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Born to be Wise: a population registry data linkage protocol to assess the impact of modifiable early-life environmental exposures on the health and development of children

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ABSTRACT

Introduction Deficiencies in childhood development is a major global issue and inequalities are large. The influence of environmental exposures on childhood development is currently insufficiently explored. This project will analyse the impact of various modifiable early life environmental exposures on different dimensions of childhood development.

Methods Born to be Wise will study a Canadian cohort of approximately 34 000 children who have completed an early development test at the age of 5. Land use regression models of air pollution and spatially defined noise models will be linked to geocoded data on early development to analyse any harmful effects of these exposures. The potentially beneficial effect on early development of early life exposure to natural environments, as measured by fine-grained remote sensing data and various land use indexes, will also be explored. The project will use data linkages and analyse overall and age-specific impact, including variability depending on cumulative exposure by assigning time-weighted exposure estimates and by studying subsamples who have changed residence and exposure. Potentially moderating effects of natural environments on air pollution or noise exposures will be studied by mediation analyses. A matched case–control design will be applied to study moderating effects of natural environments on the association between low socioeconomic status and early development. The main statistical approach will be mixed effects models, applying a specific software to deal with multilevel random effects of nested data. Extensive confounding control will be achieved by including data on a range of detailed health and sociodemographic variables.

Ethics and dissemination The study protocol has been ethically approved by the Behavioural Research Ethics Board at the University of British Columbia. The findings will be published in peer-reviewed journals and presented at scholarly conferences. Through stakeholder engagement, the results will also reach policy and a broader audience.

Strengths and limitations of this study

- Born to be Wise will analyse the impact of early-life environmental exposures, including during pregnancy, on childhood development by using a holistic measure of children's early social, emotional, cognitive and physical development.
- By using geocoded and linkable health registry data, a large number of covariates for both children and mothers will be included in the analyses.
- By focusing on modifiable environmental exposures, results from the project could inform policies aiming for healthier childhood environments with impact throughout the life course.
- Born to be Wise will use spatially varying environmental exposure data—on air pollution, noise and natural environments—to assess the joint and individual impacts on dimensions of childhood development, which can facilitate the generation of hypotheses for future investigation.
- The project only has access to developmental outcome data at one point in time, which raises issues of reverse causation and self-selection bias, but this will be addressed by subanalyses of individuals with changes in exposure over the study period, as well as by sibling analyses and a case–control study approach with matched subsamples of children with similar socioeconomic status but differing environmental exposures.

INTRODUCTION

Early childhood development is a strong predictor of health, well-being and social ability across the life course.[1] Early development includes aspects of physical health and well-being, social competence, emotional maturity, language and cognitive development and communication skills. Two series in The Lancet (2007[2] and 2011[3]) concluded that, globally, more than 200 million children under the age of 5fail to reach their developmental potential. In Canada, where this project is located, approximately one in four children is considered 'vulnerable' to deficiencies in early development prior to entering Grade 1,[4] indicating that the child may not yet have developed the skills required to gain full benefit from school education. Vulnerability rates vary significantly within and between Canadian regions and can range from 10% to 60% between different neighbourhoods in a single city.[5] These discrepancies correlate with inequalities in environmental and socioeconomic conditions, with an increased risk of vulnerability among children in socioeconomically disadvantaged environments.[6] Between 2000 and 2010, overall vulnerability rose by almost 30% in British Columbia,[7] driven by worsening trends in the social and emotional domains. Studying the impact of multiple exposures in early life is critical to identifying predictors for the increased prevalence and unequal distribution of neurodevelopmental outcomes. Earlier studies suggest that family risk factors, which are strongly related to socioeconomic status (SES), are significant predictors of early developmental vulnerabilities,[8] but neurotoxic agents and environmental pollution have been suggested to play important roles as well.[9–13] Typically, previous work has rarely included physical (natural or built) environmental exposures in their analyses, and the potential impact of these factors has been insufficiently investigated despite their potential to affect large segments of the population given their ubiquity.

