Personal assessment of the external exposome during pregnancy and childhood in Europe.

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Abstract:

The human exposome affects child development and health later in life, but its personal external levels, variability, and correlations are largely unknown. We characterized the personal external exposome of pregnant women and children in eight European cities. Panel studies included 167 pregnant women and 183 children (aged 6-11 years). A personal exposure monitoring kit composed of smartphone, accelerometer, ultraviolet (UV) dosimeter, and two air pollution monitors were used to monitor physical activity (PA), fine particulate matter ($PM_{2.5}$), black carbon, traffic-related noise, UV-B radiation, and natural outdoor environments (NOE). 77% of women performed the adult recommendation of ≥150 min/week of moderate to vigorous PA (MVPA), while only 3% of children achieved the childhood recommendation of ≥60 min/day MVPA. 11% of women and 17% of children were exposed to daily $PM_{2.5}$ levels higher than recommended (≥25μg/m^3). Mean exposure to noise ranged from Lden 51.1dB in Kaunas to Lden 65.2dB in Barcelona. 4% of women and 23% of children exceeded the recommended maximum of 2 Standard-Erythemal-Dose of UV-B at least once a week. 33% of women and 43% of children never reached the minimum NOE contact recommendation of ≥30 minutes/week. The variations in air and noise pollution exposure were dominated by between-city variability, while most of the variation observed for NOE contact and PA was between-participants. The correlations between all personal exposures ranged from very low to low (Rho < 0.30). The levels of personal external exposures in both pregnant women and children are above the health recommendations, and there is little correlation between the different exposures. The assessment of the personal external exposome is feasible but sampling requires from

one day to more than one year depending on exposure due to high variability between and within cities and participants.

Keywords: Personal exposure monitoring; Dynamic modelling, Particulate matter; Black carbon; Physical activity; Green spaces; Ultraviolet radiation; Pregnancy; Childhood

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Abbreviation list:

BC- Black carbon
BMI- body mass index
ETS- environmental tobacco smoke
GIS- Geographic information system
HELIX- The Human Early-Life Exposome project
ICC- Intraclass Correlation Coefficient
Lden- weighted day-evening-night noise level
MVPA- moderate to vigorous physical activity
NDVI- normalized difference vegetation index
NO_2- nitrogen dioxide
NOE- natural outdoor environments
PA- physical activity
PEM- personal exposure monitoring
$PM_{2.5}$ - fine particulate matter
PMabs- particulate matter absorbance
SED- Standard Erythemal Dose
UV-B- ultraviolet radiation
WHO- World Health Organization

1. INTRODUCTION

Early life and childhood are considered vulnerable periods in which exposure to environmental stressors can permanently change the body structure, physiology, and metabolism (Gluckman and Hanson, 2004). Some relevant environmental stressors during early life and childhood are air pollution, traffic-related noise and ultraviolet (UV) radiation. Early life exposure to air pollution has been linked with a myriad of health outcomes such as premature birth (Šrám Radim J. et al., 2005), childhood asthma (Clark Nina Annika et al., 2010) and impairment of brain development (Clifford et al., 2016). Exposure to traffic-related noise in childhood has been associated with increased blood pressure and stress (Hohmann et al., 2013) and exposure to UV radiation with skin damage and increased skin cancer risk in adulthood (Green et al., 2011). Interlinked with these environmental stressors, green spaces and physical activity have been shown to have benefits to early-life and childhood health. Most of the beneficial effects of green spaces or surrounding greenness are related to pregnancy-related outcomes such as fetal growth (Dadvand et al., 2012b). Physical activity has been found to improve child's cognitive development and psychosocial, bone, skeletal, and cardiometabolic health (Carson et al., 2017). It is therefore important to assess accurately the personal exposure levels among pregnant women and children.

Up to now, most of the existing evidence on exposure-health relationships comes from epidemiological studies focused on a single exposure, using self-reported exposures or residential estimates as predictors of individuals' exposure, whereas in daily life individuals face mixtures of exposures as captured by the exposome concept (Wild, 2012, 2005). Furthermore, self-reported and residential measures insufficiently characterize personal exposure, as self-reported measures suffer from information and recall biases (Althubaiti, 2016; Coughlin, 1990), and residential estimates often poorly correlate with personal exposures (Nieuwenhuijsen et al., 2015).

There are only few studies based on personal measurements of multiple environmental external exposures (Dadvand et al., 2012a). Personal measurements have the unique ability to accurately quantify the actual levels and variability of people's exposures (Steinle et al., 2013). Furthermore, they can also be used to correct the measurement error of the residential estimates (Buonaccorsi, 2010). However, until recently, the cost, inconvenience and annoyance of personal assessment methods have prevented their extensive use in research. As a consequence, existing studies using personal environmental measurements are limited to small sample sizes, adults, one city, and/or a single exposure (Johannesson et al., 2011; Lanki et al., 2007; Montagne et al., 2013; Schembari et al., 2013; Sørensen et al., 2005). Moreover, only several studies about personal exposure to air pollution have assessed the inhaled dose (Buonanno et al., 2013; de Nazelle et al., 2013, 2012; Dons et al., 2012; Int Panis et al., 2010; Rivas et al., 2016; Zuurbier et al., 2010). Recent technological advances have brought new opportunities to assess the personal external exposome (Turner et al., 2017).

The present study aims to characterize the levels, variability and correlations of personal environmental exposures, including air pollution, traffic-related noise, natural outdoor environments, and ultraviolet radiation, and levels of physical activity, of pregnant women and children in eight European cities, using a set of objective personal exposure assessment tools and Geographic information system (GIS).

