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Association between ambient air pollution a week prior to delivery and preterm birth using a nationwide study in Sweden

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ABSTRACT

Background: Air pollution exposure has been linked with increased risk of preterm birth, which is one of the leading causes of infant mortality. Limited studies have attempted to explore these associations in low-polluted areas. In this study, we aimed to assess the association between short-term exposure to ambient air pollution and preterm birth in Sweden.

Method: In this population-based study we included preterm births between 2014 and 2019 from the Swedish Pregnancy Register. We applied a spatiotemporal model to estimate daily levels of particulate matter <2.5 μm ($PM_{2.5}$), PM < 10 μm (PM_{10}), nitrogen dioxide (NO_2), and ozone (O_3) at the residential address of each participant. We applied a time-stratified case-crossover design with conditional logistic regression analysis to estimate odds ratios (OR) of preterm birth per 10 μg/m^3 (PM_{10}, NO_2, O_3) and 5 μg/m^3 ($PM_{2.5}$) increase in air pollution exposure at 0–6-day lag. Two-pollutant models were applied to evaluate the independent association of each exposure on preterm birth. We also stratified by maternal characteristics to identify potential effect modifiers.

Results: 28,216 (4.5%) preterm births were included. An increase in O_3 exposure was associated with increased odds of preterm birth [OR = 1.06 per 10 μg/m^3 (95% CI, 1.02; 1.10]. $PM_{2.5}$ and PM_{10} were not significantly associated with preterm birth, and NO_2 displayed a negative nonlinear association with preterm birth. We did not observe any notable effect modification, but we found suggestive larger associations between O_3 and preterm birth when stratifying by male sex, spontaneous delivery, and spring season.

Conclusions: Increased O_3 exposure one week before delivery was associated with an increased risk of preterm birth in Sweden, a country with levels of air pollution below the current World Health Organization air quality guidelines. Increases in O_3 levels with climate change make these findings especially concerning.

1. Introduction

Preterm birth, defined as born alive before 37 weeks of pregnancy, is a common pregnancy outcome accounting for up to 10% of all births globally (Ohuma et al., 2023). Despite significant improvements in recent decades, preterm birth remains the leading cause of under-5 child mortality (Cao et al., 2022). Infants born preterm, in particular the most immature, are at increased risk of acute and long-term poor outcomes

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and may require prolonged care and monitoring which comes at a high economic cost (Goldenberg et al., 2008; Platt, 2014). Despite improvements in the last decades in the quality of neonatal care, sequelae can be expected later in life. They include, for example, lower educational achievement, behavioral disorders, and increased risk of unemployment compared to children born to term (Crump et al., 2020, 2021; Ream and Lehwald, 2017), which account for a significant societal loss, in potential tax revenue and decreased cost of benefits (Moster et al., 2008). Despite identification of several risk factors for preterm birth, such as advanced maternal age, short interpregnancy interval, previous preterm birth, stress, low socioeconomic status and maternal comorbidities such as chronic hypertension, diabetes mellitus and previous cervical surgery for dysplasia, it has been estimated that the cause of preterm birth cannot be determined in 66% of the cases (Ferrero et al., 2016). In recent years, environmental factors such as ambient air pollution have been identified as important risk factors for preterm birth (Song et al., 2023).

Current research on the role of ambient air pollution on preterm birth is not fully conclusive, which may in part be due to methodological differences between studies and varying quality of the data (Yu et al., 2022). Existing studies have mainly focused on the effect of long-term exposure with only a handful of studies trying to assess the acute effect air pollution may have on triggering preterm birth (Guan et al., 2019; Ha et al., 2022; Lee et al., 2008; Li et al., 2018; Schifano et al., 2013, 2016; Siddika et al., 2020; Stieb et al., 2019). To our knowledge, there is only one study that has assessed the effect of acute exposure to low levels of ambient air pollution on preterm birth, undertaken in Finland (Siddika et al., 2020). They observed a positive association between exposure to particulate matter <2.5 μm ($PM_{2.5}$), particulate matter <10 μm (PM_{10}), nitrogen dioxides (NO_2) and preterm birth, but their findings are not generalizable because of a limited sample size (n = 2568) from a single city in Finland. Other studies exploring the short-term effects of ambient air pollutants were based on small study populations or specific cities or regions, limiting their study power (Yu et al., 2022). Nationwide birth registries provide a unique research opportunity because of their potential higher statistical power, accurate measurement of outcomes (e.g., gestational age), and information on individuals in both urban, peri-urban and rural areas (de Bont et al., 2022; Stephansson et al., 2018). Accounting for peri-urban and rural areas is important especially for the effect of tropospheric ozone (O_3) because it is a secondary highly reactive air pollutant that can travel far from where it was initially formed, and it peaks away from major urban areas (Eljarrat et al., 2020). Moreover, increasing global temperatures due to climate change increases levels of O_3, with potential major negative health consequences (Fann et al., 2021).

