranged from 0.01 to 60.5 µg/m³ (0.01 to 48.4 ppb), with a mean of 13.6 ± 6.9 µg/m³ (10.9 ± 5.5 ppb). A total of 27 women had NO₂ exposure above 40 µg/m³ their residential address at time of giving birth. NO₂ exposure during entire pregnancy was highest in Oslo (21.6 ± 4.4 µg/m³ (17.3 ± 3.5 ppb)) and lowest in Hordaland (6.3 ± 4.3 µg/m³ (5.0 ± 3.4 ppb)). Exposures by trimester and the whole pregnancy exposure were highly correlated and therefore we decided to use one exposure estimate: the average NO₂ exposure during the whole pregnancy. Having a nearest road within 15 meters to the house was common and reported in 46.6% of the studied population. A total of 99.8% of the women lived within 100 meters from a road. We therefore choose to categorize into less than 15 meters (exposed) and equal or above 15 meters (unexposed). It should be noted that this metric is different from those used by other authors, where the distances range up to several 100 meters.¹⁰

We found no associations of NO₂ exposure during pregnancy with preeclampsia or gestational hypertension in the overall analyses (Table 2). Residential road proximity closer than 15 meters had a statistically significant association with increased odds ratio for gestational hypertension in crude analysis of 1.23 (95% CI 1.08, 1.40), but not in the adjusted model. In the stratified analysis by area, we observed no statistically significant associations for either pregnancy NO₂ exposure or road proximity. However, the point estimates for comparing road proximity higher than 15 meters to those lower than 15 meters, was above 1.0 with the lower limit of the 95 % confidence intervals in the adjusted model for road proximity barely covering 1.0 for both outcomes (Table 2). We also noted that the point estimates for association between pregnancy NO₂ and preeclampsia were highest for Oslo (Table 3), although not statistically significant (adjusted OR 1.27, 95% CI 0.83, 1.95). The point estimate for road proximity below 15 meters and preeclampsia in Oslo was also highest in this area (adjusted OR 1.36, 95% CI 0.93, 1.98). We also found that the highest point estimate in Oslo for gestational hypertension and pregnancy NO₂ exposure (adjusted OR 1.18, 95% CI 0.87, 1.60) (Table 3).

We did not find any evidence of effect modification by the adjustment variables. When the area variable was excluded from the adjusted models the post hoc analysis, the association of road proximity with gestational hypertension became statistically significant (adjusted OR 1.16, 95% CI 1.01, 1.34). Results of the post hoc analysis without chronic hypertension

cases did not change substantially. Sensitivity analyses resulted in no substantial changes compared to the reported results.

Comments

In this study, we found no statistically significant associations for pregnancy NO₂ exposure to traffic-related air pollution exposure at residential address at birth and preeclampsia or hypertension during pregnancy. In Oslo, where pregnancy NO₂ exposure was highest, risk of developing preeclampsia was above 1.0 compared to other areas, but not statistically significant. Likewise, the risk was increased (but not statistically significant) for women living at residences with close proximity to trafficked roads at birth.

A number of studies have investigated the association of NO₂ and NO_x with preeclampsia and gestational hypertension. Associations were reported in the studies of Malmqvist *et al.* (NO_x and preeclampsia in Sweden),⁵ Pereira *et al.* (NO₂ and preeclampsia in Australia),⁸ Wu *et al.* (NO_x and preeclampsia in USA),¹⁹ Xu *et al.* (NO₂ and hypertensive disorders of pregnancy in USA),⁹ and Pedersen *et al.* (NO₂ and road traffic noise for both preeclampsia and hypertensive disorders of pregnancy in Denmark).²⁰ However, other studies did not find such association: Olsson *et al.* (NO₂ and preeclampsia in Sweden),⁶ van den Hooven *et al.* (NO₂ for both preeclampsia and gestational hypertension in the Netherlands).⁴