2. METHODS

2.1. Study design, participants and ethics

The present study included two panel studies nested within The Human Early-Life Exposome (HELIX) project, one based on children and one based on pregnant women, as previously described elsewhere (Vrijheid et al., 2014). Briefly, the HELIX project aims to implement tools and methods to characterize early-life exposure to a wide range of environmental factors and associate these with data on major child health outcomes, using six existing population-based birth cohort studies in Europe (i.e. INMA- Spain, BiB- UK, KANC- Lithuania, Rhea- Greece, EDEN- France, MoBa- Norway). The children panel study was carried out in five cities covered by the cohorts (Sabadell-Spain, Bradford-UK, Kaunas-Lithuania, Heraklion- Greece, and Poitiers-France) and was aimed to include 150 children in total. In order to ensure completeness of data, 183 children were finally recruited from the cohorts following a maximum variation sampling strategy to high traffic-density exposure at home address. The inclusion criteria for the children were: a) aged 6–12 years; b) available pregnancy blood and urine samples; c) available completed address history; and d) no chronic health problems.

The pregnancy panel study was carried out in three cities (Barcelona-Spain, Oslo-Norway, and Grenoble-France) and was aimed to include 150 pregnant women in total. In order to ensure completeness of data, 167 pregnant women were recruited during their first trimester of pregnancy. The inclusion criteria for the pregnant women were: a) singleton pregnancy; b) aged ≥18 years at the start of pregnancy; c) first visit to be conducted before week 20 of pregnancy; d) residence in the study area covered by the cohort; and e) not having high-risk pregnancy. The ethics committees of all participating cohorts approved the study protocol, and written informed consents were obtained from adult participants and legal guardian of children.

2.2. Instruments

Participants were monitored twice regarding their geographical location (i.e. which places they visited and which routes they took), physical activity (PA), and personal exposure to air pollution, traffic-related noise, ultraviolet radiation of medium wave (UV-B), and natural outdoor environments (NOE), using a personal exposure monitoring (PEM) kit (FIGURE 1). The two sampling periods were conducted during two non-consecutive normal weeks (i.e. school and working weeks) in the 2^{nd} and 3^{rd} trimester of pregnancy in the case of pregnant women and separated by 6 months in the case of children. The PEM kit was composed of: (i) a belt with an attached smartphone and accelerometer; (ii) a wrist UV-B dosimeter; and (iii) a small backpack fitted with one gravimetric sampler to measure particulate matter with aerodynamic diameter of 2.5 µm or less ($PM_{2.5}$) and one real-time sampler to measure black carbon (BC) (Table S1). Belt and wrist dosimeter were worn during waking hours (≥12 hours/day) for the full weeks and $PM_{2.5}$ and BC monitors were deployed the last day (≈24 hours) of each monitoring week. The air pollution inlets of both monitors were attached to one handle of the backpack at the breathing zone. Each cohort decided in which parts of the panel study they participated, as a result, children from Kaunas and Heraklion did not wear the backpack and pregnant women from Oslo did not wear the $PM_{2.5}$ monitor. For those using the $PM_{2.5}$ monitor, two additional gravimetric samplers for $PM_{2.5}$ were placed at the residence: one at the living room and the other outside of the main window or balcony of the house. Participants were instructed to place the PEM kit nearby while sleeping, bathing/washing or performing swimming activities, and to never place the backpack on the floor. The smartphone was equipped with an external battery (1500mAh) to guarantee at least 18 hours per day of battery life. Pregnant women were allowed to put the smartphone in flight mode and/or place it inside the backpack or their personal purse. Before being deployed, all instruments were synchronized with an atomic clock.

PA was assessed with a wGT3X-BT tri-axial accelerometer (ActiGraph, LLC, USA) and the ExpoApp application (Ateknea Solutions, Spain) running in a smartphone GT-S5360. ExpoApp is an integrated system to assess multiple personal environmental exposures (Donaire-Gonzalez et al., 2019). ExpoApp is designed to obtain information from the smartphone built-in sensors such as clock, satellite and network navigation systems, accelerometer, barometer and display, at the frequency users desire within the capabilities of the smartphone. The wGT3X-BT and ExpoApp were set to sample accelerometry at 30 Hz and 10 Hz, respectively. PA information obtained include wearing time, intensity, duration, and frequency of PA at one minute resolution (Choi et al., 2012; Crouter et al., 2013, 2010; Donaire-Gonzalez et al., 2013) (see Supporting information for smartphone to ActiGraph conversion and criteria in wearing time and intensity). Recommended physical activity thresholds for pregnant women and children were defined using international physical activity recommendations for adults (≥ 150 minutes/week) and children (≥ 60 minutes/day), respectively (WHO, 2010).

UV-B exposure was assessed by the Scienterra UV wrist dosimeter (Oamaru Otago, New Zealand). Participants were trained to wear the wrist dosimeter on top of clothing.

We transformed Scienterra output into miliWatt per square metre ($mW \cdot m^2$) and Standard Erythemal Dose (SED) using calibration equations against reference instruments and international equations (International Commission on Non-Ionizing Radiation Protection, 1995), respectively. High UV-B exposure was defined as ≥ 2 SED per day, which is the exposure needed to produce a just-perceptible erythema 8–24 h after irradiation of the skin of one individual very sensitive to the sun (ICNIRP, 2010).