New research has shown that even low levels of air pollution exposure, below the World Health Organization (WHO) guidelines, are associated with an increased risk of adverse health outcomes in adults such as cardiovascular complications, by in part increasing oxidative stress and systemic inflammation, which could be implicated in the pathogenesis of preterm birth (Dahlquist et al., 2022; Hunter et al., 2023; Samuels et al., 2022; Wolf et al., 2021). More research is needed in low-pollution settings to improve knowledge of the dose-response relationship between air pollutants and maternal and neonatal health outcomes. In this study, we aimed to evaluate the associations between ambient air pollution a week before delivery and risk of preterm birth using a nationwide population-based registry in Sweden.

2. Materials and methods

2.1. Data source and study population

In this study, patient data sourced from the Swedish Pregnancy Register (SPR) were included. The SPR is a robust population-based health registry covering over 92% of all births in Sweden (Stephansson et al., 2018), collecting detailed health information from the medical records of pregnant women in Sweden throughout the pregnancy period, starting from the first antenatal care visit. The registry also contains data on maternal health factors such as comorbidities, smoking status, and sociodemographic factors among others (Ludvigsson et al., 2011). This cohort included all live singleton preterm births in the Pregnancy Register between 2014 and 2019. Exclusion criteria were defined as: the lack of a Swedish personal identification number, gestational age <22 or >44 completed weeks, lacking information regarding residential addresses and non-residential status in Sweden during the 1-year period preceding conception. To obtain maternal and neonatal health outcome data, we linked the SPR with the national patient register using the maternal Swedish personal identity number. The same number was used to link data from Statistic Sweden for socioeconomic and residential address information. Approval for the study was obtained from the regional Ethical Committee in Stockholm, Sweden (2020/00390).

2.2. Exposure assessment: air pollution

Daily levels of multiple air pollutants ($PM_{2.5}$, PM_{10}, NO_2, O_3) were obtained using a hybrid spatiotemporal model which combined data on daily air pollutant concentrations from routine monitoring networks, satellite-derived measurements, dispersion models, meteorological variables, and land-use parameters, to estimate daily air pollution concentrations at a 1×1 km^2 spatial resolution across Sweden. The model was evaluated through cross-validation procedures, by using 90% of all monitors for training, and then projecting the model on the remaining 10% of monitors for testing and checking the performance of the model fit on the excluded sites. The procedure was replicated 10 times by changing the sets of testing monitors each time. The model predictions had a cross validated R^2 and root means square of 69% and 3.1 μg/m^3 for $PM_{2.5}$, 64% and 7.2 μg/m^3 for PM_{10}, 74% and 8.3 μg/m^3 for NO_2, and 78% and 8 μg/m^3 for O_3 of the daily air pollutant variability in left-out monitors. There were no major differences in performance across years and season (Stafoggia et al., 2020). Modelled daily levels were used for exposure assessment assigned at the geocoded residential address of the pregnant mother.

2.3. Outcome assessment: preterm birth

Preterm birth, coded as a binary variable, was defined according to the WHO as a live birth occurring before 37 completed weeks of gestation (WHO, 2012). The SPR was used to obtain gestational age information using multiple sources in the following hierarchical order: a) the time of embryo transfer, b) ultrasonographic examinations, c) the onset of the last menstrual cycle, and d) postnatal clinical assessments and scoring. In Sweden, approximately 95% of pregnant women undergo ultrasonography in the early second trimester to determine gestational age. The classification of preterm births was refined into three different sub-categories: births occurring before 28 gestational weeks were named "extremely preterm", those births between 28th and 32nd gestational week were labeled as "very preterm", and births between 32nd and 37th gestational week were identified as "moderately preterm".

