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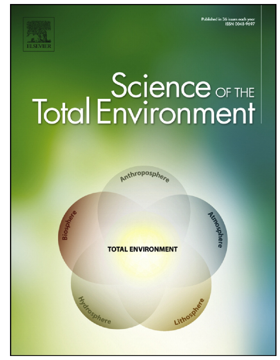

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Associations of residential greenness, traffic noise, and air pollution with birth outcomes across Alpine areas

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Running title: Greenness, noise, air pollution, and birth outcomes in Alpine areas

Abstract

Aim: This explorative study aimed to investigate the association of residential greenness, traffic noise, and air pollution with birth outcomes in several Alpine areas with unique topography.

Methods: We used data from two cross-sectional studies (UIT, n = 573 and BBT, n = 518) in the Tyrol Region (Austria/Italy). Only mothers who had lived in their current residence during the whole pregnancy were included. They completed a questionnaire, and medical records were used to draw data on birth weight, low birth weight (LBW), preterm birth, and small for gestational age (SGA). Normalized Difference Vegetation Index (NDVI) in the year of birth was assigned at the residential address as a measure of greenness. Road/railway traffic noise (L_{dn}) and air pollution (NO_2) were calculated about 10 years after birth and used as surrogates for exposure levels during pregnancy.

Results: In the UIT survey, higher NDVI $_{500\text{-m}}$ was consistently associated with lower odds for LBW and SGA, while an increase of L_{dn} was associated with higher odds for LBW. Other effect estimates were in the expected direction albeit non-significant. In the BBT survey, most findings were inconclusive (for NDVI) or present only in subgroups (for L_{dn} and NO_2).

Conclusion: This study provides inconclusive evidence that the surrounding environment might be associated with birth outcomes in mountainous areas. Given the disparate associations across the study areas, further research in larger representative samples is warranted.

Keywords: birth weight; traffic; green space; pregnancy outcomes; preterm birth

1. Introduction

Birth weight and gestational age at delivery not only have critical importance for early-life mortality (McCormick, 1985; Blencowe et al., 2012), but also affect long-term programming of health and disease (Clark, 1998; Barker, 2007). Besides well-known contributors to adverse birth outcomes, such as genetics, sociodemographics, and lifestyle (Goldenberg et al., 2008; Savitz & Murnane, 2010; Kim & Saada 2013), there is increasing recognition that the surrounding environment also takes its toll on intrauterine growth and development (Nieuwenhuijsen et al., 2013). Residential greenness (overall vegetation level, including street trees and parks) is regarded as a protective feature of the residential environment owing to its potential to mitigate noise and air pollution, reduce stress, support recovery from day-to-day stressors, and promote outdoor physical activity and social interaction (Markevych et al., 2017). A meta-analysis found a positive relationship between greenness in the mother's living environment and birth weight (Dzhambov et al., 2014). Recent years have seen growing interest in beneficial effects of greenness on birth outcomes (Grazuleviciene et al., 2015; Casey et al., 2016; Ebisu et al., 2016; Abelt & McLafferty, 2017; Nichani et al., 2017; Cusack et al., 2018; Agay-Shay et al., 2018; Fong et al., 2018; Glazer et al., 2018). For instance, earlier research (e.g., Markevych et al., 2014; Hystad et al., 2014; Agay-Shay et al., 2014; Cusack et al., 2018) indicated an increase of birth weight of about 20 g per interquartile range increase of greenness, with the largest impact of + 40 g found in Canada (Cusack et al., 2018). In addition, a meta-analysis reported some 20% lower odds for small for gestational age (SGA; birth weight below the 10^{th} percentile) in high green areas (Twohig-Bennett & Jones, 2018).

Recently, a comprehensive study on the influence of the urban exposome on birth weight (Nieuwenhuijsen et al., 2019) evaluated multiple environmental exposures simultaneously and indicated consistent associations between increasing greenness exposure and increased birth weight and decreased low birth weight (LBW; birth weight less than 2500 g) risk. Surprisingly however, only a handful of other greenness studies have considered traffic noise (e.g., Markevych et al., 2014; Hystad et al., 2014; Dadvand et al., 2014a; Cusack et al., 2018) and air pollution (e.g., Ebisu et al., 2016; Dadvand et al., 2014a; Cusack et al., 2018) as co-exposures. Some air pollutants can cross the pulmonary epithelium entering the circulation, and thus, promote systemic inflammatory responses and oxidative stress, leading to placental dysfunction and restricted fetal growth (for an overview of mechanisms see Sapkota et al., 2012; Lamichhane et al., 2015; Sun et al., 2016). The biological mechanisms underlying the effect of traffic noise involve neuroendocrine stress reaction in the maternal organism, which in turn may disrupt normal placental function, affect the hypothalamic-pituitary-adrenal axis of the fetus, and thereby lead to adverse pregnancy outcomes (e.g., Dzhambov et al., 2014b; Nieuwenhuijsen et al., 2017). Understanding the interplay between these spatially correlated exposures is essential for planning healthy settlements (Brauer & Hystad, 2014).

Another caveat is that most previous research (Dzhambov et al., 2014a; Twohig-Bennett & Jones, 2018) was undertaken in highly urbanized areas, which means that the findings cannot be directly extrapolated to settings where the spatial relationships between traffic emissions and greenness differ. Casey et al. (2016), for example, observed beneficial effects of greenness in urbanized areas, while in less urban communities with higher levels of greenness, additional greenness did not appear beneficial. Conversely, Nichani et al. (2017) found no evidence of effect modification by residential rurality. In addition to urbanicity, terrain features, such as steepness and altitude, may confound or modify the effects during pregnancy. For instance, higher altitude has been linked to intrauterine growth retardation and a subsequent reduction in birth weight (Yip, 1987; Waldhoer & Klebermass-Schrehof, 2015), while living in a hilly area may increase physical activity and protect of diabetes (Villanueva et al., 2013; Fujiwara et al., 2017), thereby supporting normal birth weight (Kc et al., 2015). No previous study has accounted for these factors though.

In the present explorative study, we had a unique opportunity to investigate the association of residential greenness, traffic noise, and air pollution with birth outcomes in several Alpine areas. The Alps cover 190 959 km^2 and are home to 14 million Europeans (Onida, 2009). Because of the idiosyncratic topography of the region, previous findings may not apply to children born there. Furthermore, given their landform, natural ventilation, and transport infrastructure, some valleys are characterized by temperature inversions and propagation of sound waves over great distances which can lead to higher levels of air pollution and noise (Heimann et al., 2007). Hence, undertaking a study in this geographic context will help advance the literature on the subject by expanding earlier research.