$PM_{2.5}$ time-integrated mass was collected gravimetrically using 37-mm Teflon filters held in a cyclone (model GK2.05 SH, BGI Inc., Waltham MA, USA) with an aerodynamic cut point of 2.5 µm and connected to a BGI/Mesa Labs A4004 pump working at 3.5L/min. Filter weighing and reflectance measurements were conducted with a microbalance of 1 µg accuracy (Model MX5, Mettler-Toledo International Inc., Switzerland) and a Smoke Stain Reflectometer (SSR) (Model 43D, Diffusion Systems Ltd., UK), respectively. Measurement procedures, quality control, as well as $PM_{2.5}$ mass concentration and absorbance estimations followed the ESCAPE project protocols (both available at www.escapeproject.eu/manuals). High daily exposure to $PM_{2.5}$ mass was defined as ≥ 25 $\mu g/m^3$ following WHO recommendations (WHO, 2006). BC exposure was measured with a MicroAeth (model AE51, AethLabs, San Francisco, CA) with a 1 min resolution. An Optimized Noise reduction Averaging (ONA) algorithm was applied in order to smooth the BC concentrations (Hagler et al., 2011). The inhaled BC dose was estimated combining the time-resolved BC exposure with the inhaled rate. The inhaled rate per minute was estimated using the intensity of PA together with age, sex, and weight of individuals, following the existing equations from the Environmental Protection Agency (U.S. EPA, 2009).

Exposure to road traffic noise and NOE (defined here as contact with major green spaces and surrounding greenness), were estimated for each participant at one-minute resolution using ExpoApp geographical location and Geographic Information Systems (GIS) (i.e. PostgreSQL 2.3.2, PostGIS 9.6.3, Spatialite 4.3.0a, SQLite 3.8.11.1). ExpoApp uses satellite and network navigation systems to fix the location of participants. Location of pregnant women using the smartphone in flight mode was determined using only satellite signal. The ExpoApp was set to sample satellite and network location at 1 Hz and 0.2 Hz, respectively. Smartphones have been shown to detect more trips than the GPS trackers and to have an overall accuracy in real-life settings of < 25 m (Donaire-Gonzalez et al., 2016). The location obtained by the smartphone was cleaned using a validated spatiotemporal map-matching algorithm (Donaire-Gonzalez et al., 2016). Road traffic noise maps were obtained from local administrations and were generated following the European Directive for environmental noise (Directive 2002/49/EC). Noise exposure was estimated overlaying or snapping each minute geo-location against a raster map/polygon layer or line layer of the weighted day-evening-night noise level (Lden), respectively. High exposure to traffic related noise was defined as a continuous variable (amount of time in places with an exposure to Lden ≥ 65 dB) and as a categorical variable (participants with an average exposure to Lden ≥ 65 dB). Major green spaces maps were obtained from the Urban Atlas of the European Environmental Agency inside cities and CORINE Land Cover 2006 (CLC2006) outside cities, and surrounding greenness from the normalized difference vegetation index (NDVI) raster maps from the Landsat 8 Operational Land Imager (OLI)/Thermal Infrared Sensor (TIRS) with 30m x 30m resolution. Contact with major green spaces (in minutes) was estimated for each geo-location as logical variable according if there was a green space within 50 meters. The recommended contact with

NOE was defined as ≥ 30 minutes at least once a week, according to the results from Shanahan et al research (Shanahan et al., 2016). Surrounding greenness of each minute geo-location was abstracted as the average NDVI in a buffer of 100 meters.

Following the recommendations for ambulatory assessments to have a representative measure of daily exposure (Heil et al., 2012), we considered a valid day of monitoring if the time-resolved measurement (i.e. PA, UV-B, BC, noise, and NOE) were correctly monitored (e.g. no missing + no device errors) at least 70% of the waking hours (8am to 8pm). For those exposures monitored the full week (i.e. PA, UV-B, BC, noise, and NOE), at least two valid weekdays and one valid weekend day were required for inclusion in the analysis. On the other hand, the time-integrated measurements of $PM_{2.5}$ and $PM_{absorbance}$ were considered valid when the elapsed time was ≥ 1200 minutes, and the flow changed less than 10% during sampling.

2.3. Additional information

Additional information was collected by questionnaire, including: (i) sociodemographic factors for all participants such as age (years), sex, environmental tobacco smoke exposure (ETS exposure; yes/no), body mass index (BMI; kg/m^2), and city of residence; (ii) sociodemographic factors specific for pregnant women such as educational level (mothers of monitored children were also asked) (high (university or higher) vs other), gestational age (weeks), and working (student or employed/others) and marital status (married/others); (iii) time-varying environmental factors of the monitoring days such as indoor exposures related to smoking (yes/no), vacuum cleaner used (yes/no), and cooking (yes/no); (iv) non time-varying environmental factors such as the height of the home floor from the street level (meters), type of household ventilation (mechanical/others), main heat system (electric or central/others), and travel time (min) and distance (km); and (v) monitoring characteristics such as working days (yes/no) and time spent outdoors (min). Data on meteorological characteristics (e.g. humidity, temperature, precipitation, visibility), nitrogen dioxide (NO_2) background levels, and ambient UV-B radiation during the monitoring days were collected from local meteorological stations, local background air pollution stations, and the Tropospheric Emission Monitoring Internet Service (TEMIS) project (http://www.temis.nl/intro.html), respectively.

2.4. Statistical Analysis

Multivariate mixed linear models adjusted for season, age, sex, and NO_2 background levels (only in models with air pollution as a dependent variable) or ambient UV-B levels (only in models with UV-B as a dependent variable) as fixed effects and with random intercept effects for participant and city were used for each exposure. NO_2 background levels and ambient UV-B levels were used to control the temporal variability of these exposures. NO_2 pollutant was chosen because it is a good marker of traffic-related air pollution and was available for all cities. Intraclass Correlation Coefficient (ICC) was used to quantify the percent of the variance explained by between- and within-participants and cities. The reliability of measurements was defined as the ratio of the between-city and between-participant variance to total variance. The Spearman-Brown prophecy formula based on ICC was used to determine the number of days required to achieve a representative measurement (ICC $\geq$ 0.8) (McGraw and Wong, 1996). Partial Spearman correlation tests adjusted by city and NO_2 background levels were performed to assess the relationship between the personal external exposome components, ambient exposures, and meteorological characteristics.