2.4. Covariates

Clinical variables were extracted from the SPR, including factors such as the sex of the infant, the method of delivery (either medically indicated, such as caesarean section or induced, or spontaneous), the season of birth, the geographic location within Sweden, the mother's age at the time of delivery, and the mother's level of education. The health status of the women was evaluated using a range of variables, including body mass index (BMI) at the first antenatal care visit, maternal smoking habits before and during pregnancy, and the presence of pre-pregnancy co-morbidities like chronic hypertension and diabetes. The urban or rural nature (urbanicity) of the women's residences was determined based on the definitions provided by the Swedish department of agriculture (The Swedish Agency for Growth Policy Analysis, 2014). Daily ambient temperature levels across Sweden were estimated at a spatial resolution of 1×1 km^2 using a similar spatiotemporal machine learning methodology as our air pollution exposure assessment. This methodology integrated data from monitoring stations, satellite land surface temperature, meteorological reanalysis data, and land-use predictors such as vegetation indexes, climate zones, and land cover features (de Bont et al., 2022).

2.5. Statistical analysis

We used a time-stratified case-crossover design to evaluate the impacts of ambient air pollution in the weeks prior to delivery on the risk of preterm birth. The case-crossover framework is a recognized design in epidemiological studies that is commonly employed to evaluate the impact of short-term exposures on health events with an abrupt onset (Maclure, 1991). The key strength of the design is its self-matching feature, in which each case serves as its own control. The control period was defined as the same days of the week, within the same month of childbirth. This approach ensures precise control over the day of the week and other short-term temporal trends, given that cases and controls are closely matched in time. This method efficiently accounts for individual-level confounders, both known and unknown, that remain constant or change minimally over time. These confounders include factors like age, genetic predispositions, smoking behaviors, and socio-economic status (Maclure, 1991). Furthermore, it is well suited to analyze short-term effects with exposure assigned at the individual level, in contrast with conventional time series designs. Our main exposure window of interest was the mean exposure level during the week prior to birth (lag 0–6 days) based on the current literature. This time frame is sufficient to observe both the exposure and outcome of interest, while minimizing the likelihood for exposure misclassification, and has been used in prior studies on air pollution and preterm birth (Arroyo et al., 2016; Sarizadeh et al., 2020; Stieb et al., 2019; Yu et al., 2022). We applied conditional multivariate logistic regression analysis to estimate odds ratios (ORs) and 95% confidence intervals (CI) of preterm birth per 10 $\mu g/m^3$ (PM_{10}, NO_2, and O_3) and per 5 $\mu g/m^3$ ($PM_{2.5}$) increase in exposure, with air pollutants modelled with linear terms. First, we applied single exposure models to evaluate the association between each pollutant ($PM_{2.5}$, PM_{10}, NO_2, O_3) on preterm birth. Second, we used two-pollutant models to evaluate the independent association of each exposure on preterm birth (e.g. the association of O_3 adjusted for NO_2). We did not run the two-pollutant model for $PM_{2.5}$ and PM_{10} as they were highly correlated ($r = 0.76$) and because one is included in the other. We chose to only assess the effect of O_3 during the spring and summer seasons due to its strong seasonal pattern, through the impact of ultraviolet radiation (Lippmann, 1989). Temperature was adjusted for by modelling it with a natural spline in all models, as it is a well-established confounder in short-term air pollution studies, with a non-linear exposure-response function (Orru et al., 2017). We further evaluated the dose-response curve of the association between air pollution and preterm birth through a natural spline with two inner knots. Results were shown on a linear scale. If nonlinearity was evident, in the two-pollutant model the nonlinear pollutant confounder was added in the model with a spline.