2. Material and methods

2.1. Study area

The present study takes advantage of data originally collected to assess relationships between environmental quality and children's well-being within the framework of two epidemiological studies in the Tyrol Region – the UIT survey (conducted in the Lower Inn valley, Unterinntal, in Austria) and the BBT survey (conducted in the Wipp valley, Wipptal, and its side valleys on both sides of the Brenner pass in Austria and Italy). The BBT study area partially overlaps with the UIT area. (See Figure 1) Both valleys are part of the most important access route for heavy goods traffic over the Brenner Pass, which links central and northern Europe's traffic to southern Europe. Both areas are surrounded by natural landscapes of renowned scenic beauty (von Lindern et al., 2016). The settlements consist of densely populated small towns and villages with a mix of industrial, small business, touristic, and agricultural activities (von Lindern et al., 2016; Dzhambov et al., 2018a). Main transportation lines (a highway and a railway) run through the valleys, with main roads connecting to the various small villages causing high levels of noise (Lercher et al., 2008; Lercher & Botteldooren, 2006; von Lindern et al., 2016)

The UIT survey site extends about 40 km east of Innsbruck towards the Austrian-German border across a relatively broad U-shaped valley floor and up to the foothills of the Alpine comb. The area is characterized by a combination of high levels of air pollution and traffic noise (Lercher et al., 1995; Lercher & Kofler, 1996; Heimann et al., 2007). The narrow V-shaped Wipp valley extends along the river Sill southward from Innsbruck up to the Brenner Pass at the Austro-Italian border. South of the border the valley stretches along the river Isarco down to Fortezza in Italy. Owing to differences in meteorology (stronger winds versus a lot of temperature inversions) and topography (north-south versus east-west), air pollution levels in the Wipp valley are considerably lower than in the Lower Inn valley.

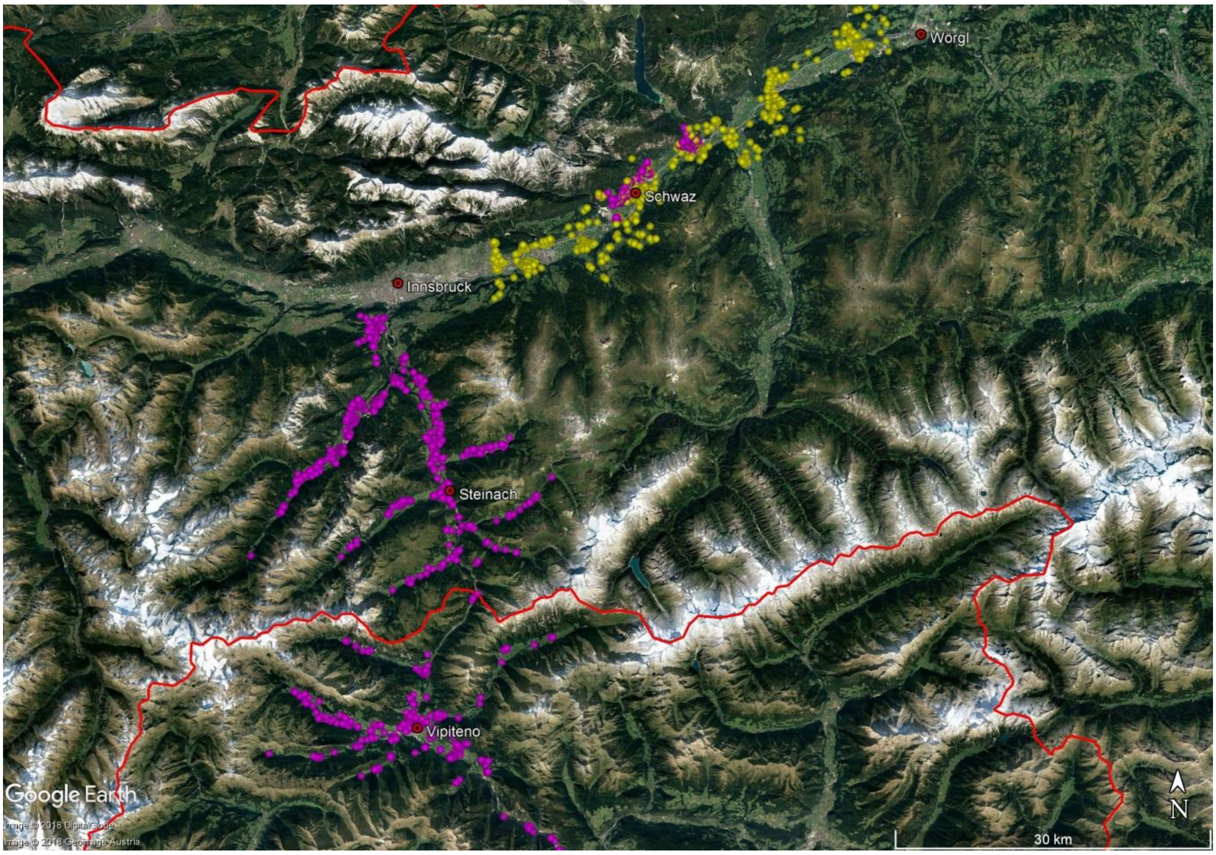

Figure 1. Participants' home addresses in the UIT (yellow dots) and BBT (purple dots) survey areas. Note. The red lines are the Austrian-German (north) and Austrian-Italian (south) borders.

2.2. Study design

We used data from two cross-sectional studies. The UIT survey was undertaken in June 1998 including a total of 1280 children recruited from 26 local schools (grades 3 – 4) in the Lower Inn valley, with a response rate of 79.5% (Evans et al., 2002; Lercher et al., 2002; Lercher et al., 2000; Lercher et al., 2013b). The BBT survey included complete records of 1251 children (response rate = 85.5%) in the same age group recruited in 2004/2005 from 49 schools in the Wipp valley around the Brenner Pass (Lercher et al., 2013a). In the BBT survey, participants from the side valleys were only exposed to main roads. The participants residing in the main valley and the subsample from the Lower Inn valley experienced exposure from more than one traffic source. In both surveys, children's mothers completed a nearly identical self-administered, standardized questionnaire which asked about sociodemographic information, lifestyle, perinatal data, housing, and duration of residence at the current address. Pregnancy-related data for the Austrian sample were taken from the so-called "Mother and Child Passport" (Mutter-Kind-Pass), an official record where the examining physician enters the findings (Bancher-Todesca, 2014). For the sample from the southern Tyrolean area (Alto Adige) equivalent data were available from the "Mother Passport". The mothers or legal guardians of all participants provided written informed consent.