In our four study areas, the mean NO₂ exposure during pregnancy was below the European Union air quality standard of 1-year average 40 µg/m³ NO₂ (Table 1). The low exposure in our study area could potentially explain finding no significant association of NO₂ exposure during pregnancy with preeclampsia and hypertension. Other air pollutants can have a more substantial contribution to the development of preeclampsia, compared to NO₂ levels. For example, in a number of studies investigating a range of air pollutants, associations was shown for PM₁₀ and PM_{2.5}, and not for NO₂.^{4,7,21,22} Associations with hypertensive disorders of pregnancy were also reported for exposure to O₃, SO₂ and CO.^{6,9,21,23} In meta-analyses, PM_{2.5} have shown an overall stronger association with these outcomes (OR 1.57, 95% CI 1.26, 1.96) as compared to NO₂ (OR 1.20, 95% CI 1.00, 1.44).¹⁰

Distance to major roads and traffic density was investigated in some studies with inconclusive results: no association with gestational hypertensive disorders²⁴ or positive association with preeclampsia.²⁵ Proximity to roads may serve as a proxy for exposure to a mixture of air pollutants, including various fractions of particulate matter. On the other hand, road proximity and traffic density measures could be associated with socioeconomic conditions. More studies are needed to address this issue.

The validity of preeclampsia registration in MoBa has been previously defined as satisfactory, with the overall positive predictive values above 83%.¹³ Our study applied standardized individual exposure assessment for the large study population and detailed information on potential confounders was collected from birth records, in addition to questionnaires filled out during pregnancy (week 17/18 and 30). Estimates of traffic-related air pollution exposure was 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 changes in GIS-variables, differences in the participant's mobility or lifestyle factors. The exposures are also averages at home-address, thus ignoring diurnal variation in NO₂ measured by e.g. peak concentration values. However, results of the sensitivity analysis only in women who did not change address during pregnancy were similar to the overall analysis. Similarly, modelling exposure at residential address could be sensitive to changes due to available historic GIS-data. The results of the sensitivity analysis restricted to pregnancies during the last period of the MoBa recruitment were similar to the overall analysis. Road proximity provides a cruder estimate of traffic-related air pollution exposure and it might be more confounded by other factors in close proximity to the residences. Confounding from unmeasured factors, e.g. co-pollutants such as PM_{2.5} from different sources, could explain the change of association of road proximity with gestational hypertension from statistically significant in crude model to non-significant after adjustment.

To our knowledge, this is the first Norwegian study of the association of traffic-related NO₂ exposure and preeclampsia. In this relatively new branch of air pollution epidemiology more research is needed in order to determine the critical levels of exposure and pollutants of primary concern for developing preeclampsia. Very few studies addressed the temporal exposure parameter and identification of critical windows of exposure in preeclampsia development. In our data, exposures by trimester were highly correlated with whole pregnancy exposure, and therefore we only assessed the exposure during entire pregnancy. In further research, residential exposure to air pollution could be accompanied by data on travelling or occupational exposures, which will also add important information to the identification of the critical windows of exposure.

In this large Norwegian pregnancy cohort we found no statistically significant associations for moderate to low levels of pregnancy exposure to NO₂ and preeclampsia or hypertension during pregnancy.

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Significance

Preeclampsia is a pregnancy-induced hypertensive disorder and is a leading cause of maternal mortality and morbidity worldwide. It is associated with adverse pregnancy outcomes such as perinatal death, preterm birth and intrauterine growth retardation. Early-onset preeclampsia has been linked to abnormal placenta implantation, whereas late-onset preeclampsia may largely reflect maternal factors such as genetic predisposition, high body mass index, maternal diabetes, anemia, multiple pregnancies, and other conditions. Exposure to air pollution may contribute to the development of preeclampsia and hypertension during pregnancy, but the evidence for such a relation is still limited. In this paper, we investigated the associations between exposure for moderate to low levels of air pollution during pregnancy and preeclampsia and gestational hypertension in selected urban and county areas of Norway for more than 17, 000 pregnancies.