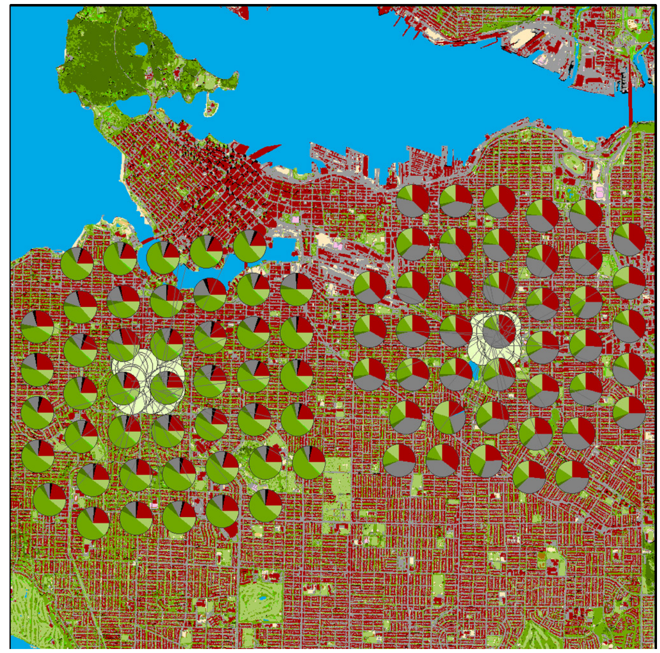

Figure 1 Postal code areas and land cover types in Metro Vancouver (Sources: Statistics Canada 2015,[118] Metro Vancouver 2017[119]). Two example areas of 50 postal codes in Vancouver west and east, respectively, demonstrate difference in proportions of land cover. The west side of the region has, on average, a higher representation, within a buffer zone of 250 m, of green (colour green in circles) than built (red) or paved (grey) areas compared with the east side.

Environmental exposures and childhood development

Over the past few decades, the rate of urbanisation has increased in Canada and elsewhere,[14] and access to natural environments (NE)—a potential health-promoting element of urban settings—is becoming increasingly threatened and unequally distributed.[15–18] The changing environments and lifestyles of children—increased indoor screen time, sedentary behaviours, less outdoor play and reduced interactions with nature—have been the focus of recent scientific and policy analyses.[19–21] The full implications of these broad changes for children's health and development remain unexplored, but preliminary studies indicate that excessive screen time may contribute to attention problems and school difficulties, while time spent outdoors, on the other hand, may improve emotional skills and support learning.[22–24]

Harmful environmental exposures, such as noise and traffic-related air pollution (TRAP), during sensitive developmental periods in early life, including in utero, may also lead to impairments in brain function, with potentially adverse consequences on early development[25–33] and downstream effects on educational attainment and mental health.[34–37] Prenatal exposure to TRAP has been associated with adverse effects on birth outcomes[38 39] and childhood health and cognitive development.[10 40] Recent research also suggests that prenatal noise exposure may have a negative impact on birth outcomes,[41 42] especially in combination with TRAP.[43]

Socioeconomically disadvantaged neighbourhoods often contain more harmful exposures and less NE,[44–48] putting children growing up in these areas at higher health risks. Recent studies indicate that exposure to NE has a positive impact on early childhood health and development, including improved attention and cognitive capacity[13 24 49 50] and fewer symptoms of attention deficit hyperactivity disorder.[51–56] These associations may be due in part to moderating effects of NE on TRAP,[57–61] heat[62–64] and noise[65–67]; thus, a positive effect of NE would be mediated by a reduction of those harmful factors. NE may also influence early childhood development through several other pathways, including: (1) providing areas for physical activity and active play[68–70]; (2) reduced stress among both parents and children[71–73]; (3) improved affect, cognition and mental health[74–77]; (4) improved social capital and positive psychosocial influences[78–81]; (5) improved immune system development by exposure to microbial diversity[82–84]; and (6) mitigation of adverse developmental outcomes related to low SES, as previous studies suggest that SES-related health inequalities are smaller in green areas.[85 86]

