ERC Consolidator Grant 2014
Research proposal [Part B2]

Part B2: *The scientific proposal:* Air pollution and noise exposure related to personal transport behaviour: short-term and longer-term effects on health

The MobiliSense project will explore the short-term and longer-term effects that air pollution and noise exposures related to personal transport behaviour may have on respiratory health and cardiovascular health. Its final aim is to develop and deliver a flexible simulation tool for decision-makers to orientate policies to mitigate the detrimental health effects of transport-related exposures. This simulation tool will allow them to assess the health impacts of different scenarios (i) of changes in personal transport behaviour and (ii) of environmental changes in the exposure to air pollutants and noise during transport. The ground-breaking nature of the project is related to the precise assessment of transport behaviour over 8 days with GPS receivers and an electronic mobility survey; to the repeated assessment of transport behaviour at baseline and after two years (longitudinal follow-up); to the joint assessment of air pollution and noise (often investigated separately) through personal sensors; and to the repeated and intensive assessment of health in two successive 8-day periods over two years with passive and active sensors.

Section a. State-of-the-art and objectives

I – SOCIETAL BACKGROUND

The MobiliSense project is strongly related to ongoing policy efforts both at the national and European levels (i) in the field of Transport, (ii) for the regulation of air pollution, and (iii) for the regulation of noise.

Regarding Transport, while the first French National Health-Environment Plan (2004–2008) did not include specific actions targeting Transport, the third version of the Plan (2014–2018) will be connected to a specific Plan under development related to "Transport and Health", in accordance with the recommendation of the "Transport, Health, and Environment" Pan-European Programme. Regarding air pollution, following the 2012 revision of the Gothenburg Protocol on the reduction of emissions, the European Commission has adopted the Clean Air Policy Package in December 2013 that includes a new Clean Air Programme for Europe with new air quality objectives and stricter national emission ceilings. In 2008–2010, France requested a postponement of the deadline by which the limit value for particulate matter with an aerodynamic diameter of 10 µm or less (PM_{10}) should be met. This request was rejected by the European Commission for most metropolitan areas, a challenge that the "National Health-Environment Plan", regional "Climate, Air, and Energy Plans", and local "Atmosphere Protection Plans" will have to address. Regarding noise, the 2002 European Directive constrains local authorities to develop Plans for environmental noise prevention. In 2013, France was urged by the European Commission to reduce delays in the production of the strategic noise maps and in the implementation of actions, e.g., to reduce noise nuisances related to transport infrastructures, as will have to be addressed in the new "National Health-Environment Plan".

Overall, in the context of the insufficient evidence available attributable to the limitations of scientific studies, it is important to develop innovative research strategies to derive more reliable data on transport-related environmental exposures and on their health effects, to support international, European, and national policy efforts.

II – STATE-OF-THE-ART

The literature review of air pollution and noise effects reported below successively considers respiratory health (symptoms and lung function) and cardiovascular health (blood pressure and heart rate variability). This review (i) particularly focuses on transport-related exposures; (ii) distinguishes between short-term and long-term effects; (iii) emphasises limitations related to the assessment of health outcomes; and (iv) finally points to the limitations related to the assessment of air pollution and noise exposures in these studies.

II.A – Respiratory health

II.A.1 – Respiratory symptoms

As our project focuses on adults, studies of children are not reviewed here. Studies of air pollution in adults have usually documented associations with respiratory symptoms.[1] Among studies of long-term exposure to air pollutants, a Swiss study documented positive associations between annual concentrations of nitrogen dioxide (NO_2) or PM_{10} and chronic phlegm production, chronic cough, breathlessness at rest, and dyspnea.[2]

Regarding studies of short-term effects, a work conducted in different European cities based on background concentrations over 24 hours measured from a central site and on a daily respiratory questionnaire completed over 6 months concluded that a high concentration of particulate matter with an aerodynamic diameter between 2.5 and 10 µm was positively associated with shortness of breath and

wheezing.[3] As another example relevant to the present project devoted to exposures during trips, a Dutch study of 489 adults found that the exposure to black smoke over 24 hours was associated with upper respiratory symptoms, in a more consistent way than the exposure to sulphate and PM_{10} (black smoke was taken into account as an indicator of black carbon emitted by diesel engines).[4]