In order to reduce exposure misclassification, the present study was limited (except for one of the sensitivity analyses) to children born to mothers who had lived in their current residence during the whole pregnancy; this was determined by adding nine months to the current age of the child at the time of the survey and subtracting that sum from the duration of residence reported by the mother: duration of residence in years – (age of child in years + 0.75). We also excluded all cases for which the exact address could not be geocoded. This resulted in final analysis samples of 573 (UIT survey) and 518 (BBT survey). (See Figure 2)

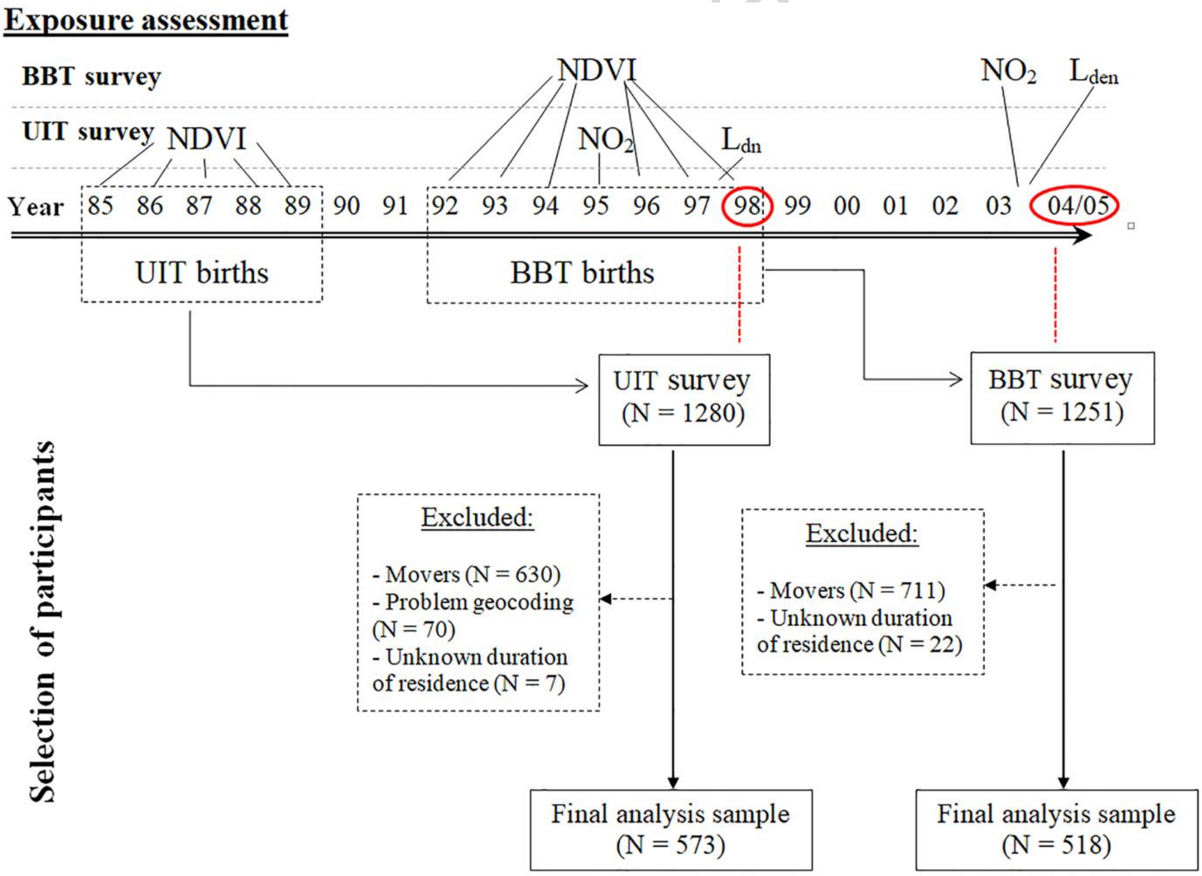

Figure 2. Flow chart of the study design and participation in the UIT and BBT surveys. Note. L_{den} – day-evening-night noise levels, L_{dn} – day-night noise levels, NDVI – Normalized Difference Vegetation Index, NO_2 – nitrogen dioxide.

Comparison between characteristics of those who lived at the residence since the time of conception and pregnancy and those who moved in later (movers and non-movers) indicated some differences (Table S1). In both surveys, non-movers were older and multiparous more often, were more likely to live in a single family home and less likely to be smokers. In the UIT survey, the prevalence of single mothers and SGA was higher in movers. In the BBT survey, the prevalence of LBW was somewhat higher in non-movers. Other statistically significant differences were materially small.

2.3. Birth outcomes assessment

Prenatal and perinatal data were drawn from doctor's entries in the Mutter-Kind-Pass which every pregnant woman in Austria receives. In the southern BBT area in Italy (Alto Adige) which has close relations to Austria, the equivalent "Mutterpass" was available. The two primary outcomes were birth weight and LBW (defined as weight less than 2500 g). We also considered preterm birth (birth before the 37th gestational week) and small for gestational age (SGA) (birth weight below the 10th percentile for the gestational age in Tyrol).

2.4. Greenness, traffic noise, and air pollution assessment

Following previous studies (Dzhambov et al., 2014a) and because of unavailability of detailed land use/cover maps dating back before the year 2000, we employed the Normalized Difference Vegetation Index (NDVI; Tucker, 1979) as a proxy for overall vegetation level. It ranges from -1 to +1, where positive values closer to 1 indicate high greenness (Gascon et al., 2016). NDVI was calculated based on the difference of surface reflectance in two vegetationinformative wavelengths – visible red and near infrared light. We assigned NDVI to each mother based on the year of delivery. For these calculations, we used single 30 m x 30 m resolution Landsat 4 – 5 Thematic Mapper (https://earthexplorer.usgs.gov/) satellite images obtained in July – August in each year in the period 1985 to 1989 for in the UIT survey and 1992 to 1998 for the BBT survey. We selected summertime images because summer is the time when variance in NDVI is the highest, whereas during other seasons the area is partially covered with snow. We used the same satellite image for all children born in the respective year. NDVI was calculated as mean values in circular buffers of 100 m, 300 m, 500 m, and 1000 m around the residential address. Prior to calculations of NDVI, we removed all water pixels from the satellite images by using the Open Street Maps water layer (Gascon et al., 2018; Dzhambov et al., 2018a). Owing to previously reported spatial clustering of water bodies (rivers) and traffic lines in the area (Dzhambov et al., 2018a), blue space was not considered as a separate exposure. In line with a previous study in Bavaria (Markevych et al., 2014) which found most consistent associations for the 500-m buffer, we considered $NDVI_{500\text{-m}}$ for the main analyses; however, we also report sensitivity analyses with the other buffers.