Preliminary data

Preliminary analyses suggest that socioeconomically disadvantaged areas of Metro Vancouver have a higher proportion of built and paved spaces, while more prosperous areas have more vegetation (figure 1). This indicates that

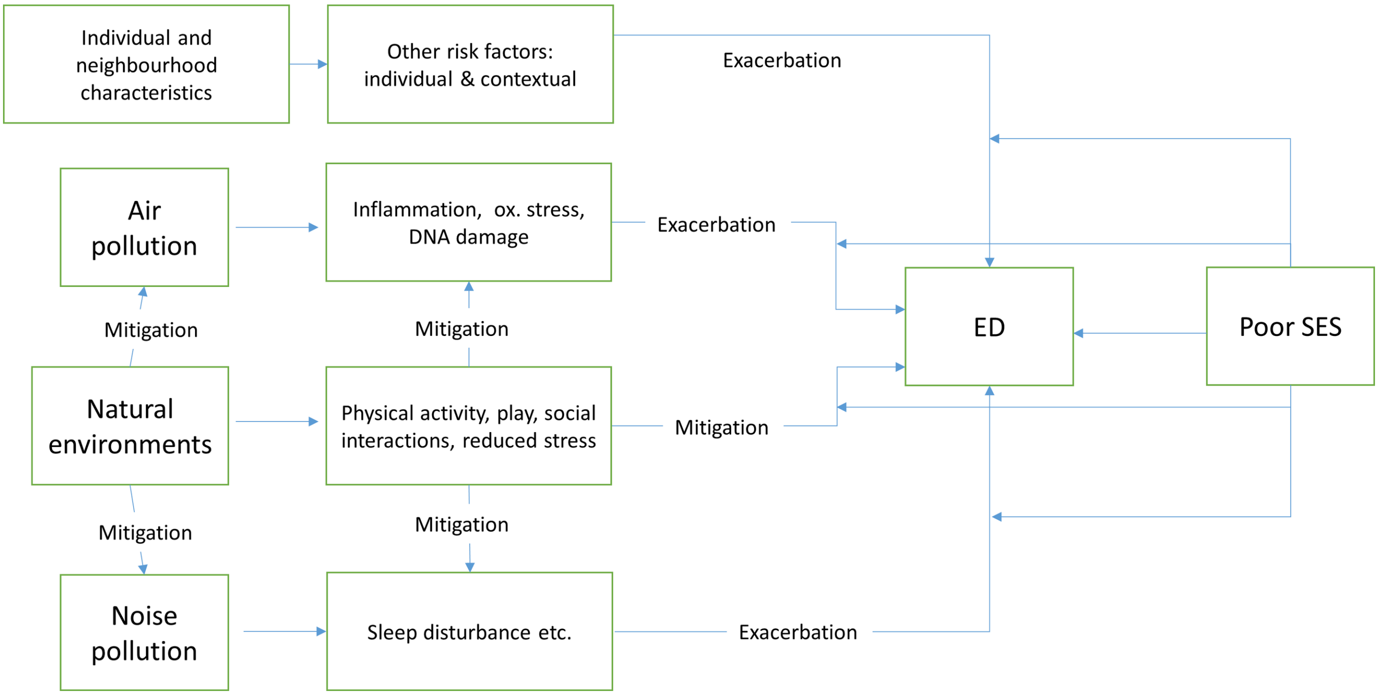

Figure 2 Exposure to natural environments (NE) in the neighbourhood reduces the negative impacts of air and noise pollution on early development (ED). NE exposure may also reduce inequalities associated with low socioeconomic status (SES), at least partly due to the mitigating impact on air and noise pollution. The combined effects of reduced risk factors and increased health-promoting behaviours (eg, physical activity, stress relief, social interactions) result in improved early development among children exposed to high levels of NE in early life.

there is a gradient in environmental exposures, but the impact on early development remains to be investigated.