All analyses were conducted with R (version 3.2.2, the R Foundation for Statistical Computing) and packages "lmer4", "ppcor", and "corrplot".

3. RESULTS

Participants' and home characteristics are presented in Table 1 (see participants' and home characteristics by city in Table S2). Pregnant women were on average 32.9 (±4) years old and 86% were highly educated. Children were on average 7.8 (±2) years old and 46% of their mothers were highly educated. Personal exposure to $PM_{2.5}$ mass and absorbance (PM_{abs}), BC, traffic noise, and NOE differed substantially between cities (Table 2). 11% of pregnant women and 17% of children were exposed to $PM_{2.5}$ levels above the World Health Organization (WHO) 24-hour threshold ambient level of 25 $\mu g/m^3$ (Table 2). Furthermore, pregnant women from Barcelona and children from Sabadell were exposed to almost double levels of PM_{abs} and BC compared to participants from other cities (Table 2). Pregnant women from Grenoble and Barcelona and children from Sabadell inhaled more than 8 µg of BC per day (Table 2). Personal air pollution mean levels were similar to home indoor and outdoor levels (Table S3). 50% of pregnant women living in Barcelona and 50% of children living in Sabadell were located in high noisy areas (Lden > 65 dB) for more than 20 and 5 hours per day, respectively (Table 2). 33% of pregnant women and 43% of children had contact with NOE during ≥ 30 minutes at least once a week, with pregnant women from Barcelona having the least NOE contact (21%) (Table 2). Regarding UV-B radiation, only 4% of pregnant women and 23% of children exceeded the 2 SED per day limit at least once a week (Table 2). 77% of pregnant women achieved the recommended levels of moderate-to-vigorous physical activity (≥ 150 min/week), while only 3% of children achieved the recommended levels for children (≥ 60 min/day) (Table 2). 31% of pregnant women and 65% of children did not fulfil the recommended exposure levels for at least 2 components of the external exposome (Table S4).

Table 3 shows the variability of personal exposures, and the percentage of this variability explained by differences between-cities (Bc), between-participants (Bp), and within-participants (Wp) as well as the number of monitoring days needed to achieve an ICC of 80%. The variability in the exposure to $PM_{2.5}$ mass, $PM_{2.5}$ absorbance, BC concentration, noise, and BC dose was mainly due to between-cities rather than to between-participants differences, both in pregnant women and children. Contact with NOE and PA (especially in pregnant women) was due to a large extent to participant characteristics. For PA, city was a stronger determinant in children than in pregnant women. The UV-B dose was found to be the most variable exposure, which requires more than 200 days of monitoring in children to achieve representative sampling (ICC>80%).

Figure 2 shows the partial correlation matrix between personal and ambient exposures and meteorological characteristics in pregnant women and children adjusted for city and NO_2 background levels. Many correlations were not statistically significant; hereinafter we only discuss the statistically significant correlations. The statistically significant correlations between the different personal exposures ranged from low (Rho = 0.15; between UV-B radiation and PA among pregnant women) to moderate (Rho = -0.29; between noise and surrounding greenness among pregnant women), and were different for pregnant women and children. Correlations between personal exposures and ambient exposures, ranged from low (e.g. Rho = 0.15; between home surrounding greenness and time in green spaces in children) to high (e.g. Rho= 0.91; between personal and home noise exposure in pregnant women), and were stronger among children than pregnant women (Figure 2). The correlations between the ambient exposures ranged from low (e.g. Rho = -0.24; between home surrounding greenness and home noise exposure in children) to moderate (e.g. Rho = -0.49; between home surrounding greenness and home exposure to NO_2), and were again stronger among children (Figure 2). Finally, the meteorological characteristics were related mainly to air pollution among pregnant women, while among children they were related to NOE contact, UV-B dose, PA, and travel distance (Figure 2).

4. DISCUSSION

This is the first study assessing multiple external exposures at the personal level. Our study is one of the few studies that, apart from quantifying the exposure levels and their interrelationships, also assesses their variability within and between participants and cities. We observed considerable variation in the external exposome experienced across cities. Also, considerable percentage of participants was exposed to high environmental exposure levels, and exposure levels were generally higher in children than in pregnant women, particularly for UV-B and physical inactivity. Furthermore, the external exposome levels are highly variable both between-cities and between-participants, but also within-participants over time. Finally, we found most of the exposures to be only weakly to moderately correlated.

4.1. Comparison with previous studies

To our knowledge, only one study examined personal exposures in the external exposome (Nieuwenhuijsen et al., 2014). This previous study was conducted in one person to discuss the challenges of carrying multiple personal monitors to assess the exposome and acute health responses. Most previous studies using personal exposure measurement methods were focused on a single exposure (Berntsen et al., 2014; Dons et al., 2012, 2011; Evenson and Wen, 2011; Johannesson et al., 2011; Lanki et al., 2007; Montagne et al., 2013; Nethery et al., 2008; Nieuwenhuijsen et al., 2015; Riddoch et al., 2007, 2004; Schembari et al., 2013; Sørensen et al., 2005; Sun et al., 2014; Thieden et al., 2004; Van Roosbroeck et al., 2007; Verloigne et al., 2012) or a single city (Buonanno et al., 2013; Dadvand et al., 2012a; Paunescu et al., 2017).