We only had data on traffic noise and air pollution calculated about 10 years after birth, therefore, they were used as surrogates for exposure levels during pregnancy. For the UIT survey, the three major noise sources (highway, railway, and local main roads) were modelled in 1997 – 1998 at a resolution of 25 m x 25 m and source-specific and total day-night noise levels (L_{dn}) were calculated for each respondent. Nitrogen dioxide (NO_2) served as a proxy for annual average traffic-related air pollution in 1995 and was calculated at a resolution of 100 m x 100 m using an adapted Gaussian propagation model procedure considering the meteorological and topographic specifics of the study area. Results were calibrated against measurements and corrected where needed (Thudium et al., 2000; Wotawa et al., 2000; Lercher et al., 2014).

In the BBT survey, noise emissions were calculated in 2003/2004. Because railways are absent in the side valleys, road and railway traffic were not considered as separate noise sources. Total day-evening-night noise level (L_{den}) was calculated at the most exposed façade, reflecting only road traffic noise for residents of the side-valleys and combined road traffic and railway noise for those living in the Wipp valley. (Given the high correlation between the two noise indicators and that using a linear conversion term to convert them to a uniform metric (e.g., L_{dn} to L_{den}) would not change the linear associations with other variables (cf. Brink et al., 2018), to minimize confusion henceforth L_{dn} will denote L_{den} when referring to noise levels in the BBT survey.) Annual means for NO_2 were calculated in 2003/2004 at 10 x 10 m² resolution along the Wipp valley and for the Lower Inn valley area east of Innsbruck. Calculations were supplemented with additional traffic counting and micro-simulations and evaluated against measurements. A full outline of the noise and air pollution modelling campaigns in the UIT and BBT surveys is provided in Supplementary Section S1.

2.5. Covariates

Potential confounders and effect modifiers were selected based on theory and literature precedent (Gehring et al., 2014; Dadvand et al., 2014a; Markevych et al., 2014; Smith et al., 2017). Mother's education was categorized in four groups (Basic – 9 years of school, Skilled labor, Vocational, or A-level). Smoking during pregnancy was included as a dichotomous factor (no vs yes). House type was used as another indicator of socioeconomic status and classified as Single family detached house, Row house, or Multiple dwellings. Duration of residence before conception was also considered.

Mothers reported on children's data. Other biological variables elicited from the Mutter-Kind-Pass are maternal age at birth, child's sex, and birth order. In the UIT survey, we had information on single mother status.

As we anticipated that season of pregnancy may influence the amount of time spent outdoors by the mothers and thus their exposure to greenness, noise, and air pollution, we defined this variable as the number of green months (April to September) during the whole pregnancy and the last trimester. Altitude and slope (steepness of terrain) were considered in light of evidence that they may relate to exposure levels (i.e., less traffic at higher altitudes) and birth weight. Hilliness (steepness) was defined as the average slope (ranging 0 to 90 degrees) of the terrain in the 500-m buffer.

2.6. Statistical analysis

Given the systematic differences between the two survey areas in terms of environmental conditions and year of deliveries and that the BBT area partially overlaps with the UIT area, we decided to analyze the two samples separately. Because less than ≈ 5 – 6% of values were missing from most of the variables, those values were imputed using the expectation-maximization algorithm (Dempster et al., 1977). Notably, missing values in noise and air pollution were only imputed if other geographic variables (e.g., NDVI, distance to traffic lines) were available.

First, we analyzed Spearman correlations (r_s), t-tests, ANOVAs, and Fisher's exact tests (depending on the distributions) to identify general patterns of association in the data. Prior to the multivariate analyses, the linearity of the shape of relationships between NDVI $_{500\text{-m}}$, L_{dn}, and NO_2 and birth outcomes was tested using restricted cubic splines with four knots at the 5^{th}, 35^{th}, 65^{th}, and 95^{th} percentiles (Orsini, 2009) and no deviation from linearity was detected. Thus, we employed multivariate linear regression models to investigate the association between continuous environmental exposures and continuously-measured birth weight, and multivariate logistic regression models for LBW, preterm birth, and SGA. These models did not suffer from multicollinearity according to tolerance (> 0.2) and Variance Inflation Factor (< 5) values. Effect estimates of NDVI, L_{dn}, and NO_2 are reported per interquartile range, 10 dB, and 10 μg/m^3 increase, respectively.

Several factors were tested as potential modifiers of the association between the exposures and birth weight. First, duration of residence represents exposure before conception that could have impacted maternal health and the pregnancy. Preterm birth and birth order were considered because preterm babies may be particularly vulnerable to environmental stressors and increasing birth order is associated with increasing birth weight. Single mother status and mother's education were indicators of socioeconomic position. Green months during pregnancy and third trimester could account for the time spent outdoors. Interactions between the three exposures were also of interest. Finally, higher altitude could restrict fetal growth. We conducted moderation analysis using the PROCESS v. 2. 16 macro for SPSS (Hayes, 2013). In addition to computing interaction terms between the exposure variable and the potential modifier to determine the presence of effect modification, the effect size estimate of the exposure was estimated across categories of the categorical modifiers and as a function of the continuous modifiers (displayed at percentile values along their distribution).

In a series of sensitivity analyses, we tested the robustness of our findings for LBW and birth weight. First, the models were repeated on all UIT and BBT mothers (movers and non-movers), hypothesizing that associations would be attenuated due to exposure misclassification. Second, the models were additionally individually adjusted for slope and altitude which could account for different spatial correlations among the exposures. Next, we adjusted for birth order. In another model, we adjusted for season of birth (Markevych et al., 2014). Then, instead of using greenness based on the year of delivery, we tested the models with NDVI calculated for an arbitrary single year (1985 for the UIT survey and 1992 for the BBT survey) to allow comparison with other studies (cf. Dzhambov et al., 2014a) that typically use single-year satellite images close to the study period to calculate surrounding greenness. Finally, because of relevant differences in the prevalence of perinatal indicators and air pollution across the BBT region, sensitivity analyses were conducted with models limited to mothers residing in the Lower Inn valley and Main valley north/Side valley north regions (in Austria), which would not differ in terms of health care compared with the southern Wipp valley (in Italy).

