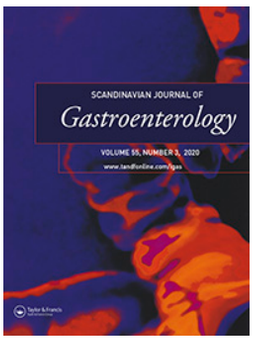

Scandinavian Journal of Gastroenterology

ISSN: 0036-5521 (Print) 1502-7708 (Online) Journal homepage: https://www.tandfonline.com/loi/igas20

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To cite this article: Bjørnar Finnanger Garshol, Geir Aamodt, Christian Madsen, Morten Harald Vatn & May-Bente Bengtson (2020) The effect of nitrogen dioxide on low birth weight in women with inflammatory bowel disease: a Norwegian pregnancy cohort study (MoBa), Scandinavian Journal of Gastroenterology, 55:3, 272-278, DOI: 10.1080/00365521.2020.1726446

To link to this article: https://doi.org/10.1080/00365521.2020.1726446

SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY
2020, VOL. 55, NO. 3, 272–278
https://doi.org/10.1080/00365521.2020.1726446

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ORIGINAL ARTICLE

The effect of nitrogen dioxide on low birth weight in women with inflammatory bowel disease: a Norwegian pregnancy cohort study (MoBa)

Bjørnar Finnanger Garshol[a], Geir Aamodt[a], Christian Madsen[b], Morten Harald Vatn[c] and May-Bente Bengtson[c,d]

[a]Department of Public Health Science, LANDSAM, Norwegian University of Life Sciences, Ås, Norway; [b]Department of Health & Inequality, Norwegian Institute of Public Health, Oslo, Norway; [c]EpiGen Institute, Akershus University Hospital, University of Oslo, Oslo, Norway; [d]Medical Department, Vestfold Hospital Trust, Tønsberg, Norway

ABSTRACT

Background: Adverse birth outcomes are more frequent among mothers with inflammatory bowel diseases (IBDs) than non-IBD mothers. In recent studies, air pollution, such as high concentrations of nitrogen dioxide (NO_2), is reckoned as a risk factor for preterm birth in the general population. In this study, we investigated whether IBD mothers are at higher risk of preterm birth when exposed to NO_2 compared to non-IBD mothers.

Methods: We used information from the Norwegian Mother, Father and Child Cohort Study (MoBa). The pregnancy cohort was linked to the Norwegian Medical Birth Registry and air-pollution exposure data available from a subset of the study cohort. The relevant outcome in this study was preterm birth. A total of 16,170 non-IBD and 92 IBD mothers were included in the study.

Results: The mean exposure of NO_2 during the pregnancy was similar for IBD and non-IBD mothers, 13.7 (6.9) $\mu g/m^3$ and 13.6 (4.2) $\mu g/m^3$, respectively.

IBD mothers with higher exposure of NO_2 in the second and third trimester were at significant risk of preterm birth compared to non-IBD mothers [OR = 1.28 (CI 95%: 1.04–1.59) and OR = 1.23 (95% CI: 1.06–1.43), respectively]. The mean NO_2 exposure was significantly higher in IBD mothers with preterm birth than in IBD mothers who delivered at term, at 19.58 (1.57) $\mu g/m^3$ and 12.89 (6.37) $\mu g/m^3$, respectively.

Conclusions: NO_2 exposure influenced the risk of preterm birth in IBD mothers. Higher risk of preterm birth in IBD was associated with higher exposure of NO_2, suggesting vulnerability of preterm birth in IBD when exposed to NO_2.

ARTICLE HISTORY
Received 1 January 2020
Revised 30 January 2020
Accepted 1 February 2020

KEYWORDS
The Norwegian Mother; Father and Child Cohort Study; air pollution; inflammatory bowel disease; pregnancy outcomes