Personal exposure levels to $PM_{2.5}$ and PM_{abs} presented in this study are in agreement with previous European personal exposure studies, which were carried out in adults (Johannesson et al., 2011; Lanki et al., 2007; Montagne et al., 2013; Schembari et al., 2013; Sørensen et al., 2005). Two of these previous studies were conducted in Barcelona (Montagne et al., 2013; Schembari et al., 2013). In the current study we observed lower personal exposure levels to $PM_{2.5}$ and PM_{abs} compared to the previous studies, with levels of $PM_{2.5}$ of 24.1, 21.7 and 16.9 µg/m^3 and levels of PM_{abs} of 3.1, 2.2 and 2.5 ($10^{-5} \cdot m^{-1}$) in 2008 (Schembari et al., 2013), 2010 (Montagne et al., 2013) and 2014 (current study), respectively. However, even with this reduction, we found that 9% of the pregnant women in Barcelona were exposed to $PM_{2.5}$ levels above the WHO recommended ambient limit of 25 µg/m^3. Personal BC levels were similar to the ones reported in adults from Ambers (Dons et al., 2012, 2011), and children from Paris (Paunescu et al., 2017) and Barcelona (Nieuwenhuijsen et al., 2015), but our BC levels were half of the exposure levels reported in children from Cassino (Buonanno et al., 2013). For the first time, we objectively calculated the inhaled dose of BC, and we found that there are cities where at least half of the people monitored inhaled more than 8 µg of BC per day, which results in 2.9 g of inhaled BC per year.

We showed that most of the variability was explained by city rather than by individual characteristics, which provides novel and very relevant information for interventions. The small variability found among individuals indicates that small-scale interventions within the city will have little or no impact on the exposure levels of its citizens. However, whole-city interventions would be beneficial for their citizens as reflected by the variability found between cities. Finally, the large variability found within people sheds light on the need to evaluate interventions over long periods of time. For these evaluations to be successful, they need to be as comparable as possible between them in regards to external temporal factors. In addition, in studies that base their personal exposure to air pollution on 24-hour measurements, we have shown that the attenuation of the relationship exposure-response will be around 50%, due to within person variability. Moreover, we observed that at least 6 days are needed to characterize personal exposure to air pollutants, which is in concordance with previous research (Johannesson et al., 2011; Lanki et al., 2007; Nethery et al., 2008). As shown in previous studies (Lanki et al., 2007; Montagne et al., 2013; Schembari et al., 2013), personal exposure levels were similar to the indoor and outdoor (or residential) levels. Personal levels correlated better with indoor levels than with outdoor levels, and this correlation was stronger in children than in pregnant women. This may be due to differences in participants' behavior (e.g. travel distance) and time spent in others micro-environments. In contrast to a previous study among pregnant women in Barcelona (Dadvand et al., 2012a), we did not find a statistically significant correlation between personal exposure to $PM_{2.5}$ and home surrounding greenness. However, we found positive statistically significant correlations between personal exposure to BC concentration and dose and personal and home surrounding greenness, although the correlation with BC dose was only observed among children.

Road traffic noise exposure was estimated using a novel approach that combines time-resolved location information of participants with road traffic noise maps instead of the more widely used home-based noise (Fu et al., 2017). As far as we know, this is the first time that this approach is used. The exposure assessment could be further improved by incorporating distance and angles to roads and barriers of insulation to produce more accurate personal exposure levels. However, our approach is promising given the difficulty to measure personal noise exposure with noise dosimeters (Nieuwenhuijsen et al., 2014). We observed that, with the exception of Poitiers, Bradford, and Kaunas, more than 50% of pregnant women and children were exposed to traffic noise levels above the recommended Lden 55 dB (European Environment Agency, 2014). Also, we found that variability in personal traffic noise exposure was greater at a city level than at participant level. To achieve a representative assessment of personal exposure to traffic noise, a week of assessment is sufficient. The observed correlations between personal and the traditional home-based exposure levels were high (Rho > 0.85) , indicating that noise measured at the home level may capture our personal noise exposure, but we believe it may be due to the previous mentioned limitations of our personal noise exposure model. Moreover, and in agreement with previous studies (Foraster et al., 2011; Ow and Ghosh, 2017), personal road traffic noise exposure was correlated positively with personal BC exposure and home absorbance levels and inversely correlated with personal and home surrounding greenness exposure levels, both in pregnant women and children. We also found inconsistent (i.e. positive for children and negative for pregnant women or vice-versa) correlations for NOE contact, UV-B dose, and travel distance.

Personal UV-B dose levels found in the present study were in agreement with the dose levels reported in Copenhagen (Thieden et al., 2004) but lower to those found in four Australian cities (Sun et al., 2014). Our variance component analysis showed that the within-participant variability appears to be a more important factor for UV-B dose than variability between individuals or cities. Further work should focus on understanding what time-dependent factors could explain this variability, using long follow-ups and repeated surveys. Moreover, to have a reliable assessment of the UV-B exposure of children (aged 6–9 years), more than 1 year of monitoring is needed, while for pregnant women 61 days are enough. Similar to previous Australian research, we also found a low correlation (Rho < 0.25) between ambient and personal UV-B levels for both pregnant women and children (Sun et al., 2014). This finding highlights the low validity of ambient estimates to represent personal exposure to UV-B. Furthermore, the UV-B dose was also low and positively correlated with surrounding greenness and NOE contact in children and pregnant women, respectively, which is plausible as both exposures are related with being outdoors.