We conducted a sensitivity analysis to explore various lag patterns, including a single-day lag (lag 0), a 2-day lag (lag 0–1), and a 4-day lag (lag 0–3), in order to identify distinct windows of vulnerability. We also evaluated if the relationship between air pollution and preterm birth was influenced by certain effect modifiers such as season of birth, delivery type, infant sex, geographic area, urbanicity, maternal age, maternal education, BMI, and smoking status. We evaluated effect modification by stratified analysis and evaluating the p-value for interaction with the likelihood ratio test. In these analyses, we only included the preterm cases with complete data regarding maternal social and health factors. We excluded cases with missing data. Every analysis was performed using the R programming language, specifically version 4.2.1, developed by the R Development Core Team. We used the packages "dlnm" and "ggplot".

3. Results

We identified 620,866 singleton births, of which 560,723 had complete data on outcome and exposure. 28,216 (4.5%) preterm births were included in the study (Fig. S1). Among all preterm births, 6.7% were categorized as extremely preterm, 9.3% as very preterm, and 83.8% as moderately preterm. 78.0% of preterm births occurred spontaneously and 22.0% were medically indicated. Descriptives of the study population are shown in Table 1 and Table S1. $PM_{2.5}$ and PM_{10} were positively

Table 1
Characteristics of singleton preterm live births in Sweden, 2014–2019.

Characteristics	Preterm births n = 28,216
Infant Sex	
Male	15,224 (54.0%)
Female	12,961 (45.9%)
Missing	31 (0.1%)
Mode of delivery	
Medical indicated	6196 (22.0%)
Spontaneous	22,020 (78.0%)
Preterm category	
Extremely preterm	1917 (6.8%)
Very preterm	2636 (9.3%)
Moderately preterm	23,663 (83.9%)
Season of birth *	
Winter	6931 (24.6%)
Spring	7196 (25.5%)
Summer	7375 (26.1%)
Fall	6714 (23.8%)
Geographic area	
North	2779 (9.8%)
Central	10,552 (37.4%)
South	14,885 (52.8%)
Urbanicity	
Urban	20,823 (73.8%)
Rural	7393 (26.2%)
Maternal Age	
≤ 24	3796 (13.5%)
25–29	8671 (30.7%)
30–34	8895 (31.5%)
≥ 35	6849 (24.3%)
Missing	5 (<0.1%)
Maternal BMI*	
Underweight	820 (2.9%)
Normal	13,233 (46.9%)
Overweight	6747 (23.9%)
Obesity	4440 (15.7%)
Missing	2976 (10.5%)
Education Level	
1–9 years	2119 (7.5%)
10–12 years	9497 (33.7%)
+12 years	10,894 (38.6%)
Missing	5706 (20.3%)
Smoking during pregnancy	
Yes	1755 (6.2%)
No	22,267 (78.9%)
Missing	4194 (14.9%)
Chronic Hypertension	
Yes	368 (1.3%)
No	26,023 (92.2%)
Missing	1825 (6.5%)
Diabetes Mellitus	
Yes	987 (3.5%)
No	25,464 (90.2%)
Missing	1765 (6.3%)

Abbreviations: Winter, December–February; Spring; March–May; Summer, June–August; fall, September–November; Underweight, BMI <18.5 kg/m^2; Normal, BMI ≥18.5–<25.0 kg/m^2; Overweight, BMI ≥25.0–<30.0 kg/m^2; Obesity, BMI ≥30.0 kg/m^2.

correlated (r = 0.76), and both pollutants were weakly to moderately correlated with NO_2, (r [$PM_{2.5}$] = 0.28) and (r [PM_{10}] = 0.40) (Fig. S2). O_3 during the warm season was negatively correlated with NO_2 (r = −0.16), weakly correlated with PM_{10} (r = 0.25) and $PM_{2.5}$ (r = 0.12). Ambient temperature was not correlated with $PM_{2.5}$ (r = 0.01) or PM_{10} (r = 0.04) exposure and was negatively correlated with NO_2 (r = −0.24) and with O_3 (r = −0.11) (Fig. S2). The levels of the air pollutants were lower than the WHO recommended maximum level of daily exposure for $PM_{2.5}$ (7.4 μg/m^3 vs the recommended 15 μg/m^3/24-h mean), PM_{10} (15 μg/m^3 vs 45 μg/m^3/24-h mean), NO_2 (13.8 μg/m^3 vs 25 μg/m^3/24-h mean), and O_3 (54.5 μg/m^3/24-h mean vs 100 μg/m^3/8-h mean) (WHO, 2021) (Table S2). The pollutants showed some seasonal variation, with $PM_{2.5}$, PM_{10} and O_3 concentrations peaking during the spring season and NO_2 concentrations peaking during the winter season (Table S3). We observed similar air pollution levels during the case period and to the control periods (Table S4). We observed some variability between the control and case period as the correlation was moderately high (Pearson correlation between 0.67 and 0.95).