Introduction

Inflammatory bowel diseases (IBDs), including Crohn's disease (CD) and ulcerative colitis (UC), represent chronic and complex diseases of the gastrointestinal tract. The aetiology of the diseases is largely unknown, but the pathogenesis is considered to be based on an interaction between genetic and environmental factors [1]. A leading hypothesis suggests that the intestinal inflammation is caused by an inappropriate immune response to commensal bacteria in genetically susceptible individuals [1,2]. The most explored environmental factors are smoking and appendectomies, both associated with an increased risk of CD and a decreased risk of UC [3]. A few studies from the last decade have revealed a link between IBD and air pollution [4,5]. High levels of air pollution have been associated with increased IBD-related hospitalization [6], suggesting that air pollution triggers inflammatory mechanisms in IBD patients. Recently, studies have demonstrated an association between particular matter (PM), an essential part of air pollution, and onset of IBD [7]. It has been hypothesized that the effects of air pollution and PM on the incidence of IBD are mediated by inflammatory processes in the mucosal immune system in interaction with changes in the intestinal microbiota. These mechanisms have been confirmed in a mice model by Kish et al. [8]. Increased level of PM was associated with enhanced intestinal pro-inflammatory cytokines, increased epithelial permeability and changes in the microbiota.

Women with IBD are more likely to experience adverse pregnancy outcomes such as preterm birth, small for gestational age (SGA), and low birth weight (LBW) [9–14], with disease activity as the most important predictor [15]. Premature birth remains the leading cause of neonatal and infant mortality and morbidity [16]. Likewise, long-term effects such as reduced cognitive ability and delayed motor function in childhood, reduced academic abilities in young adults [17], and increased risk of development of chronic diseases in adult life, such as diabetes and hypertension, have been linked to preterm birth [18]. Being born preterm is costly in terms of the suffering of infants and their families as well as the economic burden on society [19,20].

Studies have reported an association between air pollution and adverse pregnancy outcomes in the general

CONTACT May-Bente Bengtson maybente.bengtson@gmail.com Lokesvei 10, 3179 Åsgårdstrand, Norway

population [19–21]. The biological mechanisms responsible for the effects of air pollution exposure on the risk of premature birth are not fully clarified. The main hypothesis is that air pollution by inducing systemic inflammation, disturbs both foetal and placental homeostasis with negative impact on foetal growth and duration of gestation [16].

We hypothesize that women with IBD are more vulnerable to systemic inflammatory processes triggered by air pollution, and therefore at higher risk of preterm birth when exposed to air pollution. As far as we know, this is the first study exploring the effects of nitrogen dioxide (NO_2) on preterm birth in women with IBD. The aim of this study was to investigate the association between air pollution and preterm birth in mothers with IBD compared to non-IBD mothers.

Materials and methods

Study population

The Norwegian Mother, Father and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health [22]. Participants were recruited from all over Norway from 1999 to 2008. Amongst the mothers recruited in the study, consent was given for 41% of pregnancies. The cohort includes 114,500 children, 95,200 mothers and 75,200 fathers. The current study is based on version 7 of the quality-assured data files released for research in 2012.

Seven hundred and thirty-nine mothers with IBD were identified by the baseline questionnaire (Q1) prior to the first routine ultrasound examination in gestational weeks 17–20 of whom 655 IBD mothers were available for additional questionnaire in 2013. The questionnaire included IBD history: sub-classification of IBD, surgery, medication, and disease activity during pregnancy. Disease activity was defined as change in medication, IBD-related hospital admission or surgery during pregnancy. Of 328 responders, 136 suffered from CD and 192 suffered from UC. The non-responders were identified as CD and UC through the Norwegian Patient Register (NPR), including individuals who have been in contact with specialist health care services.

Based on available air pollution data (NO_2), only participants living in Oslo, Akershus, Bergen, and Hordaland were eligible for this study, which left this study with 16,262 mothers, including 92 IBD mothers; 43 with CD, and 49 with UC. We decided to merge CD and UC in the statistical analyses due to similar risk of preterm birth in the two phenotypes, and to increase statistical power [10]. Non-IBD mothers were considered as control group. The Medical Birth Registry of Norway (MBRN) are linked to MoBa [23] and used to identify birth outcomes. Only singleton births were included in the analysis.

Variables

Outcome variables

Preterm birth was defined as birth before 37 weeks of gestation, based on existing categories from the MBRN records.

Air pollution exposure

We used already existing air-pollution data and predictions of NO_2 concentration at the mothers' home addresses [24]. The production of these concentrations consisted of two steps: first measuring NO_2 at different monitoring sites and next fitting a statistical regression model of NO_2 as a function of a set of spatial variables [land-use regression (LUR)]. Only NO_2 was selected as the most important indicator of air pollution for birth outcomes [21].

