

Development of Late-Onset Preeclampsia in Association with Road Densities as a Proxy for Traffic-Related Air Pollution

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Key Words

Preeclampsia · Perinatal outcome · Placenta · Pregnancy complications · Air pollution · Traffic · Road density · Late-onset preeclampsia

late-onset PE cases ($p = 0.0078$). **Conclusions:** Exposure to TRAP during pregnancy was associated with an increased risk for the development of late-onset PE.

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Abstract

Introduction: Previous epidemiological studies indicate an association between maternal exposure to air pollution and an increased risk of hypertensive disorders in pregnancy. We analyzed the association between the occurrence of mild/severe and early-/late-onset preeclampsia (PE) and traffic-related air pollution (TRAP). **Materials and Methods:** Based on retrospective data, 50 pregnant women with PE were selected and matched with a control group of healthy pregnant women according to their age, parity, and number of fetuses. The total length of major roads around the women's home within a radius of 100, 200, 300, and 500 m and the distances from the domicile to the nearest 'first class' main road and freeway were used as a proxy indicator of TRAP. We compared a PE subgroup and control group in terms of their exposure to TRAP. **Results:** Late-onset PE cases showed a significantly higher occurrence with density of major roads within a radius of 100–300 m compared to early onset cases ($p = 0.006$; 0.02 ; 0.04). In addition, a significantly shorter distance to the nearest 'first class' main road was observed in

Introduction

Preeclampsia (PE) is a serious complication of the second half of pregnancy in up to 8% of all pregnancies. It is one of the 3 leading causes of maternal morbidity and mortality worldwide [1]. PE is clinically defined as the new onset of hypertension (blood pressure $\geq 140/90$ mm Hg at least on 2 measurements 6 h apart from each other) and significant proteinuria (>0.3 g/24 h) after 20 weeks of gestation. The severe type of PE is specified as hypertension over 160/110 mm Hg and proteinuria above 0.5 g/24 h [2]. Furthermore, signs of a significant organ involvement like neurological symptoms, renal failure or HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet) belong to the category of severe PE [3]. Depending on the time of appearance of the first clinical symptoms, PE can also be classified into 2 distinct subtypes. Early onset is defined as less than 34 weeks of gestation, while late-onset is

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defined as after 34 + 0 weeks of gestation [1, 4–7]. Early-onset PE is a rare disease with a high maternal and neonatal morbidity and mortality [5]. Late-onset PE, however, has a lower maternal and fetal morbidity and occurs more frequently. Besides the different clinical aspects and maternal and fetal outcomes, there is a discussion about different etiologies of these 2 subtypes. Several studies propose that generalized endothelial dysfunctions in the placenta and the impaired trophoblastic invasion of the maternal placental bed in early pregnancy might be the origins of the early-onset disease [3]. These 2 factors may lead to systemic endothelial cell dysfunction and systemic inflammation with neutrophil activation in the maternal body [8, 9]. PE presenting at term is associated with a lower frequency and severity of fetal growth restriction compared to early-onset PE. Late-onset PE could be hypothesized to present a process leading to maternal endothelial damage, which is unrelated to impaired early trophoblast invasion [10]. Predisposing cardiovascular factors or metabolic risks for endothelial dysfunction as part of an exaggerated systemic inflammatory response might dominate the origin of late-onset PE [11–13]. Currently, the only causal treatment for PE is delivery and the removal of the placenta. The prediction of PE is a major challenge in contemporary obstetrics, and some authors could recently show added value of angiogenic factors for the prediction of early- and late-onset PE in the first trimester of pregnancy [14].