We observed that a 10 μg/m^3 increase in O_3 0–6 days before delivery was associated with 5.90% increased odds of preterm birth [OR = 1.06 (95% CI, 1.02; 1.10)]. We did not observe associations for $PM_{2.5}$ or PM_{10} exposures and preterm birth [OR ($PM_{2.5}$ per 5 μg/m^3) 1.02 (95% CI, 0.98; 1.06 and OR (PM_{10} per 10 μg/m^3) 0.98 (95% CI, 0.93; 1.023), respectively (Fig. 1). NO_2 was associated with a decreased odds for preterm birth [OR = 0.94 (95% CI, 0.88; 0.99)]. However, we also observed a strong nonlinear association for NO_2 exposure, as the shape of the relationship showed a positive association until 11 μg/m^3 levels of NO_2, but the association inverted with higher NO_2 with a negative association (Fig. S3). In the two-pollutant model, we observed similar effect estimates for each pollutant when adjusting for other pollutants (Fig. 1).

We observed the strongest associations using the week before pregnancy (lag 0–6 days) for ozone and NO_2. For $PM_{2.5}$ and PM_{10} the estimates remained similar when evaluating different lag patterns (Fig. S4). We further did not observe any notable effect modification regarding environmental and maternal health factors on preterm birth (Table S5). For ozone, only maternal education had a p-value for interaction <0.05, finding slightly higher estimates for women with higher levels of education. In addition, we found slightly larger effect estimates (p-value interaction >0.05) for O_3 when stratifying by male sex, spontaneous

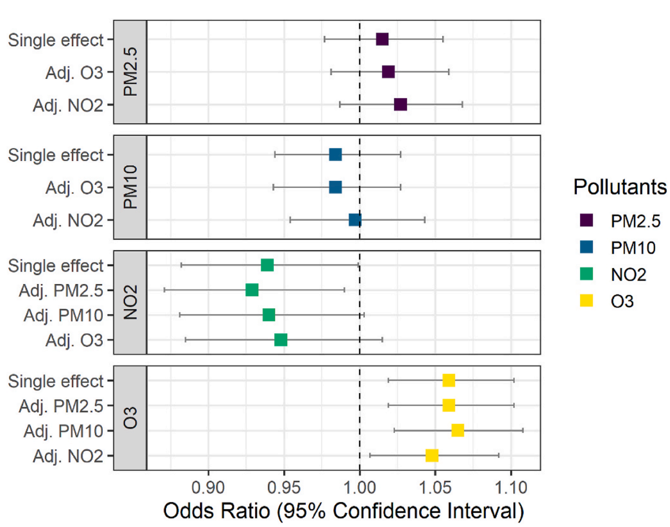

Fig. 1. Association between the exposure to ambient air pollution the week before delivery and preterm birth in the two-exposure models. (OR are shown per 5 μg/m^3 for $PM_{2.5}$ and per 10 μg/m^3 for PM_{10}, NO_2, O_3) Abbreviations: $PM_{2.5}$, Particulate Matter with aerodynamic diameter ≤2.5 μm; PM_{10}, Particulate Matter with aerodynamic diameter ≤10 μm, NO_2, Nitrogen dioxide; O_3, Ozone; Temp, Temperature.

delivery, and spring season (Fig. 2 and Table S5). No effect modification was observed for the other pollutants (Table S4). When stratifying by sub-categories of preterm birth, both O_3 and NO_2 showed larger effect estimates for moderate preterm births (Table S6).

4. Discussion

To our knowledge, this is the first nationwide case-crossover study on the association between exposure to low levels of ambient air pollution ($PM_{2.5}$, PM_{10}, NO_2, O_3) the week before delivery and the risk of preterm birth. Our results suggest that O_3 exposure the week prior to delivery (lag 0–6) was associated with an increased risk for preterm birth, based on a nationwide sample of singleton live births in Sweden between 2014 and 2019. We found no associations between $PM_{2.5}$ or PM_{10} and preterm birth. We observed a nonlinear association between NO_2 exposure and preterm birth, and larger effect estimates between O_3 and preterm birth during the spring season, among male infants, and spontaneous deliveries.