Results were considered statistically significant at the $p < 0.05$ level (two-tailed). Statistical analyses were conducted with SPSS v. 21 (Armonk, NY: IBM Corp.), except for the non-linear modeling which was done in Stata v. 13 (College Station, TX: StataCorp LP.).

3. Results

3.1. Characteristics of the UIT and BBT samples and bivariate associations

Characteristics of the UIT and BBT participants are presented in Table 1. Table S2 shows the distributions of the continuous variables. The two samples had some notable differences. The BBT area had a higher prevalence of LBW and SGA. Altitude and slope were greater than in the UIT survey. The most pronounced difference was in the air pollution levels. Figure S1 and Table S3 show that participants in the BBT survey (except for those living in the Lower Inn valley) were exposed to considerably lower air pollution than in the UIT survey. In addition, NDVI $_{500\text{-m}}$ was stronger correlated with L_{dn} (r_s = -0.42) and NO_2 (r_s = -0.58) in the UIT survey than in the BBT survey (r_s = -0.23 and -0.48, respectively); the same applies to the correlation between L_{dn} and NO_2 (r_s = 0.69 vs 0.50).

Table S4 shows a comparison of participant characteristics with all singleton hospital deliveries in the state of Tyrol, Austria in women 25 years or older (Mutz-Dehbalaie et al., 2014). Although the available official data do not match fully our samples in terms of time and maternal age, birth weight was in the same range, while the other perinatal indicators (LBW, preterm, SGA) varied more, but within the observed range of small area statistics reported in the literature (Thompson et al., 2005)

Supplemental Tables S5 – S8 show results from the tests of the bivariate associations between participants' characteristics and birth outcomes. Briefly, birth weight was positively related to male sex, higher birth order, and older age of the mother. In line with observations in previous literature, higher greenness was associated with lower levels of traffic noise and air pollution, higher altitude, and steeper terrain.

Table 1. Participant characteristics in the UIT and BBT surveys

Characteristic	UIT survey (N = 573)	BBT survey (N = 518)
Maternal and pregnancy factors		
Maternal age (mean years, SD)	28.52 (4.77)	30.07 (4.60)
Male child (n, %)	290 (50.61)	262 (50.58)
Single mother (n, %)*	27 (4.71)	-
Smoking during pregnancy (n, %)	45 (7.85)	49 (9.46)
Mother's education (n, %)		
Basic	147 (25.65)	130 (25.10)
Skilled labor	188 (32.81)	168 (32.43)
Vocational	148 (25.83)	128 (24.71)
A-level	90 (15.71)	92 (17.76)
Birth order (n, %)		

1st	194 (33.86)	145 (27.99)
2nd	229 (39.97)	236 (45.56)
3rd	99 (17.28)	98 (18.92)
≥ 4th	51 (8.90)	39 (7.53)
Birth outcomes		
Birth weight (mean grams, SD)	3384.99 (528.76)	3221.72 (564.71)
Low birth weight (n, %)	26 (4.54)	53 (10.23)
Preterm birth (n, %)	81 (14.14)	64 (12.36)
Small for gestational age (n, %)	22 (3.84)	34 (6.56)
Housing		
Duration of residence (median years, SD)	4.00 (6.00)	3.76 (5.24)
House type (n, %)		
Single family detached	401 (69.98)	383 (73.94)
Row house	103 (17.97)	61 (11.78)
Multiple dwelling	69 (12.04)	74 (14.29)
Environmental factors		
$NDVI_{100\text{-m}}$ (median, IQR)	0.67 (0.16)	0.59 (0.14)
$NDVI_{300\text{-m}}$ (median, IQR)	0.67 (0.14)	0.64 (0.11)
$NDVI_{500\text{-m}}$ (median, IQR)	0.68 (0.11)	0.66 (0.09)
$NDVI_{1\text{-km}}$ (median, IQR)	0.70 (0.09)	0.67 (0.07)
$L_{dn\ total}$ (median dB, IQR)	52.26 (10.64)	52.53 (14.39)
$L_{dn\ main\ road}$ (median dB, IQR)	46.36 (13.80)	49.66 (14.30)
$L_{dn\ railway}$ (median dB, IQR)**	49.88 (10.32)	-
NO_2 (median μg/m^3, IQR)	31.23 (6.87)	12.32 (9.92)

Green months pregnancy (median, IQR)	5 (3.00)	5 (3.00)
Green months 3rd trimester (median, IQR)	1 (3.00)	1 (3.00)
Altitude (median meters, IQR)	560.28 (78.15)	987.50 (214.00)
Slope $_{500\text{-m}}$ (median degrees, IQR)	8.42 (9.18)	15.14 (9.01)

Note. IQR – interquartile range, LBW – low birth weight, L_{dn} – day-night noise levels, NDVI – Normalized Difference Vegetation Index, NO_2 – nitrogen dioxide, SD – standard deviation. *Data on this factor were available only in one of the surveys. **Not comparable: no railways in the side valleys (only main roads).

3.2. Associations between greenness, traffic noise, air pollution and birth outcomes

There were differences in associations between exposure variables and birth outcomes across the study areas (Table 2). (See Table S9 for the crude models) In the UIT survey, the single exposure models indicated that higher NDVI $_{500\text{-m}}$ was associated with lower odds for LBW and with higher birth weight (borderline). This trend was also observed for the other buffers and for SGA (Table S10). Conversely, increase of L_{dn} from all considered sources was associated with higher odds for LBW. Associations with NO_2 were in the same direction as with noise but non-significant. In the two-exposure models, further adjustment for total L_{dn} attenuated the association for NDVI $_{500\text{-m}}$, and the association between NO_2 and LBW was reduced after controlling for L_{dn}.

In the BBT survey, the associations of NDVI and L_{dn} with birth weight and LBW were in the expected direction but with wide confidence intervals including 0 and 1, respectively. Still, when adjusted for NO_2, L_{dn} was associated with lower birth weight. Unexpectedly, we observed lower odds for SGA in relation with higher L_{dn}.

3.3. Effect modification

Results of the effect modification analyses are shown in Supplementary Tables S11-S13. In the UIT survey, the association of NDVI $_{500\text{-m}}$ with birth weight was more pronounced in first born babies and when air pollution was low. No effect modification was observed for L_{dn}. For NO_2, the association was more pronounced in first born babies and mothers living with a partner. We saw borderline interactions between L_{dn} and NO_2 – inverse associations with birth weight were only seen when the other exposure was low.