Major risk factors for the development of PE [12, 15] are previous chronic hypertension, kidney disease, diabetes mellitus, nulliparity, obesity, multiple pregnancies, maternal age >40 years, African-American race [16], and family history of PE. It is known that local air pollution exposure, especially pollution due to motor vehicle traffic [17], is associated with adverse cardiovascular and respiratory effects like systemic inflammation, elevated blood pressure and asthma [18, 19]. Previous studies also indicate a potential harmful effect of local air pollution on pregnancy outcome, including an increased risk of preterm delivery and PE [20–22]. Recently, a meta-analysis including 17 studies evaluated the exposure to ambient air pollution and pregnancy-induced hypertensive disorders. Most studies measured air pollutant levels like nitrogen oxides (NO₂, NO_x), particulate matter (PM₁₀, PM_{2.5}), carbon monoxide (CO), ozone (O₃), but few took traffic density and the proximity to major roads into account, which can be used as estimates of air pollution. The meta-analysis showed an increased risk of hypertensive disorders in pregnancy including all pollutants as well as the proximity to major roads and traffic density [23]. In this context, several studies have reported that traffic-related air pollution (TRAP) is associated

with endothelial dysfunction, a potential predictor of PE [24, 25]. Air pollutants may also contribute to an anti-angiogenic state which can also lead to PE [26]. The aim of the present study was to analyze the association between the occurrence of PE and TRAP in the North Western area of Switzerland in a case-control study. The PE cases were stratified into mild/severe and early-/late-onset subgroups according to the common definitions [6] and analyzed for their association with air pollution.

Materials and Methods

Study Design and Study Population

This case-control study was performed at the University Hospital of Basel, Switzerland. The catchment area of the study was the Canton of Basel-City and its surroundings (Canton of Basel-Country). A few study participants were enrolled from the Cantons of Aargau, Solothurn, Zurich and Berne. Based on retrospective data from the electronic medical records of the Department of Obstetrics and Fetomaternal Medicine and the home addresses, indicated at booking, 50 pregnant women were selected for the study group. These women were treated for PE and sent to our institution between January 1, 2011, and December 31, 2011. The criteria included were all singleton or multiple pregnancies after 20 + 0 weeks of gestation. The excluded criteria were pregnancies before the 20 + 0 weeks of gestation, the women's domicile outside of Switzerland, women with an abortion due to PE or eclampsia before the 24th week of gestation as well as fetuses with severe malformation. The study group was matched with a healthy control group of 50 pregnant women with uncomplicated pregnancies. Age at delivery (\pm 1 year, if necessary), parity and number of fetuses (singleton or twin pregnancy) were used as matching criteria. According to our statistics, there were 79 women in total treated for PE at the University Hospital of Basel in 2011. Overall, 2,286 births were registered at our institution. This study was approved by the Ethics Committee of Basel (Ethikkommission beider Basel).

TRAP Exposure

In the present study, the exposure to TRAP, especially nitrogen dioxide (NO₂), particulate matter (PM_{2.5}, PM₁₀), sulfur dioxide (SO₂) and carbon monoxide (CO) [27], was estimated by a surrogate measure of road density in the surroundings, in particular the densities of major roads, which is defined as a combination of all freeways and 'first class' main roads (at least 6 m wide) [28, 29]. The geographic information system (GIS) data with the road network of Switzerland was provided by the Swiss Federal Office of Topography (swisstopo) [30]. Two parameters for estimating the road density were defined; first, the total length of all major roads within a radius of 100, 200, 300, and 500 m around the geocoded location of each woman's home during their pregnancy, and second, the distance in meters from each woman's domicile to the nearest 'first class' main road and freeway.

Statistical Analysis

The statistical data set included a total of 100 pregnant women, whereof 50 women developed PE during pregnancy (study group) and 50 women showed no health problems (control group). PE cas-

es differed in severity, 'mild' or 'severe', and in time of onset, 'early' or 'late'. Mean, standard deviation, median, minimum and maximum for each road density parameter were calculated for each group. Both case and control groups as well as each PE subgroup (mild vs. severe; early vs. late onset) were compared by a Mann-Whitney test. Statistically significant results were defined as $p \leq 0.05$.