AIMS OF BORN TO BE WISE

This project will investigate the following specific aims to determine whether:

Aim 1: exposure to NE is positively associated with early childhood development and health;

Aim 2: exposure to TRAP and noise are negatively associated with early childhood development;

Aim 3: areas of high NE are associated with reduced negative effects of TRAP or noise exposures on early development; and

Aim 4: exposure to NE moderates the effect of poor SES on early childhood development.

See figure 2 for a conceptual model of the suggested pathways and moderators.

Methods and analysis

Born to be Wise is based on individual-level data linkage and analysis of existing population-based data held by Population Data BC (PopData BC, https://www.popdata.bc.ca/), including person-specific data on early development and demographic, health and socioeconomic variables. Individual estimates of exposure are based on existing models, maps and remote sensing products, all of which are linked to the population data with high spatial resolution.

To address the aims, the project will link indicators of multiple domains of early development to data on: (1) exposures to TRAP, noise and NE in the residential environment (time-weighted based on residential address history); (2) SES of children's neighbourhoods; and (3) covariates, such as maternal and child health status. Participant data are geocoded at the six-digit postal code of the residential address, which corresponds to the centroid of one block face or an apartment building in the study area, and all linkages, apart from SES, will occur at this spatial level.

Study area

Metro Vancouver.

Key study variable, primary outcome and cohort

The project will draw on a province-wide population-level data set on children's early development, the Early Development Instrument (EDI).[87] The EDI measures children's readiness to learn at school across five domains (see table 1): (1) physical health and well–being; (2) social competence; (3) emotional maturity; (d) language and cognitive development; and (e) communication skills and general knowledge. The five domains are all predictors of later achievement in school—individually and as a composite score.[88 89] The instrument demonstrates good psychometric properties,[90–92] including reliability across different groups of children.[91 93] The EDI database represents the only population-based database

Table 1 Early Development Index (EDI) domains and subdomains

EDI domain	EDI subdomain
Physical health and well-being	Physical readiness for school Physical independence Gross and fine motor skills
Social competence	Overall social competence Responsibility and respect Approaches to learning Readiness to explore new things
Emotional maturity	Prosocial and helping behaviour Anxious and fearful behaviour Aggressive behaviour Hyperactivity and inattention
Language and cognitive development	Basic literacy Interest in literacy/numeracy, and uses memory Advanced literacy Basic numeracy
Communication skills and general knowledge	Communicates easily and effectively Participates in storytelling Articulates clearly Shows adequate knowledge Uses native language proficiently

Each is scored on a scale of 0 to 10. If a child falls in the bottom 10th percentile, he or she is considered 'vulnerable' in that domain. An 'overall vulnerability' flag is set if a child is vulnerable in one or more domains.

on early childhood development in British Columbia and numerous other jurisdictions in Canada.[5]

Since 1999, the EDI has been administered in kindergarten classrooms throughout Metro Vancouver to children at age 5. For the Born to be Wise Project, EDI data for 34 402 children from 2005 to 2010 (corresponding to birth cohorts 2000–2005) are linkable to exposure data and will provide a population-based and representative cohort.

Born to be Wise will follow standard approaches for operationalising vulnerability via EDI scores. For logistic regression analyses, children are classified as being 'vulnerable' in a given EDI domain, using a 10th percentile cut-off score based on a normative Canadian data set of children.[94] Children with at least one EDI domain score in the bottom 10th percentile are categorised as 'vulnerable in at least one developmental domain'.[87] For linear regression analyses, continuous EDI scores, ranging from 0 to 10 for each domain and from 0 to 50 for the overall EDI score, will be used.