Our results differ, in part, from previous studies on the risks of short-term exposure to ambient air pollution on preterm birth. A similar case-crossover study conducted in 8 counties in the San Joaquin Valley of California, United States (US), (n = 196,970) found a positive association between increased O_3 exposure the week prior to delivery and preterm birth during the warm season (May–October) with similar effect estimates as our study OR (per 41.12 μg/m^3) 1.09 (95% CI, 1.06, 1.11) (Ha et al., 2022). This is despite the Californian study having significantly higher levels of O_3 compared to our study (mean 116.3 μg/m^3 vs mean 54.5 μg/m^3). Our results therefore suggest that the association between O_3 on preterm birth can be seen even at low levels of exposure. Other studies have similarly found an association between short-term O_3 exposure and preterm birth across Canada, Rome (Italy) and Barcelona (Spain), using time-to-event models. Similar to our study, no statistically significant associations were found between $PM_{2.5}$ and NO_2 exposures and preterm birth except for Barcelona where PM_{10} and NO_2 showed a statistically significant association for preterm birth (Schifano et al., 2016; Stieb et al., 2019). In contrast, older time-series studies conducted in Rome (2013), Ningbo (China) (2018), and London (England) (2008) found no significant association between short-term O_3 exposure and preterm birth. However, the Ningbo study found an association between $PM_{2.5}$, PM_{10}, NO_2 exposure and preterm birth (Lee et al., 2008; Liu et al., 2018; Schifano et al., 2013). Lastly, a study in Espoo (Finland) (n = 2568) found no association between O_3 exposure and preterm birth, but did find an association with $PM_{2.5}$, PM_{10}, and NO_2 (Siddika et al., 2020).

All the aforementioned studies, except for the Espoo study, relied on fixed monitoring stations to estimate daily air pollution levels, thereby relying fully on temporal contrasts in exposure, and did not model individual air pollution exposures levels among the study population. The differences in results between the studies could be due to methodological differences. To our knowledge, our study is one of only two that applied a case-crossover study design and individual spatio-temporal modelling to evaluate the association of both temporal and spatial short-term exposure to ambient air pollution on preterm birth. This allows for effective control of time-invariant confounders among the study population, while the previously mentioned studies could have been subject to residual confounding in their analysis. Previous studies were also limited to specific cities or regions compared to our nationwide cohort, which increases the generalizability of results. Furthermore, as O_3 can travel with air masses, away from where it was initially formed, previous studies may have underestimated the public health implications of O_3 when only assessing associations in urban areas, which was addressed in our study by including nationwide data (Eljarrat et al., 2020).

NO_2 exposure had a slight protective association on preterm birth, but this should be interpreted with caution given the strong non-linear shape of the relationship. Heterogenous results have been previously observed in previous studies on preterm birth with similar protective