Maternal and fetal characteristics were measured and differences between the case and control groups were tested using Fisher's exact test for continuous variables and the Kruskal-Wallis rank-sum test for categorical variables. p values were not adjusted for multiple testing. We did not perform a power calculation. Our main objective was the comparison between the case and control group.

Results

Subject Characteristics

We included 100 pregnant women and 106 newborns in the study. Maternal and fetal characteristics are represented in tables 1 and 2. The control group was matched for maternal age and parity, but, due to the retrospective design and logistical restrictions, not for other risk factors like hypertension, previous PE or twin pregnancy, which could increase the risk for PE. All relevant diseases were absent in the control group, with the exception of 1 case of asthma (table 1: 'other disease'). There were 2 women with gestational diabetes and 2 with preconceptional diabetes. Newborns from mothers suffering from PE had a preterm birth more often, were born by cesarean section and transferred to the neonatal intensive care unit.

Cases versus Control

Figures 1 and 2 show the descriptive analyses of road density parameters for the study versus the control group. The control group showed a significantly higher total length of major roads within a radius of 500 m compared to the study group (fig. 1). For all other road density parameters, no statistically significant difference between study and control group was found.

Early- versus Late-Onset PE Cases

Descriptive analyses of road density parameters for early- versus late-onset PE cases are shown in figures 3 and 4.

Late-onset PE cases showed a significantly higher occurrence with a total length of major roads within a radius of 100, 200, and 300 m (fig. 3) and a significantly shorter distance to the nearest 'first class' main road compared to early-onset PE cases (fig. 4). In addition, in late-onset PE cases, both a higher total length of major roads within a radius of 500 m and a shorter distance to the

Table 1. Description of Maternal characteristics

Maternal characteristics	Case	Control	p value
Patient, n	50	50	1.00
Age at delivery, years	32.02±5.75	32±5.61	0.99
Insurance status			0.80
Private	9 (18)	11 (22)	
Nonprivate	41 (82)	39 (78)	
Origin			0.26
Europe	40 (80)	45 (90)	
Others	10 (20)	5 (10)	
Domicile in			0.26
City	40 (80)	45 (90)	
Countryside	10 (20)	5 (10)	
BMI	30.08±5.68	26.76±3.93	0.007
Parity			1.00
1	38 (76)	38 (76)	
2	8 (16)	8 (16)	
>2	4 (8)	4 (8)	
Pregnancy modus			0.06
Spontaneous	43 (86)	49 (98)	
Infertility treatment	7 (14)	1 (2)	
Number of fetuses			1.00
Singleton	47 (94)	47 (94)	
Twins	3 (6)	3 (6)	
Relevant diseases			
Earlier PE	5 (10)	0 (0)	
Diabetes mellitus and gestational diabetes	4 (8)	0 (0)	
Hypertension	5 (10)	0 (0)	
Others ¹	7 (14)	1 (2)	
PE severity			
Mild	10 (20)		
Severe	40 (80)		
HELLP	12 (24)		
PE onset			
Early onset	24 (48)		
Late onset	26 (52)		

Values represent mean ± SD or n (%).

¹ Chronic kidney disease, asthma bronchiale or cigarette consumption.

nearest freeway were found, although these differences were not statistically significant.

Mild versus Severe PE Cases

No significant difference was found in any road density parameter between severe and mild PE cases. However, some tendency in the results could be observed: severe PE cases showed a higher total length of major roads within all radiuses (fig. 5) and a shorter distance to the nearest freeway and to the nearest 'first class' main road compared to mild PE cases (fig. 6).