Similar to our noise assessment, our time-resolved assessment of personal contact with NOE and surrounding greenness is a novel approach. To the best of our knowledge, only few studies have used a similar (Almanza et al., 2012; James et al., 2017) or the same approach (Triguero-Mas et al., 2017). However, the studies of Almanza (Almanza et al., 2012) and James (James et al., 2017) are difficult to interpret. They looked at the relationship between greenness and physical activity at minute resolution and this analysis may present biases related to selective daily mobility (Chaix et al., 2013). Among the cities of the Triguero-Mas study (Triguero-Mas et al., 2017) were Barcelona and Kaunas, but the median duration of contact with NOE found in that adult population was much higher (median (IQR) of Barcelona 15(39) and Kaunas 40(70) min/day) than in our study with pregnant women and children participants (Barcelona 6 (11) and Kaunas 6(11) min/day, respectively). In our study, the contact with a NOE was mainly determined by between-participants variability, while surrounding greenness exposure was due to between-city variability. We found that less than one week of monitoring might be enough for a reliable assessment of both exposures. We observed that those pregnant women exposed to higher levels of NOE and surrounding greenness are more physically active and receive a higher dose of UV-B radiation. As suggested by a previous study (Dadvand et al., 2012a), pregnant women surrounded by higher greenness levels tend to spend more time outdoors, which could explain these associations. Moreover, the lack of association between the contact with a NOE and children's PA level is similar to previous research showing that most of children's activity take place in streets and external venues with a parent nearby (McGrath et al., 2015). NOE contact was weakly related to surrounding greenness, which reinforces the idea that both exposures could represent different concepts, especially in specific situations (e.g. a non-green park designed for leisure vs. a green sidewalk designed for mobility).

The levels of PA of pregnant women in this study were higher to those observed in the United States (Evenson and Wen, 2011) but similar to those found in Oslo (Berntsen et al., 2014). The PA levels of children were in concordance with those observed in

England (Riddoch et al., 2007), but lower than those of the ENERGY-project (Verloigne et al., 2012) and the EYHS-project (Riddoch et al., 2004), which included children from Belgium, Greece, Hungary, the Netherlands, Switzerland, Denmark, Portugal, Estonia, and Norway. Our variance component analysis showed that PA variability of both pregnant women and children was mainly explained by between-individual rather than between-city variability. This is a novel and relevant finding that should be taken into account in future interventions focused on promoting an active lifestyle. This highlights that, apart from variability due to temporal factors (such as rainfall, temperature, season of the year, etc.), it is the local factors that make the difference. These local factors must be the target of interventions and can be addressed in the local environment (such as improved access to blue spaces (Vert et al., 2019)) but also by behavioral interventions at neighborhood level. In addition, this study also shows that the exposure-response relationships based on 3-day PA assessment will be attenuated around 42% and 67% in pregnant women and children, respectively, due to within person variability. Moreover, the within-individual variability finding is in agreement with previous studies in pregnant women and children (Cramp and Bray, 2009; Mattocks et al., 2007).

4.2. Strengths and limitations

The study has some limitations. The exclusion of pregnant women with ´´at risk´´ pregnancy could have excluded women with worse environmental exposure levels. The design of the two measurements points was thought to characterize the variability during the school year, but under represents summer and winter seasons, both periods of holidays. The 24 hours of air pollution monitoring was too short to properly characterize personal exposure. Although personal exposure to noise, NOE and surrounding greenness was modeled using an advanced approach (i.e. including an objective time-resolved time-activity assessment), it may still not capture the full variability of exposures and therefore the variability may have been underestimated. The inability of the model to capture all variability was due to the lack of a temporally varying noise model and to the impossibility of including barriers that block noise and impede visibility or access to NOE. Finally, the Spearman-Brown equation used to calculate the needed number of measurement days assumes that no other sources of variation play a role, but this may well not be the case (e.g. variation by season-related factors).

This study is an important step forward in the monitoring of the personal external exposome. This type of research is specially needed to understand the between- and within- personal external exposures' relationship. In addition, the present study has extended what has been done so far in the relationship between personal and residential exposures. These results are useful in reducing the effect that the measurement error of residential exposures has on models that study the relationship between environmental exposure and health (Buonaccorsi, 2010). The number of measurements per participant and the number of cities involved are clear improvements from what has been done so far. Although the sample size is enough to characterize the correlation between exposures or variability of exposures, it remains small to characterize the population exposure levels. We involved both pregnant women and children to obtain a more complete picture of the personal external exposome during vulnerable periods of life. We used the most objective and accurate tools and methods available to quantify the exposure levels and variability of participants. Using an ambulatory assessment is a clear strength of the study because of the representativeness and external validity of this type of assessments (Conner and Mehl, 2015).

5. CONCLUSION

This study has shown the possibility to perform a comprehensive assessment of the personal external exposome of pregnant women and children. The levels of personal external exposures in both pregnant women and children are above the health recommendations, but there is little correlation between the different exposures. The assessment of the personal exposures requires between 1 day of monitoring for surrounding greenness exposure to more than one year for UV-B exposure because of the high variability within–participants. Our evaluation of the variability and interrelationship of personal external exposome can be used by intervention, exposure and risk assessment studies to optimize future monitoring designs, reduce exposure misclassification, and improve dose-response estimations.