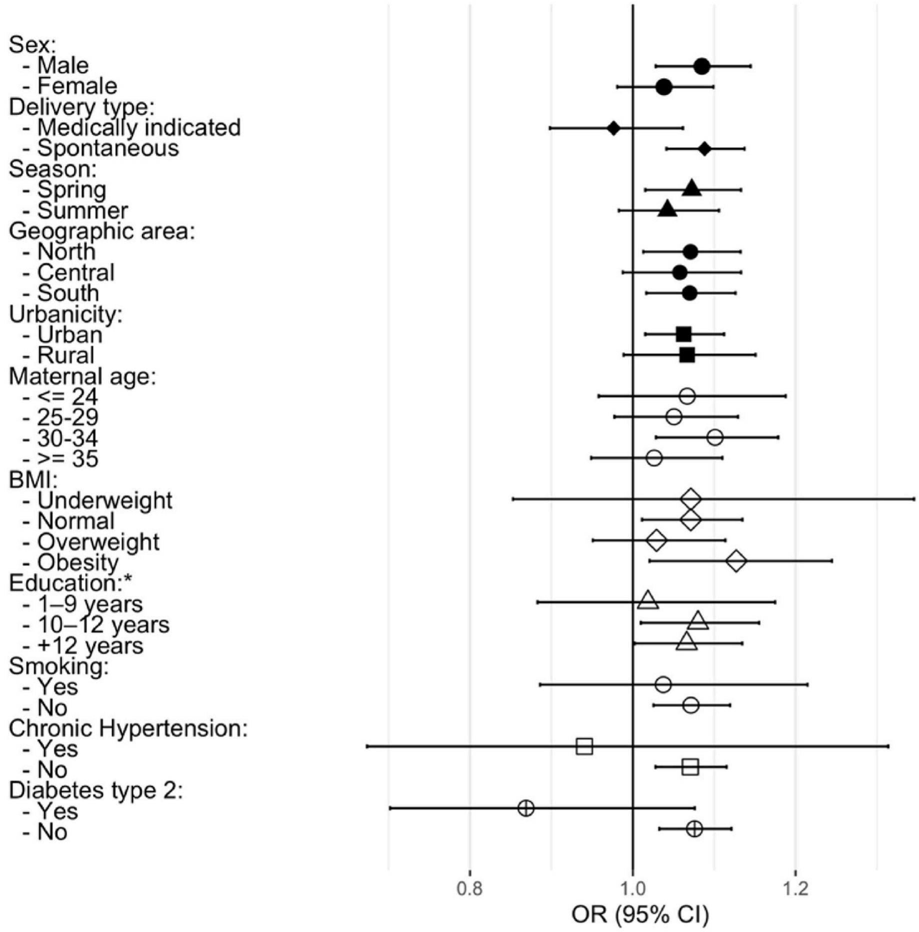

Fig. 2. Stratified analysis of effect modifiers in the associations between the exposure to O_3 the week before delivery and risk of preterm birth. Abbreviations: CI, Confidence Interval; DM, Diabetes Mellitus; HT, Chronic hypertension; OR, Odds Ratio. * P-value for interaction <0.05.

and non-linear findings (Johnson et al., 2016; Lee et al., 2008; Qian et al., 2016; Smith et al., 2020; Stieb et al., 2016). While unlikely that NO_2, with its known toxicity demonstrated in experimental studies, could reduce the risk of preterm birth, the possibility of a protective effect warrants further investigation (Li et al., 2010). The non-linear association of NO_2 could be explained through its negative correlation with O_3, as O_3 in the presence of sunlight is formed through a reaction of NO_2 and O_2, reducing the levels of NO_2. When we accounted for O_3 and temperature in our models, the association of NO_2 on preterm birth became nonsignificant but the estimates remained similar. In addition, no association was observed between $PM_{2.5}$ and PM_{10} and risk of preterm birth. This result could be related to the low levels and lower variability of PM exposure present in Sweden reducing our statistical power. PM composition also varies across regions with different contributory sources depending on the local environmental exposures and geographic area, perhaps reflecting variable levels of toxicity. On the other hand, O_3 has the same chemical composition across Sweden and the O_3 exposure model had the best predictive value of the air pollutants, which may have improved the likelihood of observing significant associations. The increased risk for preterm birth during the spring season can be explained by the increased O_3 seen during the spring season (Table S3) (Goldenberg et al., 2008). Future studies should also consider the association of increased O_3 levels with climate change and model the portion of adverse outcomes attributable to climate change.

The underlying biological mechanisms by which acute exposure to O_3 may trigger preterm birth are not well understood. A recent study, conducted under a randomized double-blind design, discovered that brief exposure to O_3 led to notable alterations in coagulation, lipid metabolism, fibrinolysis, and immune response mechanisms. A hypercoagulable state could potentially lead to vascular complications, such as placental abruption, and induce preterm birth (Gargano et al., 2010; Keren-Politansky et al., 2014). O_3 exposure has also been linked to an increased activation of the hypothalamic-pituitary-adrenal axis, which is responsible for the secretion of cortisol (stress hormone), which plays a crucial part in both term and preterm birth onset (Palmsten et al., 2020). An increase in cortisol levels in both the mother and fetus could potentially trigger the placenta to produce and release corticotropin-releasing hormone into the circulatory systems of both the mother and the fetus. Further, cortisol levels impact on time of delivery, preterm birth, and short-term neonatal outcomes (Aucott et al., 2008; Liggins, 1994; Ng et al., 2002). An dysregulation or premature initiation of these processes could potentially contribute to the development of preterm birth (Palmsten et al., 2020; Thomson et al., 2019). Cortisol could also contribute to the oxidative stress that follows pollutant exposure by increasing production of reactive oxygen species and increasing susceptibility to infections by downregulating the immune system (Moore et al., 2018). All of these potential pathways could interact with each other and other unknown risk factors, increasing the risk of a preterm birth.