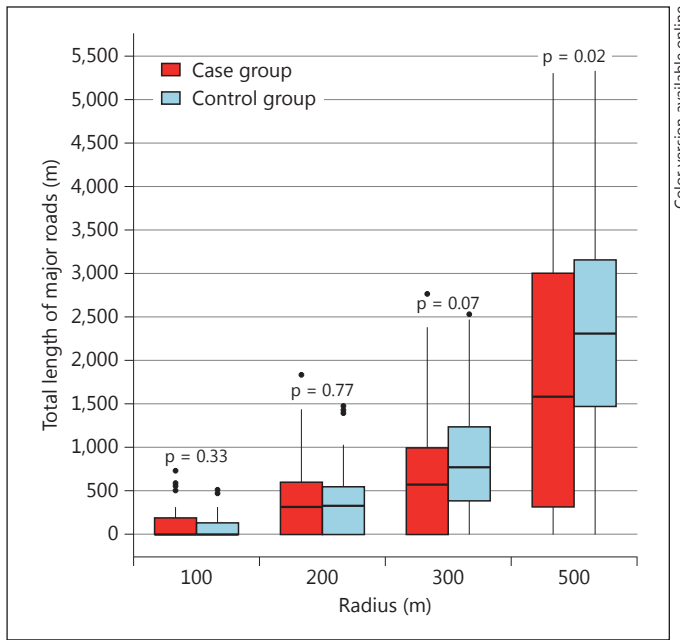


Fig. 1. Total length of major roads around the women's domicile for cases (n = 50) and controls (n = 50).

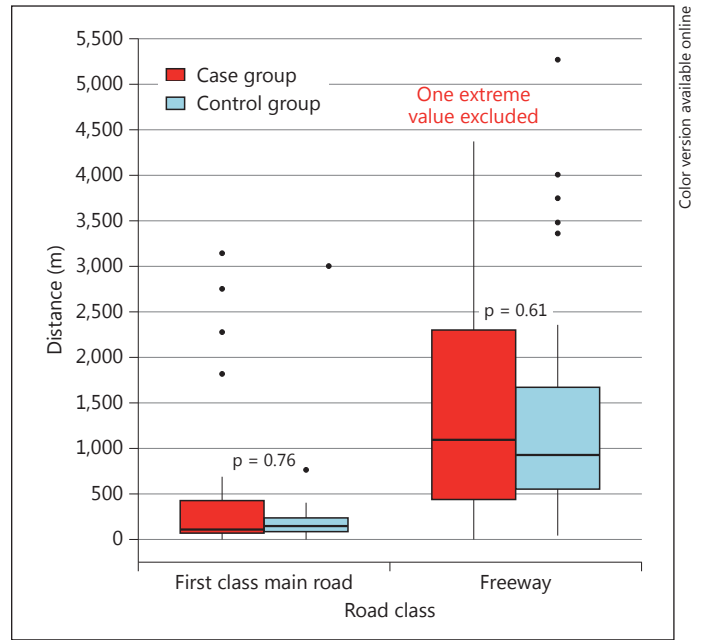


Fig. 2. Distance of the women's domiciles to the nearest freeway and the nearest 'first class' main road for cases (n = 49; one extreme value was excluded for better presentation of the figure) and controls (n = 50).

Discussion

There is growing interest in analyzing environmental factors and influences on pregnancy and neonatal outcome [22, 31–33]. According to our findings, women who developed late-onset PE were exposed to significantly higher TRAP in general than women who had early-onset PE. Various studies suggest that a late onset of PE impaired trophoblastic invasion of myometrial arteries and is phenotypically balanced unless predisposing factors will set off a cascade of placental and systemic inflammation [12]. In general, it is thought that early-onset PE involves a placental defect, which is not as evident in late-onset PE. It appears that late-onset PE involved a different inflammatory component [34]. The impaired trophoblastic invasion of the placental bed and the following cascade in the early onset of PE might already determine the severity of the disease, and external factors like TRAP become less obvious. Local air pollution may be an important risk factor for the development of late-onset PE. Epidemiological studies highlighted an association between a steeper increase in arterial blood pressure in pregnancy, an increased risk for pregnancy-induced hypertension, PE and a higher PM₁₀ exposure [22]. Potential pathways