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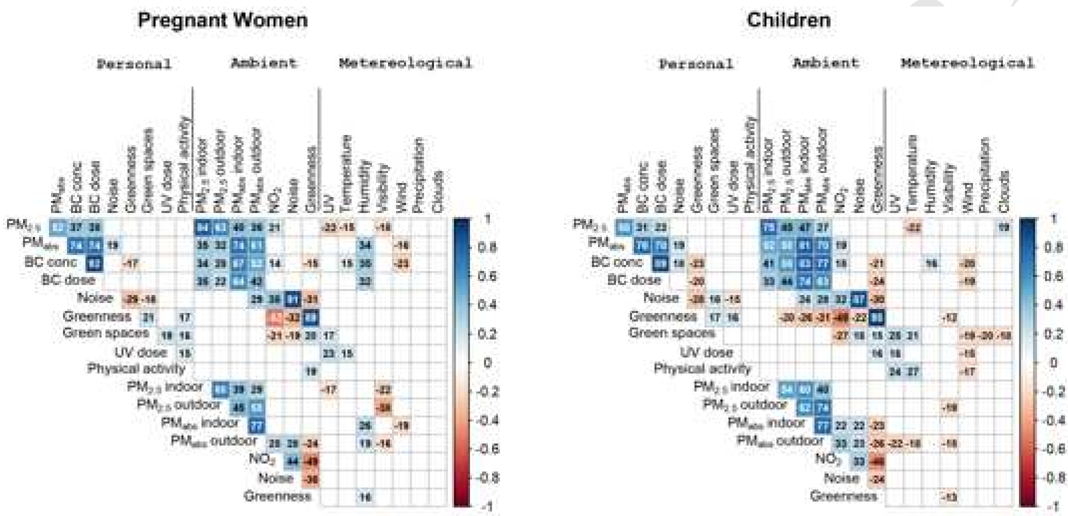
FIGURE 1. Personal exposure monitoring (PEM) kit used in the panel studies of the HELIX project.

(1) ActiGraph wGT3X+; (2) Samsung Galaxy Young (GT-S5360) running ExpoApp; (3) Wrist Scienterra UV-B dosimeter; (4) MicroAeth Model AE51; (5) GK2.05 SH Cyclones and BGI/Mesa Labs 4004 Pumps (see details in Table S1).

Figure 2. Partial Spearman correlation matrix# of personal and ambient external exposome and meteorological characteristics in pregnant women and children adjusted for city and NO_2 background levels.



Only the correlation coefficients with a p-value<0.05 are printed in a percentage format.

Table 1. Baseline descriptive characteristics of panel participants.

	Pregnant Women	Children
	n = 167	n = 183
Participants characteristics		
Age: years, mean (SD)	32.9 (4)	7.8 (2)
Gender: female, n (%)	167 (100)	78 (43)
Educational level (pregnant women/mother): high, n (%)	144 (86)	84 (46)
Work status: student or employed, n (%)	139 (83)	-
Travel distance: km/day, median (IQR)	1.3 (1.8)	0.5 (0.9)
Marital status: married, n (%)	99 (59)	-
ETS exposure, yes, n (%)	58 (35)	75 (41)
Gestational age: weeks, mean (SD)	19 (3)	-
BMI: normal, n (%)	127 (76)	130 (71)
Home characteristics		
Floor height: meters, median (IQR)	11 (6-19)	4 (2-6)
Kitchen type: gas, n(%)	53 (32)	113 (62)
Main heater system: electric or central, n (%)	88 (53)	136 (74)
Controlled mechanical ventilation: yes, n (%)	53 (32)	93 (51)

IQR: Interquartile range; ETS: Environmental Tobacco Smoke; BMI: Body Mass Index.

Normal BMI was defined as the BMI from 18.5 to 25from 18.5 to 25 kg/m^2

Table 2. Descriptive of the overall exposure to the external exposome of participants of both monitoring periods across cities.

	Pregnant Women				Children					
	All (n = 167)	Oslo (n = 60)	Grenoble (n = 49)	Barcelona (n = 58)	All (n = 183)	Poitiers (n = 32)	Bradford (n = 42)	Kaunas (n = 31)	Heraklion (n = 36)	Sabadell (n = 42)
Personal Air Pollution Exposure										
$PM_{2.5}$ (≥25 µg/m^3), N (%)	11 (10.8)	-	6 (12.8)	5 (9.1)	19 (17.3)	1 (3.4)	11 (27.5)	-	-	7 (17.1)
$PM_{2.5}$ (µg/m^3), median (IQR)	11 (10)	-	6 (9)	13 (9)	13 (12)	8 (8)	11 (18)	-	-	19 (9)
PM_{abs} (10^{-5}/m^1), median (IQR)	1.7 (1.3)	-	1.2 (0.7)	2.3 (1.1)	1.1 (1.4)	0.6 (0.5)	0.6 (1.1)	-	-	1.9 (0.8)
BC (µg/m^3), median (IQR)	0.9 (0.9)	0.4 (0.4)	0.9 (0.5)	1.4 (0.7)	0.9 (1.0)	0.6 (0.4)	0.6 (0.6)	-	-	1.7 (0.6)
Inhalation BC (µg/day), median (IQR)	7.8 (7.6)	3.5 (3.5)	8.1 (4.4)	11.5 (6)	5.1 (7.1)	3 (2.5)	2.4 (2.6)	-	-	10.3 (5.7)
UV-B (SED)										
UV-B Dose (SED/day), mean (SD)	0.3 (0.2)	0.3 (0.3)	0.2 (0.2)	0.3 (0.3)	0.7 (0.5)	0.9 (0.6)	0.8 (0.4)	0.6 (0.4)	0.6 (0.6)	0.6 (0.3)
Individuals exposed to ≥ 2 SED at least once a week, N (%)	6 (3.6)	2 (3.3)	1 (2.0)	3 (5.2)	41 (22.7)	15 (46.9)	8 (19.5)	4 (12.9)	8 (22.9)	6 (14.3)
Road Traffic Noise (Lden)										
Noise (dBA), median (IQR)	60.5 (8.5)	57.8 (5.1)	58.1 (5.3)	65.2 (5.6)	56.5 (7.7)	52.5 (2.9)	51.1 (3.5)	51.1 (3.1)	58 (2.6)	59.6 (4.9)
Time ≥ 65 dBA (hours/day), median (IQR)	4.1 (21.7)	1.2 (4.4)	0.8 (2.7)	21.8 (17.8)	0.4 (4.8)	0.2 (0.5)	0.1 (0.3)	0.2 (0.3)	1.2 (14.6)	5.2 (17.2)
Noise, ≥ 65 dBA, N (%)	36 (31.9	6 (18.2)	1 (3.8)	29 (53.7)	10 (6.8)	0 (0)	0 (0)	0 (0)	3 (8.8)	7 (17.1)
Natural Outdoor Environments (NOE)										
Contact with NOE (min/day), median (IQR)	6 (15)	6 (29)	8 (15)	6 (11)	9 (20)	17 (29)	7 (10)	6 (11)	17 (35)	9 (20)
Individuals in contact with NOE for at least 30 min once a week, N (%)	47 (32.6)	22 (39.3)	13 (40.6)	12 (21.4)	72 (43.1)	14 (46.7)	12 (33.3)	10 (35.7)	18 (56.2)	18 (43.9)
Surrounding greenness (NDVI), median (IQR)	0.3 (0.3)	0.5 (0.2)	0.4 (0.1)	0.2 (0)	0.4 (0.2)	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)	0.3 (0.2)	0.2 (0.1)
Physical Activity (PA)										