In the BBT survey, NDVI $_{500\text{-m}}$ was stronger associated with higher birth weight as altitude increased. L_{dn} was related to lower birth weight in preterm babies (β = -140.57 g; 95% CI: -260.51, -20.63), as was NO_2 (β = -168.45 g; 95% CI: -321.66, -15.25).

3.4. Sensitivity analyses

Table S14 shows results of the sensitivity analyses. When all mothers (non-movers and those who moved after delivery) were included, the effects in the UIT survey were considerably reduced. Adjusting for slope considerably enhanced the observed associations for NDVI $_{500\text{-m}}$, L_{dn}, and NO_2 in the UIT survey. Adjusting for altitude, birth order or season of birth, or using NDVI calculated for a single year did not substantively change the associations. Of note, when we limited the analysis to residents of the northern (Austrian) BBT subregion, higher L_{dn} was stronger associated with lower birth weight (β = -62.47 g; 95% CI: -115.52, -9.41).

Table 2. Multivariate associations between greenness, traffic noise, and air pollution and primary birth outcomes

	UIT survey (N = 573)		BBT survey (N = 518)	
	LBW	**Birth weight**	**LBW**	**Birth weight**
	OR (95% CI)	**β (95% CI)**	**OR (95% CI)**	**β (95% CI)**
Single-exposure models				
NDVI $_{500\text{-m}}$	0.52 (0.30, 0.89)*	54.11 (-3.58, 111.79)	0.77 (0.51, 1.16)	10.08 (-41.19, 61.35)
$L_{dn\ total}$	2.03 (1.16, 3.54)*	-17.63 (-71.77, 36.51)	0.96 (0.66, 1.39)	-35.45 (-73.43, 2.53)
$L_{dn\ road}$	1.76 (1.03, 3.00)*	-5.50 (-54.58, 43.58)	0.90 (0.61, 1.32)	-31.49 (-72.80, 9.82)
$L_{dn\ railway}$	1.93 (1.11, 3.33)*	-11.96 (-67.55, 43.64)	-	-
NO_2	2.04 (0.87, 4.79)	-31.37 (-103.62, 40.88)	1.06 (0.68, 1.65)	11.56 (-33.91, 57.03)
Two-exposure models				
NDVI $_{500\text{-m}}$ (+ $L_{dn\ total}$)	0.62 (0.34, 1.13)	55.80 (-7.97, 119.57)	0.76 (0.50, 1.15)	2.11 (-49.75, 53.96)
NDVI $_{500\text{-m}}$ (+ NO_2)	0.57 (0.31, 1.05)	54.76 (-11.49, 121.00)	0.75 (0.48, 1.17)	17.76 (-37.79, 73.32)
$L_{dn\ total}$ (+ NO_2)	1.99 (0.95, 4.17)	-2.59 (-77.65, 72.48)	0.93 (0.61, 1.40)	-47.05 (-88.49, -5.60)*
NO_2 (+ $L_{dn\ total}$)	1.04 (0.34, 3.21)	-28.98 (-129.18, 71.22)	1.10 (0.67, 1.81)	34.26 (-15.22, 83.73)

Note. LBW – low birth weight, L_{dn} – day-night noise levels, NDVI – Normalized Difference Vegetation Index, NO_2 – nitrogen dioxide. The UIT models are adjusted for: sex of child, age of mother at birth, gestational age, single mother status, mother's education, smoking during pregnancy, duration of residence before conception, and house type. The BBT models are adjusted for: sex of child, age of mother at birth, gestational age, mother's education, smoking during pregnancy, duration of residence before conception, and house type. As indicated, the two-exposure models are additionally adjusted for L_{dn} or NO_2. Coefficients are odds ratios (OR) or unstandardized linear regression coefficients (β) with their 95% confidence intervals. Effect estimates of NDVI, L_{dn}, and NO_2 are reported per interquartile range, 10 dB, and 10 μg/m^3 increase, respectively. *Coefficient is statistically significant at $p < 0.05$.

4. Discussion

4.1. General findings

In the present study, we investigated the associations of greenness, traffic noise, and air pollution with birth outcomes in several Alpine areas with unique geographic features. Surprisingly, we saw contrast across the study areas. In the Lower Inn valley, there were consistent negative associations between greenness and LBW and SGA in all buffers, and noise was associated with higher odds for LBW. Conversely, in the BBT survey, most findings were inconclusive (for NDVI) or present only in subgroups (for L_{dn} and NO_2).

There are a number of possible reasons for this discrepancy. The most apparent difference between the study areas is the much higher air pollution levels in the Lower Inn valley (Figure S1). However, greenness in the UIT survey was associated with higher birth weight only when air pollution was low. Readers should be mindful that although we did not detect multicollinearity in the models, the three exposures were moderately-to-highly correlated; therefore, interpretation of two-way interactions needs cautious.

Another noteworthy difference between the surveys is the higher prevalence of perinatal outcomes (LBW and SGA) in the BBT area which may reflect other confounding/modifying factors unaccounted for, such as healthcare. Compared with official data for the state of Tyrol (Mutz-Dehbalaie et al., 2014), the UIT sample had closer prevalence of LBW and SGA.

Another interpretation of the inconsistent findings in the BBT survey could be structural confounding (systemic differences in covariates related to both the exposure and the outcome across communities) in the data, as reported by Casey et al. (2016) previously. The BBT villages are smaller than the UIT villages, and the relationship between socioeconomic position and residential location differs from village to village depending on the residential layout. We reckon that the higher geographic heterogeneity of the BBT area, including the

Wipp valley, Inn valley, and several side valleys, coupled with heterogeneity in prevalence of birth outcomes, might have contributed to a greater overdispersion in the data, which might have translated into larger standard errors of some estimates making them less precise and not reaching statistical significance. We are also mindful of the temporal difference between the two surveys that could explain part of the differences in the results. Unfortunately, at this point we cannot offer a straightforward explanation of our findings.

Our results for greenness with the UIT survey are consistent with precedent. Several studies summarized in recent systematic reviews (Dzhambov et al., 2014a; Banay et al., 2017; Twohig-Bennett & Jones, 2018) indicated that higher residential greenness is associated with higher birth weight/lower risk for LBW and SGA. Compared with many previous studies where only small effect sizes were found (cf. Dzhambov et al., 2014a; Banay et al., 2017), the effect sizes in our surveys were larger. This could be due to the high level of greenness compared with other study sites; however, we cannot rule out that residual confounding may be at play here. According to Casey et al. (2016), in less urban communities with higher levels of greenness additional greenness did not appear beneficial.