Table 2. Description of fetal characteristics

Fetal characteristics	Case	Control	p value
Number of children, n	53	53	1.00
Sex			0.56
Male	29 (54.7)	25 (47.2)	
Female	24 (45.3)	28 (52.8)	
Gestational age, days	250.47 ± 23.13	279.17 ± 8.64	<0.001
Delivery			<0.001
Preterm	32 (60.3)	0 (0)	
Term	21 (39.7)	50 (100)	
Birth modus			<0.001
Vaginal	12 (22.6)	47 (88.7)	
Cesarean section	41 (77.4)	6 (11.3)	
Birth weight, g	2,362.9 ± 820.1	3,335.9 ± 419.5	<0.001
Length, cm	45.4 ± 3.6	49.7 ± 2.0	<0.001
Transfer to neonatal intensive care unit	26 (49)	0 (0)	

Values represent mean ± SD or n (%).

for a pro-hypertensive effect of air pollution have been suggested to include an increase in sympathetic tone and/or the modulation of basal systemic vascular tone as a result of increased endothelin-1 concentrations as well as

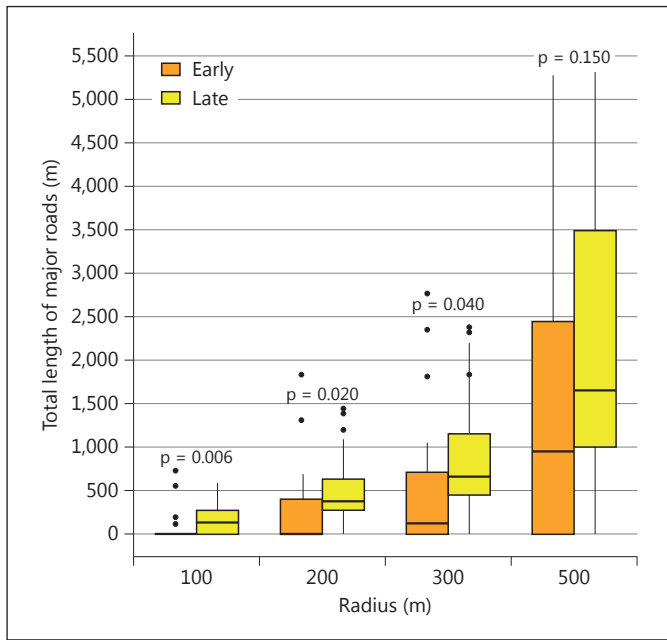


Fig. 3. Total length of major roads around the women's domicile for early- (n = 24) and late-onset (n = 26) preeclampsia cases.

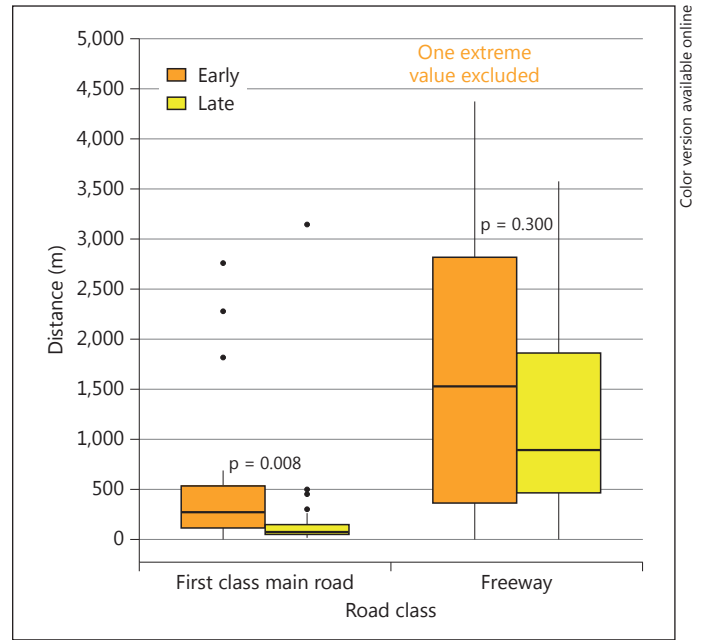


Fig. 4. Distance of the women's domiciles to the nearest freeway and the nearest 'first class' main road for early- (n = 23, one extreme value was excluded for the better presentation of the figure) and late-onset (n = 26) preeclampsia cases.