Air-pollution measurements were conducted in Oslo and Akershus in 2010 and in Bergen and Hordaland in 2011. The measurement period was three separate rounds of measurements during 1 year. Each round had a duration of about 2 weeks: one was conducted in winter, one in summer, and one in an intermediate season (either spring or autumn). Measurement sites were chosen to represent the range of residential exposure in each area. To obtain a yearly mean NO_2 level, the mean exposure from the three different measurement periods was averaged.

The predicted values using LUR-methodology was developed for the ESCAPE-project [25]. The regression models were fitted for each of the studied areas to account for regional differences based on measurements from the different measurement sites; Oslo and Akershus separately, but a joint model for Bergen and Hordaland due to few valid measurement sites in Hordaland. The idea with LUR was to model the concentration of NO_2, available from the measurement sites, as a function of a set of geo-referenced variables such as distance to major roads, population density, and closeness to green areas. We used land-use data (N50, Norwegian Map Authorities) and road-maps from the Norwegian Road Authorities (VBASE). Once the models were fitted, they were used to predict the concentration of NO_2 for each address point in the study cohort. Leave-one-out-cross validation (LOOCV) was used to evaluate the goodness-of-fit of the model [24]. Mean NO_2 levels were estimated for the first, second, and third trimesters as well as the whole pregnancy. NO_2 was included as a continuous variable.

Potential confounding variables

Sociodemographic variables and socioeconomic status

Maternal age was based on self-reported age at birth and was categorized into two categories: <30 years and ≥ 30 years. Education level was used as a proxy for socioeconomic status and the subjects were allocated to three separate groups: high school or less, college (3 years), and master degree or higher.

Health status and behaviour

Body mass index (BMI) was based on self-reported weight and height pre-pregnancy and categorized into four categories: underweight ($<18.5\,kg/m^2$), normal weight ($18.5–24.9\,kg/m^2$), overweight ($25–29.9\,kg/m^2$) and obese ($\geq 30\,kg/m^2$), according to the World Health Organization (WHO Expert Consultation 2004). Information about smoking status was obtained from Q1 at weeks 15–17, shortly before

the first ultrasound examination, defined in terms of non-smokers, occasional smokers and daily smokers, the latter two merged and considered to represent the smokers. Maternal diabetic condition, recorded as a dichotomous variable, includes diabetes I and II as well as gestational diabetes. Maternal hypertension defined as; systolic blood pressure $\geq$140 mm Hg, and diastolic blood pressure $\geq$90 mm Hg.

Mothers with IBD were asked to report disease activity during the month before pregnancy and during pregnancy. Disease activity was defined as fulfilment of at least one of the following consequences of flares: change of medication, IBD-related surgery, or IBD-related hospital admissions.

Statistical analysis

We used *t*-tests to investigate associations between NO_2 exposure and birth outcomes or the distribution of exposure among the IBD mothers and non-IBD mothers. Chi-square tests were used to investigate the association between the birth outcome and categorical variables: maternal age, BMI, maternal education level, and maternal smoking status. Furthermore, chi-square tests were used to study differences between the IBD mothers and the non-IBD mothers.

Logistic regression models estimated the association between NO_2 exposure during pregnancy and birth outcome in mothers with IBD compared to non-IBD. We produced separate models for the separate trimesters and the whole pregnancy. To estimate excess risk for the IBD mothers when compared to the non-IBD mothers we included an interaction term between NO_2 and IBD in all the logistic regression models. This interaction term captures the excess risk for the IBD mothers exposed to NO_2 compared to the main risk for all mothers and is the main parameter of interest in these analyses. We report main risk for all mothers (OR_{main}) and excess risk (OR_{int}). We report results from adjusted and unadjusted models. Adjusting variables were maternal age, BMI, maternal education level, and maternal smoking status. Diabetes and hypertension were excluded from the analysis due to too few cases among the IBD mothers. In sub-analyses including only IBD mothers, logistic regression models were fitted to analyse the association between NO_2 and the outcome variable adjusting for disease activity.

p-values $<$.05 were considered statistically significant. The statistical analyses were performed using the free software R version 3.5.1. We used multiple imputation methods to accommodate missing values [26]. Five new datasets were produced where values were generated and imputed for the missing values. The imputations were based on a missing at random (MAR) assumption. We used the R-package mice [26] to conduct the imputation analyses.

Ethical considerations

The establishment and data collection in MoBa was previously based on a license from the Norwegian Data Protection Agency and approval from The Regional Committee for Medical Research Ethics, and it is now based on regulations related to the Norwegian Health Registry Act. The current study was approved by The Regional Committee for Medical Research Ethics (Protocol no. 2011/1317).