Individual children and parental covariates

Multiple child-level and parent-level variables that have been found to be predictors of early development[8] (eg, maternal health, medication use and hospital records for mother and child) will be acquired from person-specific administrative British Columbia data sets, and aggregate-level socioeconomic and demographic variables (eg, median income, high school graduation rates, lone parent family rate and employment rates) will be drawn from Statistics Canada.

Environmental exposures and variables

Natural environments

In this project, NE will be defined as green and blue spaces. Most of the earlier research using remote sensing for estimating natural environments has used the Normalised Difference Vegetation Index (NDVI) with 30 m resolution from Landsat images. At this relatively coarse resolution, however, it can be difficult to interpret objects, because the minimum spatial unit (pixel) may not be homogenous. This mixed pixel problem[95] may result in misclassification of exposure to NE. This project will therefore take advantage of high resolution data from Planet (3 m), WorldView2 (2 m) and NASA imagery (0.5 m), to minimise errors in exposure estimates. These higher-resolution images will yield highly detailed estimates of NE exposure over the entire study area. Images will be radiometrically corrected and presented in pixel values (digital numbers) that will be converted to the Top of Atmosphere (TOA) radiance through established algorithms. The NDVI will be derived to represent the degree of vegetation or water at a location. The NDVI is calculated as[96]: NDVI = (NIR - VIS)/(NIR +VIS) where VIS and NIR stand for the spectral reflectance measurements acquired in the visible (ie, red band) and near-infrared regions, respectively. NDVI ranges between −1 and 1 with higher numbers indicating more green vegetation. Freestanding water, such as oceans, lakes and rivers, usually has very low NDVI values, so hydrography data from Natural Resources Canada will also be used to classify water bodies. NDVI values will be assigned to study participants through a raster overlay to their residential location and through a series of network buffers with radii of 50 m, 100 m, 200 m, 300 m, 400 m, 500 m and 1 km. While it is often assumed in urban planning that approximately 300 m represents a 'healthy' maximum distance to NE, there is no scientific consensus[97] and the project will therefore test for different distances, assuming potentially different health pathways depending on buffer size (eg, larger buffers for physical activity and smaller buffers for immediate stress recovery). Using residential locations, average exposure will be calculated across the full period by calculating precise time-weighted personal exposure estimates (at the defined time windows— prenatally, at birth and at 1, 3 and 5 years of age).

A limitation of remotely sensed metrics is that different types or qualities of NE cannot be sufficiently identified, obscuring potential differences in effect depending on the type of NE exposure. We will address this issue by adding three recently described NE metrics, specifically developed for Metro Vancouver: a categorised land cover map, a Natural Space Index (NSI) and a street-level Green View Index (GVI). The land cover map was developed from RapidEye satellite imagery and LiDAR data sets that were combined and processed to produce a high-resolution (5 m) land cover map of Metro

Vancouver. It includes 14 different land cover categories, distinguishing between deciduous and coniferous trees, grass, shrubs and herbs, among other classifications.[98] The NSI integrates assessments of presence (assessed from NDVI values), form (extracted from municipal and private databases), access (evaluation of restrictions such as private ownership) and quality (appraised by using the Public Open Space Desktop Appraisal Tool[99]) of NE.[100] The GVI was developed by using panoramic images from Google Street View,[101] creating an urban greenery assessment tool that captures human perceptions of NE from the street,[102] which might represent the influence of NE views from outside the home.