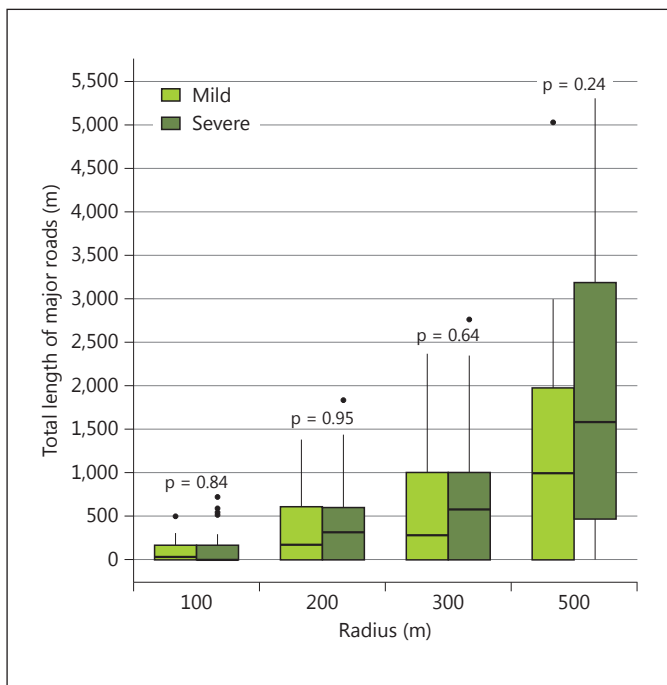


Fig. 5. Total length of major roads around the women's domicile for mild (n = 10) and severe (n = 40) preeclampsia cases.

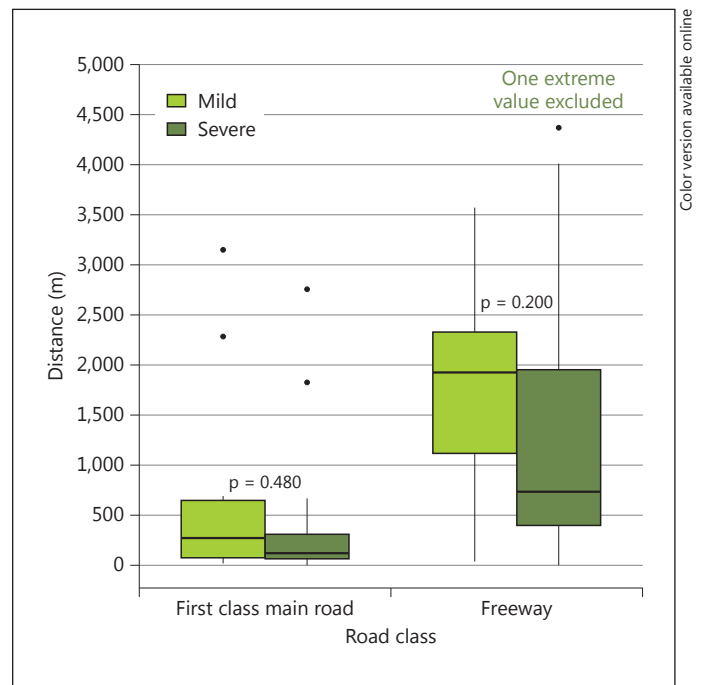


Fig. 6. Distance of the women's domiciles to the nearest freeway and the nearest 'first class' main road for mild (n = 10) and severe (n = 39; one extreme value was excluded for better presentation of the figure) preeclampsia cases.