Results

The study sample characteristics are reported in Table 1, showing distribution of the exposure variables, birth outcomes, demographic data, and potential confounders among the IBD mothers and the non-IBD mothers. The typical woman who participated in our study was about 31 years old, with normal BMI, 3 years of college or university education and nonsmoker. The distribution of preterm birth was almost similar among non-IBD mothers (5%) and IBD mothers (4%). The mean level of modelled NO_2 exposure was $13.6 \pm 4.2\ \mu g/m^3$ in non-IBD mothers and $13.7 \pm 6.9\ \mu g/m^3$ in IBD mothers. The range of NO_2 exposure was wider in non-IBD (0.1–60.5) than in IBD mothers (0.1–32.0). Similar mean exposure levels were observed for the different trimesters (data not shown).

Table 2 shows the differences in exposure of NO_2 for term and pre-term mothers and for IBD and non-IBD mothers separately. Mean NO_2 exposure during pregnancy was associated with preterm birth outcome only in IBD mothers ($p = .002$). Higher NO_2 exposure during the first ($p = .011$) and third trimester ($p = .013$) was significantly associated with preterm birth in IBD mothers. In contrast to the effect of NO_2 exposure in IBD-, mean NO_2 exposure was not associated with preterm birth in non-IBD ($p = .906$), with similar results in all trimesters. IBD mothers who experienced preterm birth had a higher mean NO_2 exposure during pregnancy, compared to both IBD mothers with full-term delivery and non-IBD mothers with preterm or term delivery (Table 2).

Chi-square tests were performed to investigate the association between the categorical variables (confounders) and preterm birth (data not shown). Among the non-IBD mothers, the following variables were associated with preterm birth: maternal age ($p = .025$), BMI ($p = .001$) and education level ($p = .009$). Smoking ($p = .114$) was not associated with preterm birth among the non-IBD mothers. None of the variables was associated with preterm birth among the IBD mothers (data not shown).

Table 3 presents results from the logistic regression analyses. The crude and adjusted analyses, including all mothers, did not show any association between preterm birth and exposure to NO_2. However, excess odds of preterm birth were significantly higher in IBD mothers with higher NO_2 exposure, compared to non-IBD mothers. The significant excess risk effect of preterm birth in IBD appeared in the second and third trimesters, with almost similar results in the crude and adjusted models $OR_{int} = 1.28$ (95% CI: 1.04–1.59) and $OR_{int} = 1.23$ (95% CI: 1.06–1.43), respectively.

The results from the sub-analyses including only women with IBD are presented in Table 4. The mean NO_2 exposure in the second and third trimester was significantly higher in IBD mothers with preterm birth compared to those with term birth. As an example, the adjusted odds of preterm

Table 1. Characteristics of the study participants in the Norwegian Mother and Child Study Cohort (1999–2008) and with exposure variables on air pollution.

	All women	Non-IBD mothers	IBD mothers
Total	16,262	16,170	92
Mothers' age			
Years (mean (SD))	31.0 (4.5)	31.0 (4.5)	31.3 (3.8)
<30 years	7210 (44%)	7172 (44%)	38 (41%)
≥30 years	9052 (95%)	8998 (95%)	54 (96%)
Missing	0 (0%)	0 (0%)	0 (0%)
BMI (kg/m^2)			
Mean (SD)	23.7 ± 4.2	23.7 ± 6.9	26.8 ± 7.3
<18.5	525 (3%)	523 (3%)	2 (2%)
18.5–24.9	10,299 (68%)	10,235 (68%)	64 (72%)
25.0–29.9	3036 (20%)	3019 (20%)	17 (19%)
≥30	1208 (8%)	1202 (8%)	6 (7%)
Missing	1194 (7%)	1191 (7%)	3 (3%)
Mothers' education			
High school or less	4221 (29%)	4194 (29%)	27 (31%)
College 3 years	5782 (40%)	5744 (40%)	38 (44%)
Master or higher	4547 (31%)	4525 (31%)	22 (25%)
Missing	1712 (11%)	1707 (11%)	5 (5%)
Mothers' smoking			
Nonsmoker	13,105 (94%)	13,022 (94%)	83 (92%)
Smoker	883 (6%)	876 (6%)	7 (8%)
Missing	2274 (14%)	2272 (14%)	2 (2%)
Diabetes			
No	16,001 (98%)	15,910 (98%)	91 (99%)
Yes	261 (2%)	260 (2%)	1 (1%)
Missing	0 (0%)	0 (0%)	0 (0%)
Hypertension			
No	16,174 (99%)	16,082 (99%)	92 (100%)
Yes	88 (1%)	88 (1%)	0 (0%)
Missing	0 (0%)	0 (0%)	0 (0%)
Preterm birth			
No	15,520 (95%)	15,432 (95%)	88 (96%)
Yes	742 (5%)	738 (5%)	4 (4%)
Missing	0 (0%)	0 (0%)	0 (0%)
NO_2 exposure (μg/m^3)	13.6 (4.2)	13.6 (4.2)	13.7 (6.9)
Mean (SD)			
Range			
Pregnancy	0.1–60.5	0.1–60.5	0.1–32.0
First trimester	0.1–60.4	0.1–60.4	0.1–33.5
Second trimester	0.1–68.2	0.1–68.2	0.1–29.8
Third trimester	0.1–59.1	0.1–59.1	0.1–35.7