Table 1

Characteristics of the study population (MoBa cohort, Norway).

	Oslo N 4669	Akershus N 7554	Bergen N 3869	Hordaland N 1441	Total N 17533
Preeclampsia	144 (3.1)	217 (2.9)	157 (4.1)	72 (5.0)	590 (3.4)
Hypertension during pregnancy	294 (6.3)	323 (4.3)	220 (5.7)	104 (7.2)	941 (5.4)
Women who changed address during pregnancy	629 (13.5)	1023 (13.5)	513 (13.3)	171 (11.9)	2336 (13.3)
Maternal age, years	31.3 ± 4.1	31.4 ± 4.5	30.5 ± 4.6	29.5 ± 4.8	31.0 ± 4.5
Body Mass Index	23.0 ± 3.4	23.8 ± 3.9	23.5 ± 3.7	24.2 ± 4.1	23.5 ± 3.8
Parity					
0	2819 (60.4)	3032 (40.1)	1930 (49.9)	529 (36.7)	8310 (47.4)
1	1424 (30.5)	3052 (40.4)	1314 (34.0)	538 (37.3)	6328 (36.1)
2	426 (9.1)	1470 (19.5)	625 (16.2)	374 (26.0)	2895 (16.5)
Boys	2413 (51.7)	3808 (50.4)	1950 (50.4)	754 (52.3)	8925 (50.9)
Girls	2256 (48.3)	3746 (49.6)	1919 (49.6)	687 (47.7)	8608 (49.1)
Marital status					
Married/cohabit	4530 (97.0)	7335 (97.1)	3576 (92.4)	1339 (92.9)	16780 (95.7)
Other	139 (3.0)	219 (2.9)	293 (7.6)	102 (7.1)	753 (4.3)
Maternal education					
Less than high school	140 (3.2)	495 (7.0)	207 (5.7)	144 (10.7)	986 (6.0)
High school	804 (18.1)	2062 (29.1)	842 (23.3)	467 (34.5)	4175 (25.3)
Up to 4 years of college	1734 (39.1)	2768 (39.0)	1455 (40.2)	523 (38.7)	6480 (39.3)
More than 4 years of college (master or professional degree)	1762 (39.7)	1772 (25.0)	1115 (30.8)	218 (16.1)	4867 (29.5)
Maternal smoking during pregnancy					
Overweight	171 (3.8)	555 (7.8)	225 (6.2)	134 (9.9)	1085 (6.6)
Diabetes mellitus	965 (22.3)	2041 (29.9)	947 (27.0)	457 (35.1)	4410 (27.6)
Chronic hypertension	75 (1.6)	87 (1.2)	83 (2.2)	42 (2.9)	287 (1.6)
Season of birth	24 (0.5)	49 (0.7)	12 (0.3)	8 (0.6)	93 (0.5)
Winter	1042 (22.3)	1650 (21.8)	1015 (26.2)	392 (27.2)	4099 (23.4)
Spring	1224 (26.2)	2052 (27.2)	1020 (26.4)	390 (27.1)	4686 (26.7)
Summer	1292 (27.7)	2102 (27.8)	900 (23.3)	336 (23.3)	4630 (26.4)
Autumn	1111 (23.8)	1750 (23.2)	934 (24.1)	323 (22.4)	4118 (23.5)

	Oslo N 4669	Akershus N 7554	Bergen N 3869	Hordaland N 1441	Total N 17533
Mean NO ₂ whole pregnancy, µg/m ³	21.6 ± 4.4	10.3 ± 3.8	13.2 ± 6.2	6.3 ± 4.3	13.6 ± 6.9
Trimester 1, µg/m ³	21.7 ± 6.1	10.2 ± 4.2	13.4 ± 6.4	6.5 ± 4.4	13.7 ± 7.4
Trimester 2, µg/m ³	22.0 ± 6.1	10.4 ± 4.3	13.3 ± 6.5	6.3 ± 4.3	13.8 ± 7.5
Trimester 3, µg/m ³	21.5 ± 6.1	10.3 ± 4.2	13.1 ± 6.3	6.3 ± 4.3	13.6 ± 7.3
Distance to road <15 m	2971 (63.6)	2457 (32.5)	2153 (55.7)	583 (40.5)	8164 (46.6)

The numbers are *n* (%) or mean ± standard deviation.