1. Traffic related air pollution: Residential TRAP exposure will be quantified using high-resolution land use regression (LUR) models for nitrogen dioxide (NO_2) and particulate black carbon (BC). Specific NO_2 and BC LUR models are available for Metro Vancouver. These models combine detailed monitoring of TRAP in various locations and geospatial predictor variables that define land uses related to TRAP sources and geographic determinants around the sampling locations. The models have been used previously to examine associations with birth outcomes.[38 43] LUR models are also available for fine particle mass concentrations (≤2.5 µm) and for ultrafine particles (≤0.1 µm).[103 104] Traffic proximity measures will also be derived.
2. Noise: Born to be Wise will estimate noise exposure levels using multiple metrics, all in A-weighted decibels: (1) annual average 24 hours noise levels (Lden,A), which integrates noise levels during the day, evening and night, with 5 dB(A) weighting added to evening noise and 10 dB(A) weighting added to night noise to reflect increased sensitivity to noise during these periods; (2) daytime exposure (Lday,A); and (3) night-time exposure (Lnight,A). The project will apply a previously developed predictive model[105] that uses noise prediction software (Computer Aided Noise Abatement; Datakustik, Greifenberg, Germany) to estimate annual average community noise levels during the study period.[105] The noise exposure data include road type, intersection locations, traffic speed and volume, railway data, aircraft data (noise forecasts produced by Vancouver International Airport Authority), topography and building heights and footprints. The annual A-weighted equivalent continuous noise level will be calculated for a 10×10 m grid that will then be averaged for each postal code area.

Linkage of data and temporal variation

Through the British Columbia Perinatal Data Registry, mothers will be linked to their children, with prenatal geocodes based on each mother's residential address. Individuals living in the same household can also be identified by this method, making it possible to link siblings to each other and to their residential location. Environmental exposures will be linked to participants through their six-digit residential postal codes, using the average of all 10×10 m grid values within postal code boundaries (noise) and postal code centroids (TRAP and NE). Because the study region is highly urbanised, the majority of postal codes represent small geographic areas, comprising about 35 residents for a typical cohort. Based on results from previous studies, the spatial patterns of environmental exposures are assumed to be highly correlated over time.[106] Thus, the project will use existing models and extrapolate, both backcasting and forecasting, in accordance with previously applied methods,[106] to predict exposures for different time periods. Earlier studies suggest that residential mobility is high during children's first 5–7 years (up to 30%),[107 108] which will provide opportunities for assessing variation in environmental exposures. The linked data allow for residential history assignment through coding of participants' residence locations, and for distinguishing exposures at various time windows.

Statistical design and analysis strategy

In modelling the effects of environmental exposures, Born to be Wise will treat EDI outcome data both dichotomously and continuously. Apart from area-level SES, all covariates will be defined at an individual level. When considering the impact of contextual neighbourhood variables, the project will apply multilevel mixed models with two levels: level 1 is the individual level and level 2 represents the area level. Standard multilevel mixed models assume independence between clusters at a hierarchy level. The project will apply the multilevel Geographic and Multilevel Models for Environmental Public Health Indicators and Tracking (GAMEPHIT) software[109–111] to deal with potential spatial autocorrelation in residual variation that is not accounted for by fixed predictors in the model. This software works with both continuous and dichotomous outcomes. Stratified gender analyses will be conducted to assess whether gender differences exist in effect estimates. The project will include the following statistical analyses:

1. Mixed effects models to identify the independent effects of TRAP, noise and NE on early development

The project will first investigate the independent effects of TRAP on EDI with the following equation (eq. 1):

$$Y_s = \beta_0 + \beta_1 C_s + \beta_2 P_s + \beta_3 N_s + \theta_a + \varepsilon_s$$

Y_s and C_s are, respectively, the EDI score (continuous or dichotomous and summary score or separate domain) and TRAP exposure for child s. β_0 is the model constant. β_1 is the coefficient for TRAP exposure. β_2 is a vector of coefficients for the individual characteristics. β_3 is a vector of coefficients for possible neighbourhood confounding factors. P_s represents the individual characteristics of child s, such as age, sex and race/ethnicity. N_s represents neighbourhood confounding or modifying factors that might impact the relationship. θ_a is the random effect of neighbourhood census tract a to account for non-independence of children living in the same area and ε_s is the error term of child s. The project will investigate the association in eq. 1 assuming spatial dependency between level 2 neighbourhoods using the random effects model (GAMEPHIT)[111]. It is assumed that each neighbourhood has a spatial dependency in EDI outcome to its immediate neighbourhood (i.e., queen's adjacency).