impairment of nitric oxide-induced vasodilation. Furthermore, exposure to air pollution might result in systemic inflammation, which could predispose to the development of gestational hypertensive disorders [22, 35]. Few studies have investigated PE and gestational hypertension. A California birth cohort study of air pollution investigated PE based on birth certificates and reported positive associations with higher carbon monoxide (CO) and sulfur dioxide (SO₂) exposures during pregnancy [27]. Two further studies conducted in the USA reported an increased risk with ambient CO, PM_{2.5} or NO_x exposures [22, 31]. More recently, Lee et al. [7] reported that exposure to particles, mostly PM_{2.5} and ozone in the first trimester, may increase the risk of developing PE and gestational hypertension. In contrast to these studies, we found no significant association of road density at the women's domicile with an incidence of PE. This may be due to the characteristics of the control group: healthy pregnant women going to the University Hospital have a nearby domicile, i.e. in an urban setting. The larger radiuses (300 and 500 m) may reflect an urban versus rural environment rather than a TRAP coming from a closer source (radiuses 100 – 200 m). Nevertheless, considering previous studies [7, 22, 27, 31], data suggest a detrimental effect of near road density on any onset of PE: the study group showed a higher total length of major roads within the shorter radiuses of 100 and 200 m. The lack of statistical significance might be determined by the relatively small number of study participants or the origin of the participants, which belonged mostly to Caucasians. To our knowledge, one research group from Sweden has also investigated possible associations between PE and air pollution by using road density as a proxy indicator of TRAP [20]. Traffic density within a radius of 200 m has been observed. According to their results, PE was associated with high traffic density, but the odds ratio was not significant. Our results were in agreement with the previous research if we only considered radiuses of 100 and 200 m.

No significant evidence was found for an association of local air pollution with the severity of PE in this study. Nevertheless, a potential association between the occurrence of severe PE cases and higher traffic air pollution could be shown.

The current study provides, for the first time, data and references for the local situation in Switzerland. Instead of birth certificates, we used detailed clinical data with accurate gestational age based on a first ultrasound and maternal parameters, which allowed us to classify the 2 subtypes of PE.

To date, there has only been 1 study reporting on the impact of air pollution on early- and late-onset PE separately [36]. They found the strongest associations observed for late-onset PE in relation to third-trimester exposure to fine particulate pollutants and for early-onset PE.

The present study could replicate a significant difference in exposure to TRAP between early- and late-onset PE. This observation may provide some further indices for the pathogenesis of PE. If the association between air pollution and pregnancy complications represents a causal relation, it would have profound implications for public health, particularly in countries with limited maternal health care.

The retrospective study design bears 2 caveats. First, we did not match for risk factors like hypertension, previous PE or twin pregnancy, which could increase the risk of PE. This could cause bias and has to be considered in the interpretation. Second, since changes of address during pregnancy were not considered in our study, the real duration at the residence of each woman during her pregnancy is actually uncertain. This could be a potential bias for calculating the local air pollution exposure.

The road density is just a proxy for TRAP. However, the roads are the source of TRAP and are the most relevant predictors in the currently most used air pollution models (Land Use Regressions and Dispersion models). The consequence of using a less precise exposure assessment (road density versus NO₂ modelling or measuring) could lead to less power and nonsignificant results. We could show that even by using a far more simple approach to estimate 'traffic-related air pollution' exposure, we found evidence of the effect.

Conclusions

Our study shows that the exposure to TRAP during pregnancy was associated with a significantly increased risk for the development of late-onset PE compared to the early-onset cases. No statistical significance, but a potential association between local air pollution exposure and severity of PE, as well as an association between the occurrence of PE in general and traffic exposure within radiuses of 100 and 200 m, were observed in this study. More prospective studies with more participants are needed to understand local air pollution as a possible risk factor for late-onset PE and its pathogenesis.

If the association between air pollution and late pregnancy complications represents a causal relation, it would have profound implications for public health, particularly in countries with limited maternal health care [20].

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