Table 2. Mean exposure levels of NO_2 for IBD mothers and non-IBD mothers in the MoBa cohort (1999–2008).

Exposure interval of NO_2	Birth outcome	*N*	Mean (μg/m^3)	SD (μg/m^3)	*p*-value
IBD mothers					
Mean pregnancy	Preterm	3	19.58	1.57	.002
	Normal	82	12.89	6.37	
First trimester	Preterm	4	23.76	4.37	.011
	Normal	81	12.90	6.74	
Second trimester	Preterm	2	24.72	9.68	n.a.*
	Normal	85	13.71	7.21	
Third trimester	Preterm	4	22.77	4.03	.013
	Normal	89	13.34	6.38	
Non-IBD mothers					
Mean pregnancy	Preterm	713	13.77	7.73	.906
	Normal	14,782	13.74	7.42	
First trimester	Preterm	650	13.57	7.64	.58
	Normal	13,190	13.73	7.36	
Second trimester	Preterm	263	13.12	7.43	.514
	Normal	13,318	13.42	7.08	
Third trimester	Preterm	712	13.60	7.16	.967
	Normal	14,778	13.61	6.79	

p-values are results from *t*-tests.
*Too few participants among the preterm group to perform a *t*-test.

birth was 1.29 times higher (95% CI: 1.04–1.60) for those IBD mothers who had higher exposure to NO_2 during pregnancy. The risk of preterm birth appeared in the second and third trimester.

Table 3. Risk of preterm birth dependent on NO_2 exposure.

Exposure interval	Model term	Crude OR (95% CI)	Adjusted OR (95% CI)
First trimester	Main effect	1.00 (0.99–1.01)	1.00 (0.99–1.01)
	Excess risk	1.11 (0.97–1.27)	1.11 (0.97–1.27)
Second trimester	Main effect	1.00 (0.99–1.01)	1.00 (0.99–1.01)
	Excess risk	1.28 (1.04–1.59)	1.28 (1.03–1.59)
Third trimester	Main effect	0.99 (0.98–1.00)	1.00 (0.99–1.01)
	Excess risk	1.23 (1.06–1.43)	1.23 (1.06–1.43)
Mean pregnancy	Main effect	1.00 (0.99–1.01)	1.00 (0.99–1.01)
	Excess risk	1.27 (1.04–1.55)	1.27 (1.04–1.55)

Main effect and excess risk effects of NO_2 for all participants (main) and IBD mothers (excess risk) for participants in the MoBa study cohort (1999–2008).

Table 4. Risk of preterm birth dependent on NO_2 exposure including 92 IBD mothers.

NO_2 exposure interval	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
First trimester	1.13 (0.99–1.3)	1.16 (0.99–1.37)
Second trimester	1.29 (1.04–1.61)	1.32 (1.04–1.66)
Third trimester	1.24 (1.06–1.45)	1.24 (1.05–1.47)
Mean pregnancy	1.26 (1.04–1.54)	1.29 (1.04–1.6)

Results from multiple imputation methods. Data from the Norwegian Mother and Child Study Cohort (1999–2008).

We compared results from models accommodating the missing values (multiple imputations) and complete-case analysis. The results from the complete-case (data not

shown) show similar magnitude as the results presented above. Disease activity did not change the association between NO_2 and preterm birth in the final sub-model. The p-values for the association between disease activity and preterm birth varied from 0.07 to 0.22 for NO2 measured in the different trimesters and mean pregnancy.