Overall PA level (counts/min), mean (SD)	321 (104)	333 (115)	293 (86)	330 (104)	580 (139)	417 (123)	595 (118)	609 (105)	670 (129)	557 (107)
MVPA duration (min/day), median (IQR)	35 (27)	38 (20)	21 (25)	41 (27)	25 (20)	9 (12)	26 (12)	22 (19)	34 (22)	24 (18)
Meet MVPA recommendation, N (%)	116 (76.8)	45 (84.9)	21 (50)	50 (89.3)	5 (3.2)	0 (0)	2 (5.7)	0 (0)	2 (5.6)	1 (2.5)

IQR: Interquartile range; $PM_{2.5}$: particulate matter with aerodynamic diameter of 2.5 µm or less; PM_{abs}: $PM_{2.5}$ absorbance; BC: Black Carbon; SED: Standard Erythemal Dose; L_{den}: noise weighted day-evening-night level; MVPA: Moderate-to-Vigorous physical activity;

Recommendations: (i) Exposure to $PM_{2.5} \leq 25$ µg/m^3 according to the WHO (WHO, 2006); (ii) UV-R exposure ≤ 2 SED according to the ICNIRP (ICNIRP, 2010); (iii) Noise exposure (L_{den}) < 65 dBA from (WHO, 2011); (iv) adults physical activity (≥ 150 min/week) and children physical activity (≥ 60 min/day) according to WHO (WHO, 2010); and (v) spent ≥ 30 minutes at least once a week in contact with NOE according to Shanahan et al research (Shanahan et al., 2016).

Table 3. Variance Component Analysis of the personal exposure to external exposome from the multivariate mixed linear model*.

	Pregnant Women					Children				
External exposome	**σ²**	**Bc (%)**	**Bp (%)**	**Wp (%)**	**Nº days, to reach a 80% ICC**	**σ²**	**Bc (%)**	**Bp (%)**	**Wp (%)**	**Nº days, to reach a 80% ICC**
$PM_{2.5}$ (µg/m³)	2.67	3	39	58	6	3.71	11	20	69	9
PM_{abs} ($10^{-5} \cdot m^{-1}$)	1.90	38	16	46	3	2.97	40	17	43	3
BC (µg/m³)	3.71	38	9	53	4	2.35	52	3	45	3
BC dose (µg/day)	3.47	41	10	49	4	3.84	60	2	38	2
Noise (dBA)	40.05	44	52	2	1	36.01	51	47	2	1
Greenness (NDVI)	0.03	69	26	5	1	0.02	68	29	3	1
NOE contact (min/day)	$4.0e^4$	1	85	15	2	$3.5e^4$	2	92	6	1
UV-B (SED)	0.07	1	15	84	61	0.41	2	0	98	533
MVPA (min/day)	594	11	47	42	9	274	8	25	67	25

σ^2: Variance; Bc: Between-cities; Bp: Between-participants; Wp: Within-participants; ICC: Intraclass Correlation Coefficient, defined as 100-Wp%; $PM_{2.5}$: particulate matter with aerodynamic diameter of 2.5 µm or less; PM_{abs}: $PM_{2.5}$ absorbance; BC: Black Carbon; NDVI: normalized difference vegetation index; NOE: Natural Outdoor Environment; UV-B: ultraviolet radiation of medium wave; SED: Standard Erythemal Dose; MVPA: Moderate-to-Vigorous Physical Activity.

* Multivariate mixed linear models adjusted for the season, age, sex, and NO2 background levels as fixed effects and with random intercept effects for participant and city were used for each exposure. The model was computed between two measurements (one for each monitoring

period), for week measures it implies the average of at least 3 days (see methods), while air pollution measures implies one day.

Highlights

- The assessment of the personal external exposome is feasible.
- Personal external exposures are above the health recommendations.
- Personal external exposures are highly variable within person.
- External exposure variability can bias health effects estimation.
- There is little correlation between the different external exposures.