The key strength of our study is the large study population. The SPR is one of many national patient registries in Sweden covering 92% of all births in Sweden (Stephansson et al., 2018). Health registries with high level of coverage and quality of data such as those in the Nordic countries minimize the risk for selection bias, which increases the validity of our findings. The large study population also made it possible to conduct stratified analysis to evaluate potential modifiers, such as lifestyle factors and comorbidities. Additionally, previous studies have mainly relied on air pollution data from fixed monitoring stations, whereas in our study we were able to obtain daily exposure levels at a high resolution using a nationwide spatiotemporal model. This allowed us to study pollution levels across the country, including rural areas, which further increases the validity of our findings. Furthermore, the case-crossover design allowed for control of time-invariant confounders while the time-stratified selection strategy effectively controls for seasonality and time-trend bias (Maclure, 1991).

There are certain limitations that should be mentioned. First, the exposure estimations were based on the residential addresses of the mothers. This could potentially lead to inaccuracies in exposure classification, as it does not accurately consider daily routines of the pregnant women such as indoor activities, time spent at work, or changes in residence. However, we expect that this bias would most likely cause a non-differential exposure misclassification, which would bias the results towards the null and underestimate the true association. Additionally, the case-crossover design allows for the estimation of the association of short time periods of exposure to maintain validity in the results. This could potentially mean that we missed longer periods of lag that may have showed a delayed or stronger association between the air pollutants and preterm birth. In addition, the sparse population distribution across Sweden with relatively few people living in the northern regions also means that there are fewer pollutant monitors that can be used to calibrate the exposure model, which may contribute to lower accuracy in rural areas compared to urban areas. Additionally, the uneven distribution of monitors in Sweden leads to an overall accuracy range of 64–78% for the exposure model (Stafoggia et al., 2020). The models estimate O_3 exposure based on a 24-h average rather than the typical 8-h average which may make it difficult to compare our results with other studies. Finally, in our study, we did not perform adjustments for multiple testing to account for falsely discovered significance. However, given that our primary analysis relied on four separate models (one for each pollutant), the impact of multiple testing is expected to be minimal.

5. Conclusion

In this large, low air pollution nationwide study including 28,216 preterm births between 2014 and 2019, we found that an increase of O_3 exposure the week before delivery increased the risk of preterm birth. These findings add to the evidence that increased levels of O_3, even in a setting with average O_3 levels below the recommended WHO guidelines, may still negatively affect human health, highlighting the importance of further research to better inform decision-maker and regulatory agencies who shape public policies regarding acceptable levels of O_3 exposure.

Ethical committee

The study was approved by the regional Ethical Committee in Stockholm, Sweden (2020/00390).

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CRediT authorship contribution statement

Nabeel Aziz: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Massimo Stafoggia:** Writing – review & editing, Data curation, Conceptualization. **Olof Stephansson:** Writing – review & editing, Data curation, Conceptualization. **Nathalie Roos:** Writing – review & editing, Funding acquisition, Conceptualization. **Sari Kovats:** Writing – review & editing, Funding acquisition, Conceptualization. **Matthew Chersich:** Writing – review & editing, Conceptualization. **Veronique Filippi:** Writing – review & editing, Conceptualization. **Cherie Part:** Writing – review & editing, Conceptualization. **Britt Nakstad:** Writing – review & editing, Conceptualization. **Shakoor Hajat:** Writing – review & editing, Conceptualization. **Petter Ljungman:** Writing – review & editing, Supervision, Resources, Conceptualization. **Jeroen de Bont:** Writing – review & editing, Validation, Supervision, Methodology, Data curation, Conceptualization.

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Appendix A. Supplementary data

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