Discussion

The main finding in this birth cohort study was that preterm birth in IBD mothers was associated with NO_2 exposure. The excess risk of preterm birth was significantly higher in IBD mothers with higher NO_2 exposure in the second and third trimester than in non-IBD mothers. Furthermore, in contrast to non-IBD mothers, in IBD mothers preterm birth was associated with a higher concentration of NO_2 compared to IBD mothers who delivered at term. These results suggest vulnerability for preterm birth in IBD mothers when exposed to NO_2. To our knowledge, no other studies have investigated the link between air pollution and birth outcomes in women with IBD. Several investigations have revealed an association between NO_2 exposure and preterm birth in the general population [20,27,28], but not all [29]. Gehring et al. [30] explored the association between traffic-related air pollution and preterm birth in a prospective Dutch birth cohort study, including 3853 singleton births. They did not find a significant association, but they reported a tendency towards an increased risk for preterm birth with increasing air pollution exposure, possible due to low statistical power.

Although the biological mechanisms of NO_2 exposure on risk of preterm birth is still unclear, air pollution has been hypothesized to influence the risk of preterm birth by triggering the bidirectional interaction between oxidative stress and systemic inflammation. Oxidative stress and systemic inflammation are closely related and have tightly linked pathophysiological processes [31]. Systemic inflammation exaggerates the generation of reactive oxygen and nitrogen species in response to pro-inflammatory cytokines and oxidative stress trigger inflammation through activation of transcription factor NF-kB [32] and NOD-like receptor protein 3 [33]. Oxidative stress disturbs the neonatal development by interfering with transplacental nutrient exchange [34] and/or by direct toxic effects on the foetus [27]. These effects on foetal cells and intrauterine tissue promote foetal cell senescence (aging), which in turn generates biomolecular signals that are uterotonic and trigger the labour process [35].

IBD mothers with preterm birth were exposed to higher NO_2 concentration than IBD mothers who delivered at term. We speculate that IBD mothers might be more vulnerable to preterm birth when exposed to NO_2, caused by an already triggered and changed systemic immune system by the interplay with the gut mucosal immune system [36]. The link between systemic and gut inflammation was shown by Nalleweg et al. [37] IL9 mRNA expression in inflamed tissue from patients with UC was significantly increased as compared to controls, and furthermore, stimulated peripheral lymphocytes from UC patients produced more IL-9 than control cells. Similar results were found by Matusiewicz et al. [38], who showed higher systemic IL9 level in IBD patients than in healthy controls, and a correlation between endoscopic inflammation in UC patients and circulating IL9. Furthermore, the study revealed that not only IBD patients with active disease, but also IBD in remission, was associated with raised circulating level of IL9.

Mothers with preterm birth were exposed to higher levels of NO_2 only in IBD mothers, although there were no differences in mean exposure of NO_2, and the range of NO_2 exposure was wider in non-IBD mothers than IBD mothers (Table 1).

There are a number of plausible mechanisms by which air pollution exposure might impact the intestine: By direct effects on the gut epithelium, by alteration of the immune system or by interfering with the microbiota [4]. Pollutants might either trigger mucosal inflammation [31] or interact with already existing mucosal inflammation. Studies revealed that pollutants were toxic to inflamed epithelium inducing oxidative stress with increased permeability in contrast to no effect on healthy epithelium [39]. Although investigations suggest an association between disease activity and air pollution in IBD [7,8], the present study could not confirm the impact of disease activity on the association between NO_2 and preterm birth.

Strengths and limitations

The strengths of this study include the large and nationwide sample size and the linkage to the national birth registry and NPR, which has limited loss-to-follow up. Of those invited in the MoBa study, only 41% participated [22]. A comparison between the MoBa participants and all women giving birth in Norway in 1999–2007, using data from the population-based MBRN, has revealed a self-selection bias concerning prevalence estimates of exposure and outcomes. However, this bias did not significantly affect the estimates of exposure-outcome associations [40], but it could cause selection of exposure.

The standardized method of assessing individual exposure for the study population was based on the methodology developed for the ESCAPE project, and the LUR models from that project. These methods explain a substantial fraction of the variation of the exposure variables in the study areas [41]. However, the use of exposure at home addresses in the estimates, might introduce a non-differential misclassification. The women could have moved or they could have had a different exposure at work or when traveling, which means that the results could be biased towards null (attenuated) due to the potential non-differential misclassification.