Traffic noise was associated with higher risk for LBW in the UIT survey, while in the BBT survey this association was weaker and observed when noise was adjusted for air pollution and in subgroups. In line with Cusack et al. (2018), adjusting for noise and air pollution did not appreciably reduce the impact of greenness in the UIT survey. The recent WHO review on traffic noise and birth outcomes found few studies and low quality evidence that traffic noise leads to LBW, preterm birth, and SGA (Nieuwenhuijsen et al., 2017). In general, the evidence is mixed, with some studies pointing to an increased risk (e.g., Gehring et al.; 2014; Díaz et al., 2016; Arroyo et al., 2016), whereas others were not supportive of such associations (e.g., Barba-Vasseur et al., 2017; Dadvand et al., 2014a; Wallas et al., 2019). In the UIT survey, we evidenced associations for both road traffic and railway noise.

Nieuwenhuijsen et al. (2017) pointed out the need for studies on different sources of noise, but to our knowledge, only a few earlier studies (Gehring et al.; 2014; Hjortebjerg et al., 2016; Hystad et al., 2014; Cusack et al., 2018) have considered combined exposure to road and railway traffic noise. Gehring et al. (2014) reported a 19 g (95% CI: - 23, - 15) decrease of term birth weight for every 6-dB increase in road traffic noise exposure and similar estimates for combined road, aircraft, and railway noise. Using the same data, Hystad et al. (2014) found that total noise exposure was also associated with small for gestational age. Hjortebjerg et al. (2016), conversely, did not observe an association of noise with newborn's size indicators.

The evidence from air pollution studies is larger and more convincing. A comprehensive meta-analysis of 14 population-based mother-child cohorts indicated 9% higher odds of term LBW for 10 $\mu g/m^3$ increase of NO_2 (Pedersen et al., 2013). Another meta-analysis yielded a decrease in birth weight of 28.1g per 20 ppb NO_2 (Stieb et al., 2012). In the present study, no consistent associations were observed for NO_2 – in the UIT models, the estimates had the expected sign albeit they were non-significant, but in the BBT survey, such association was observed only in preterm babies. The effect modification by preterm birth in the BBT survey is in line with the conjecture that preterm babies may be particularly vulnerable – environmental stressors may be stronger associated with fetal growth restriction during developmental periods before the 37th gestational week (Iñiguez et al., 2012; Wu et al., 2018), whereas infants who have reached full maturity may have had time to “catch-up” on weight gain, thus, partially offsetting the adverse environmental influences. However, this could also be a statistical artefact.

Ours is one of the few attempts to disentangle the interplay of traffic noise and air pollution (cf. Gehring et al.; 2014; Hystad et al., 2014; Hjortebjerg et al., 2016; Smith et al., 2017; Nieuwenhuijsen et al., 2019). For instance, in a population-based cohort study in

London, an increase in NO_2 was associated with 3% increased odds for term LBW and 1% increased odds for term SGA (Smith et al., 2017), while the effect of road traffic noise was strongly attenuated when adjusted for primary traffic-related air pollutants. According to Hjortebjerg et al. (2016), traffic noise was not related to newborn's size at birth in Denmark, whilst in Canada (Gehring et al., 2014), joint air pollution-noise models revealed that associations between noise and term birth weight were robust to adjustment for air pollution but not the other way around. Our findings are suggestive of some interaction between noise and air pollution in the UIT survey. It stands to reason that the interplay between the exposures is complex and area-specific.

4.2. Strengths and limitations

The present study has several novel features. First, the Alpine region is a unique setting which differs from settings of previously reported studies. Residents of the Lower Inn and Wipp valleys are surrounded by rich natural landscapes with high aesthetic value and recreational potential, but at the same time, exposed to high levels of traffic immissions due to transit traffic. Looking into the relationships of greenness, noise, and air pollution with perinatal outcomes is another strength. In addition, this study relied on high-quality biomedical and environmental data. With some exceptions (e.g., Casey et al., 2016; Cusack et al., 2018; Agay-Shay et al., 2018; Fong et al., 2018), other studies typically used single-year satellite images close to the study period to calculate surrounding greenness, while we relied on measures based on the year of delivery. We also employed state-of-the-art noise and air pollution modeling tailored to the Alpine region which was of higher quality and precision compared with other population-based studies (cf. Nieuwenhuijsen et al., 2017). Moreover, before us only a few studies have reported effects of different noise sources on birth outcomes. The availability of extensive data on biological, housing, and environmental covariates factors is another strength. For instance, residential history before conception is typically not available when large obstetric databases with limited personal information are used.

We also recognize several limitations of the current study. The sample sizes were modest which could explain some null findings despite trends in associations in the expected direction. Lack of statistical power and temporal mismatch of environmental variables prevented us from conducting mediation analyses. Concerns about raising type II error prevented us from controlling for the increase in familywise error across the reported statistical analyses (Rothman et al., 1990; Perneger, 1998). For example, results of the modification analyses could suffer from inflated type I error rate. Furthermore, excluding mothers whose address at the time of pregnancy was unknown could have resulted in residual self-selection bias and undermined the representativeness of the reduced analysis samples. Half of the mothers were excluded because they did not live at the same address during the whole pregnancy. This potential bias could be differential, and we have no way of refuting that.

In terms of exposure assessment, noise and air pollution levels were originally calculated for the year of the surveys, that is, about 9 – 10 years after children's birth. This inherent design feature could not be overcome. Traffic volume has steadily increased in the period 1995 – 2005 in most segments, with some 20 – 30% along the Inn valley study area and 30 – 40% across the BBT area (Tirol Atlas, 2018) (See Figure S2). This gives us reason to suggest that it increased in a homogeneous manner possibly preserving spatial contrasts in traffic immissions. In addition, previous literature indicates long-term validity of air pollution land use regression models in the Netherlands and Canada (Eeftens et al., 2011; Wang et al., 2013). However, no such local data were available for each participant dwelling and we could not confirm that the increase of traffic was the same in smaller road segments; therefore, point estimates could have gone any direction. A further limitation is that we assigned annual mean air pollution to each pregnant woman's address, rather than using time-varying season-specific NO_2. We attempted to address the seasonal variation in air pollution exposure patterns by adjusting the air pollution models for season, and that did not materially change the estimates.