European Union air quality standard for NO₂: 1-year average 40 µg/m³.

Table 2

Associations between pregnancy exposure to NO₂ and residential proximity to roads with preeclampsia and hypertension.

	Crude			Adjusted ^a		
	N total	N cases	OR (95% CI)	N total	N cases	OR (95% CI)
Preeclampsia						
NO ₂ overall analysis, per 10µg/m ³	17 533	590	0.92 (0.82, 1.04)	15 839	526	0.89 (0.74, 1.08)
NO ₂ women who did not move, per 10µg/m ³	15 197	506	0.93 (0.82, 1.06)	13 824	449	0.89 (0.73, 1.10)
Road within 15 m, overall analysis	17 533	590	1.18 (1.00, 1.39)	15 839	526	1.16 (0.96, 1.39)
Road within 15 m, women who did not move	15 197	506	1.21 (1.01, 1.44)	13 824	449	1.16 (0.96, 1.42)
Hypertension during pregnancy						
NO ₂ overall analysis, per 10µg/m ³	17 533	941	1.09 (0.99, 1.20)	15 839	841	0.91 (0.78, 1.06)
NO ₂ women who did not move, per 10µg/m ³	15 197	806	1.09 (0.99, 1.21)	13 824	722	0.92 (0.78, 1.09)
Road within 15 m, overall analysis	17 533	941	1.23 (1.08, 1.40)	15 839	841	1.12 (0.96, 1.29)
Road within 15 m, women who did not move	15 197	806	1.27 (1.10, 1.47)	13 824	722	1.15 (0.98, 1.34)

^a Adjusted for maternal age, BMI, diabetes, chronic hypertension, maternal education, maternal marital status, parity, smoking during pregnancy, birth season, area, year of birth.

Table 3

Stratified analysis by study area of the associations between pregnancy exposure to NO₂ with preeclampsia and hypertension.

	Crude			Adjusted ^a		
	N total	N cases	OR (95% CI)	N total	N cases	OR (95% CI)
Preeclampsia						
Oslo, per 10µg/m ³	4 669	144	1.25 (0.85, 1.85)	4 285	133	1.27 (0.83, 1.95)
Akershus, per 10µg/m ³	7 554	217	0.80 (0.55, 1.14)	6 766	195	0.77 (0.52, 1.14)
Bergen, per 10µg/m ³	3 869	157	1.03 (0.80, 1.33)	3 493	136	0.84 (0.63, 1.13)
Hordaland, per 10µg/m ³	1 441	72	0.62 (0.35, 1.10)	1 295	62	0.72 (0.39, 1.33)
Hypertension during pregnancy						
Oslo, per 10µg/m ³	4 669	294	1.19 (0.90, 1.56)	4 285	266	1.18 (0.87, 1.60)
Akershus, per 10µg/m ³	7 554	323	0.93 (0.69, 1.25)	6 766	293	0.86 (0.63, 1.19)
Bergen, per 10µg/m ³	3 869	220	0.94 (0.75, 1.17)	3 493	193	0.78 (0.60, 1.01)
Hordaland, per 10µg/m ³	1 441	104	0.73 (0.45, 1.18)	1 295	89	0.73 (0.43, 1.24)

^a Adjusted for maternal age, BMI, diabetes, chronic hypertension, maternal education, maternal marital status, parity, smoking during pregnancy, birth season, area, year of birth.