The IBD mothers were identified based on responses to the mail-out questionnaire sent in 2013 (65%) and on data from NPR (35%). No studies have validated the IBD diagnosis in the registry. However, Bakken et al. [42] found a satisfactory agreement between NPR and the Norwegian Cancer Registry for different cancer outcomes. Outcomes in this study were based on records from MBRN and the validity of these outcomes has been shown to be satisfactory [43]. The IBD diagnosis is relatively rare and the number of IBD

mothers included in this study was consequently small. The number of adverse outcomes within the IBD group is thus smaller still, but the prevalence of preterm birth is comparable with the non-IBD mothers. The small IBD population has consequences on the internal validity of the findings. The small number of observations limited the statistical power when adjusting for important variables like diabetes, hypertension and smoking habits among the IBD mothers. And it also potentially affects external validity. Hence, the conclusions cannot be generalized to other populations.

We included a number of potential confounders in our logistic regression models. Nevertheless, hypertension and diabetes were excluded from the analysis due to none or too few cases among the IBD mothers. However, the prevalence of both conditions are low among the IBD mothers and are not likely associated with the risk of preterm birth in this sample.

Several studies [44,45] have noted problems with separating the effect of NO_2 and the effects of particulate matter (PM), as we have, because PM-exposure could potentially be a confounding factor to the association between preterm birth and IBD. Further research should therefore aim to include a broad spectrum of confounders and several types of air pollution to estimate the potentially different effects and correlation between the different pollution types. In this study, the concentration of NO_2 was relatively low.

Disease activity did not change the association between NO_2 and preterm birth in the final sub-model. However, there are considerable limitations with the study design concerning disease activity, which cannot be corrected. The information of disease activity was collected retrospectively in 2013, introducing a lag of 5–13 years; furthermore, disease activity was self-reported. Disease activity was defined as at least one of three options: change in medication, IBD-related surgery and/or hospital admission. These proxies are usually used in register studies and do not represent objective markers. However, these proxies were chosen, well aware of not including mild or moderate disease activity, but we believed that it would be easier to recall severe disease during pregnancy with the introduced time lag.

Conclusions

This study revealed that IBD mothers with excess risk of preterm birth were exposed to higher NO_2 concentration in the second and third trimester than non-IBD mothers and IBD mothers with term birth. Furthermore, preterm birth was associated with higher concentration of NO_2 only in IBD mothers. These results suggest vulnerability for preterm birth especially in IBD mothers when exposed to NO_2. We speculate that this vulnerability for preterm might be explained by an interaction between the intestinal mucosa exposed to NO_2 and an already triggered systemic inflammation in IBD mothers with active disease as well as those in remission. However, the study is flawed by several weaknesses, especially the low number of IBD mothers with preterm birth included in the study and also the retrospective design of recording disease activity. The results must be treated with caution and further research is required to explore the association between air pollution and preterm birth in IBD.

Acknowledgements

We are grateful to all the families in Norway who took part in this ongoing cohort study.

Consent for publication

The participants have given consent for the publication of the data from the MoBa study.

Author contributions

The concept and design was worked out by GAA, BFG, MHV, CM, and MBB. Analyses and interpretation of data were performed by GAA. BFG wrote the paper. All authors contributed to drafting and editing the manuscript. All authors have read and approved the manuscript for publication.

Disclosure statement

Morten H. Vatn: Advisory board, Genetic Analysis. The authors listed below do not have any financial or other relationshiip(s) to disclose: Bjørnar Finnanger Garshol, May-Bente Bengtson, Geir Aamodt, Christian Madsen.

Funding

The Norwegian Mother and Child Cohort Study is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research, NIH/NIEHS [contract number N01-ES-75558]; NIH/NINDS [grant no.1 UO1 NS 047537-01 and grant no.2 UO1 NS 047537-06A1]; and South-Eastern Norway Regional Health Authority.

ORCID

May-Bente Bengtson http://orcid.org/0000-0002-5615-7141

Data availability

The consent given by the participants does not open for storage of data on an individual level in repositories or journals. Researchers who want access to data sets for replication should submit an application to datatilgang@fhi.no. Access to data sets requires approval from the Regional committees for medical and health research ethics in Norway and a formal contract with MoBa.

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