We relied on a single summertime satellite image for calculating NDVI in the birth year guided by the proposition that vegetation contrasts during same season are fairly stable over years (Fuertes et al., 2016). However, the spatiotemporal uncertainties in this greenness measure may be area-specific and have not been confirmed in the study area (cf. Helbich, 2019). We were also unable to explore critical or sensitive exposure windows during pregnancy (trimester-specific greenness).

Because the major traffic lines in the area mostly follow the course of the rivers Inn, Sill, and Isarco, we could not account for the effect of fresh water, which may support higher birth weight (Glazer et al., 2018). Furthermore, some types of vegetation such as trees may be associated with birth outcomes more consistently than overall vegetation level (NDVI) (Abelt & McLafferty, 2017). However, no detailed tree cover data were available for the study periods. Reassuringly, using NDVI based on the year of delivery and single-year NDVI for all births yielded similar results; that suggests that it should not be concerning if future studies have to rely on single-year greenness data.

Various air pollutants have been linked to adverse birth outcomes (Stieb et al., 2012; Pedersen et al., 2013), but we only considered NO_2. Another limitation was that we had no information on area-level socioeconomic status which may modify relationships between greenness (or other exposures) and birth outcomes (e.g., Hystad et al., 2014; Agay-Shay et al., 2014). We also lacked data on maternal pre-pregnancy body mass index which is an additional determinant of birth weight, and may mediate the effects of greenness (Persson et al., 2018), noise (An et al., 2018b), and air pollution (An et al., 2018a). Unaccounted for residual confounding/mediation could have led to counterintuitive findings such as the protective associations between traffic noise and SGA in the BBT survey and the decreased risk of preterm birth recently reported by Wallas et al. (2019); conversely, it could have also resulted in spuriously strong associations. Finally, we are mindful that future research should look beyond the interplay of the factors considered here and evaluate how the totality of environmental exposures from conception onwards shapes human health (Nieuwenhuijsen et al., 2019).

5. Conclusions

Our findings provide inconclusive evidence that the surrounding environment might be associated with birth outcomes in mountainous areas. Given the disparate associations across the study areas, further research with larger representative samples is warranted.

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Competing financial interests

The authors declare they have no actual or potential competing financial interests.

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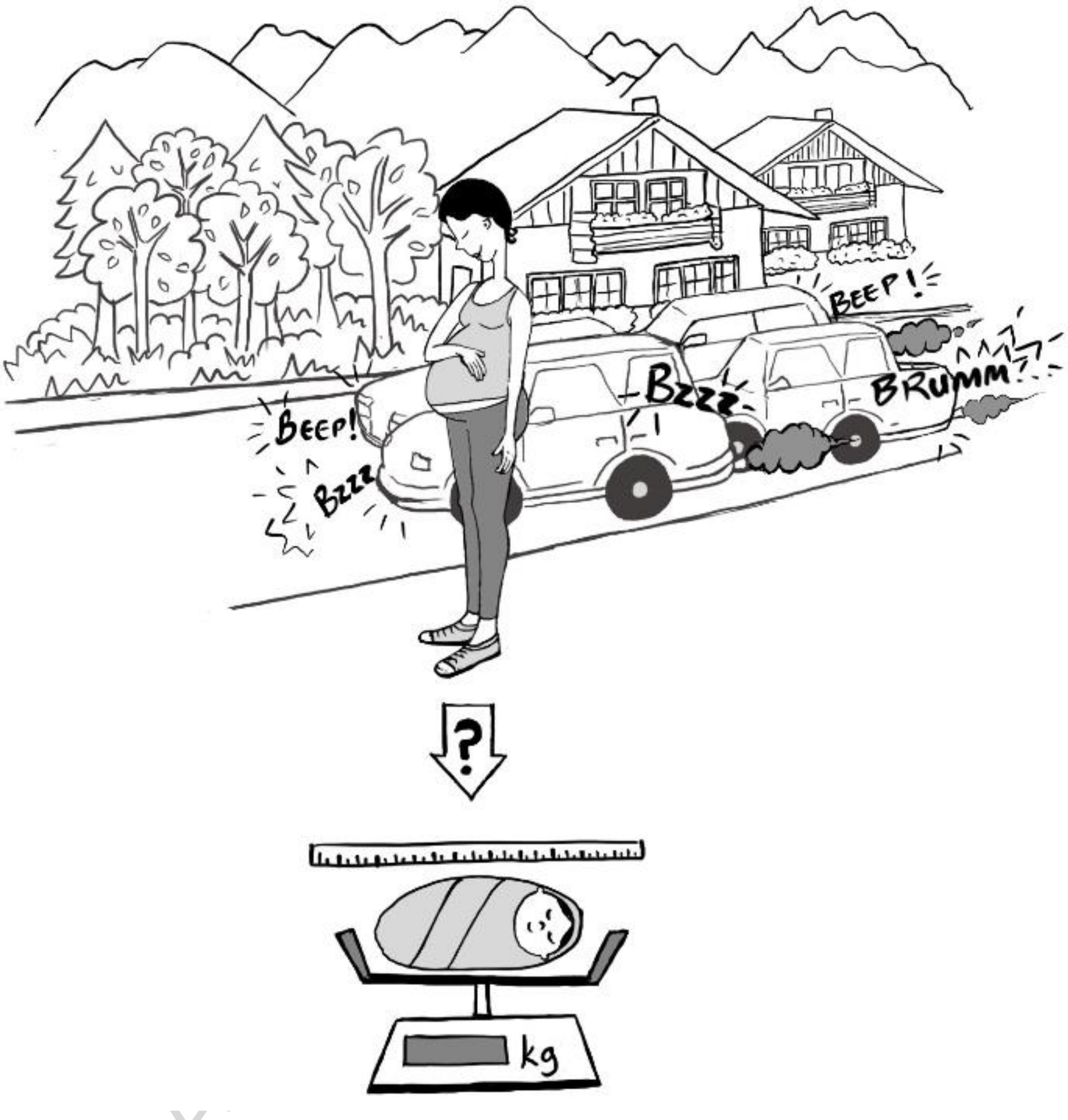
Graphical abstract



Highlights

- The surrounding environment during pregnancy may impact on birth outcomes
- We investigated the effects of greenness, traffic noise, and air pollution in the Alps
- The strength of associations varied across the study areas
- In one area, greenness was beneficial, and noise – harmful
- In the other, associations were weaker and inconsistent