Second, the project will investigate the independent effects of noise on EDI. The relationship is similar to eq. 1 with Y_s and C_s, being, respectively, the EDI score and 24-hour, day, night or peak hour noise levels at home address of child *s*. Other variables have the same definition as in eq. 1.

Third, the project will estimate the independent effects of NE on EDI. We will estimate NE measures for different buffer distances around residential addresses. These measures will be used separately to model their possible positive impacts on early child development. The relationship is similar to eq. 1, with Y_s and C_s, being, respectively, the EDI scores and NE measures at the residential address of child *s*. Similar to eq. 1, the associations between NE and EDI will be adjusted for confounding or cluster dependency.

For the above models, Born to be Wise will apply time-weighted average exposures from the prenatal period to the age of EDI assessment to identify the overall impact and changes. The project will also investigate age-specific impacts and critical exposure windows for effects on EDI. Subanalyses of children who have changed residences and associated exposures during the study period will be conducted to enable assessment of whether the length of exposures has an impact on outcomes. For example, it will be possible to define groups of children who have: (1) always had low exposure to NE (or other environmental exposures); (2) moved from low to high exposure; (3) moved from high to low exposure; or (4) always had high exposure. This will also enable identification of whether a certain time window has a stronger impact than another.[112]

Sensitivity analyses on siblings will be conducted to allow for identifying differences in exposure in the same family. Due to differences in age, residential moves may create variation in cumulative exposure (eg, an older sibling who moves at age 4 and a younger one at age 3 would have different time-weighted average exposures). These sensitivity analyses reduce the risk that self-selection bias affects the results by using the mobility data with the SES factor kept constant.

2.Mixed effects models to identify the moderation effects of NE on associations of TRAP or noise with early development:

Moderation effects of NE on associations of EDI with: (1) TRAP, (2) noise and (3) TRAP and noise combined will be identified by using a formal moderation model, thus assessing if a positive effect of NE on EDI might be mediated by a reduction in TRAP, noise or both. The statistical analysis method proposed by Preacher and Hayes[113] will be used to test the hypothesised moderation effects. This method allows for testing the statistical significance of the moderation effect, while adjusting for confounding or neighbourhood dependency.[114 115] To identify a moderation effect of NE on combined TRAP and noise effects on EDI, the additive or multiplicative effects will be analysed, and a formative variable (addition or multiplication of the TRAP and noise values) will be created to summarise the total effect.

Table 2 Pair matched case–control analysis

NE		Case (High EDI vulnerability) High	Low
Control (low EDI vulnerability)	High	a	b
	Low	c	d

EDI, Early Development Instrument; NE, natural environments.

The project will also include causal analyses on the impact of NE on EDI among children of low SES, using a pair-matched case–control study design (see table 2). To do this, children of low SES will be matched by age, sex, TRAP and noise levels. Pairs of controls with high NE will be calculated and cased with low NE (*b*), and pairs of controls with low NE will be cased with high NE (*c*); *b*/*c* is the OR of impact of NE on EDI.

Power calculations

Previous research suggests that TRAP has an effect size of 11%–22% on cognitive development outcomes[26] and noise has been linked to half an SD in this outcome.[32] In earlier analyses,[94 116] effects from neighbourhood income in the range of 0.1 were observed on EDI, which has a mean of 7.4 and an SD of 2.6. This is much smaller than the observed effects of other environmental variables, but this smaller effect size was used to be conservative in power calculations. Calculations were based on a one-sided alternative hypothesis ('greater than') and desired power of 0.90. A continuous outcome was assumed and alpha=0.01, which yielded a sample size of 1296 subjects, well below the projected study sample size.

The potential for detecting the moderation effect of NE on TRAP or noise was also calculated. The moderation effect is the indirect effect of product of two standard coefficients: (1) slope of air pollution/noise (β_{21}) in association with the moderator NE and (2) slope of NE (β_{32}) in impacts of NE and TRAP/noise with outcome EDI. Using the same small effect size and a conservative estimate of the effects of NE on air pollution demonstrated in other studies with a power of 0.9 and alpha 0.05, 5133 subjects are required. Power calculations were computed in R using the 'pwr.r.test' function in the 'pwr' package (https://cran.r-project.org/package=pwr) and in MedPower (https://davidakenny.shinyapps.io/MedPower/).

Patient and public involvement

Neither patients nor the public were involved in the development of this protocol.

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ETHICS AND DISSEMINATION

Born to be Wise conforms to Canada's TriCouncil Policy and UBC's 'Policy on Research and Other Studies Involving Human Subjects'. The project has been ethically approved. The project is considered minimal risk due to the anonymised nature of the data. All data will be securely stored and managed by PopData BC.

The findings from Born to be Wise will be communicated through international peer-reviewed scientific journals and through popular-scientific and policy channels. The project has broad connections and collaborations with numerous knowledge translation partners and provincial stakeholders, including regional health authorities and alliances for healthy living and healthy families. Meetings with involved stakeholders and data stewards are planned and strategies for dissemination of the results will be outlined in collaboration with knowledge users, including PopData BC, Perinatal Services BC, Metro Vancouver, Health Canada, the British Columbia Centre for Disease Control and knowledge transfer members of the Canadian Urban Environmental Health Research Consortium.[117] This process will be iterated with regularly planned dissemination meetings and seminars/webinars. The aim is to disseminate the results of the project to provide data linkages and methodological input to future studies and to influence public health policies and evidence-based urban planning.

CONCLUSION

Many studies on environmental exposures, especially on NE, have focused on adult populations, but less is known about their influence on children. By investigating the links between several modifiable environmental exposures and early childhood development, Born to be Wise will provide new evidence about how the environment affects health in childhood with subsequent impacts across the life course. The project addresses four major gaps in current knowledge: (1) the effects of noise and TRAP on various dimensions of childhood development; (2) the influence of early life (including prenatal) exposure to neighbourhood NE and the possible moderating effects of NE on harmful exposures; (3) the effect of these exposures on children of poor SES, and whether their early development can be particularly enhanced through access to NE; and (4) critical time windows and differences depending on the length of exposures for the influence of environmental exposures on early development.

Born to be Wise is relevant to a key set of contemporary challenges related to rapidly changing living environments and harmful exposures that may influence early childhood development. In many areas, these exposures are ubiquitous, thus affecting large populations with the potential for major impacts on population health. Results from the project will provide empirical evidence on the impact of environmental exposures on early development and may ultimately inform effective policies and interventions to support healthy urban planning for vulnerable populations, particularly children in socioeconomically deprived areas.

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Contributors MvdB drafted this manuscript on the basis of a grant proposal that was devised and written by her, MB, RB, HWD, MG, MJ, TO, HS and JGS. All of the authors contributed to the introduction and aims sections, providing input on existing knowledge, study design and falsifiable hypotheses (specifically MvdB, MG and TO on socioeconomically related health inequalities, the Early Development Instrument and developmental disorders; MB, RB, HWD, MJ, HS and JGS on harmful environmental exposures, exposure metrics and analytical tools; and MvdB, ZD, IJ, MJ, LN and ER on natural environment metrics and analytical tools). IJ drafted the primary data and preliminary analysis section and developed the map, and ER developed the NSI and corresponding text. The conceptual model was developed by MvdB, MG, MJ and JGS. The methods and analytical section, in which the conception and design of aspects of the work for which the respective authors are responsible in the Born to be Wise project are described, was developed with specific input from MvdB, MB, RB, HWD, MG, MJ, LN, HS and JGS. All coauthors contributed to the writing of the implementation and conclusion sections. MvdB subsequently prepared a final version of the manuscript based on coauthor contributions. All authors then read the final version, approved it for submission for publication and agreed to be accountable for all aspects of the work.

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