Several studies have focused on the effects of high concentrations of air pollutants on the exacerbation of symptoms among asthmatics or chronic obstructive pulmonary disease (COPD) patients. For example, a study of 75 asthmatic or COPD patients from the United Kingdom reported that high concentrations of NO_2 and ozone (O_3) over 24 hours were associated with wheezing or dyspnea within one or two days.[5] As another example, a more recent study that relied on a median follow-up of COPD patients of more than 500 days suggested that a higher concentration of PM_{10} was associated with dyspnea one day after.[6] However, certain studies also reported negative findings. Paradoxically, a study of 16 COPD patients that analysed, in addition to the background concentrations of particulate matter with an aerodynamic diameter of 2.5 µm or less ($PM_{2.5}$), data from a personal monitoring of the exposure to $PM_{2.5}$ did not identify an association with any of the respiratory symptoms examined,[7] probably because of the weak number of participants.

Limitations related to the assessment of the outcome to address in the present project: A key limitation is related to the methods that were used to survey respiratory symptoms: paper questionnaires referring to relatively long recall periods (24 hours, one week, one month) likely implied reporting biases and did not permit to ensure that participants effectively completed the questionnaire repeatedly over the observation period (two limitations that we propose to address with a smartphone survey).

II.A.2 – Lung function

A relatively weak number of studies have focused on the relationships between the long-term exposure to air pollutants and lung function. For example, a Swiss study showed that elevated annual concentrations of sulfur dioxide (SO_2), NO_2, and PM_{10} were associated with a lower forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1), with stronger relationships observed for PM_{10}.[8] A longitudinal analysis from the same study subsequently documented that a decrease in the concentration of PM_{10} was associated with a lower decrease of lung function over time.[9] More recently, a French study reported that a higher concentration of PM_{10} over the preceding 12 months was associated with a lower FVC and FEV_1.[10] However, it is important to emphasise that, comparing different exposure areas with each other, these studies of the long-term effects of air pollutants are vulnerable to residual confounding.[11]

Apart from long-term exposure, studies of the effects of short-term exposure to air pollutants were conducted[12] based on repeated spirometry measurements. For example, an Italian study of 29 participants found that a higher daily concentration of NO_2 was related to a decrease in FEV_1 among asthmatics but not among coronary patients.[13] The strength of the associations identified in studies seemed to depend on the average concentration of pollutants over the territory, with stronger associations at higher average concentrations. In a study of 16 COPD patients in Vancouver where the average concentration of PM_{10} was of 18 µg/m^3, each 10 µg/m^3 increase in the concentration of PM_{10} measured over one day was associated with a 3% larger decrease in FEV_1 between the morning and the evening measure.[7] In a study in which the average concentration of PM_{10} over 24 hours was above 150 µg/m^3, a 10 µg/m^3 increase in the concentration was related to a decrease of up to 7% in FEV_1.[14] However, a recent study also emphasised that even a "moderate" (compared to a "good") range of exposure to $PM_{2.5}$, NO_2, and O_3 over 24 hours according to the classification of the US Environmental Protection Agency was associated with a decreased FEV_1.[15]

Some studies of short-term effects of air pollutants have focused on the size of the time window to consider to better identify associations with lung function. A Korean study that compared different strategies to proxy the individual residential exposure from measures performed at fixed monitoring stations showed that a high concentration of PM_{10} was associated with a reduced FVC, especially when concentrations were assessed over 24 hours two days before the spirometry test.[16] This finding is coherent with another study that reported that an elevated concentration of PM_{10} over the 37–60 hours preceding the spirometry assessment was associated with a decreased FVC and FEV_1.[17] However, it must be emphasised that certain studies did not observe a relationship between the exposure to air pollutants and lung function.[18]

Few studies were able to connect the analyses of the relationships between air pollution and lung function with the issue of transport. An experimental (thus poorly generalisable) study of 60 participants demonstrated that walking for two hours in Oxford Street was associated with more important reductions in FVC and FEV_1 than that observed in the same participants when walking through Hyde Park.[12] This difference in the observed effect was particularly attributable to the higher exposure to ultrafine particles and black carbon (as markers of road traffic with diesel engines) in Oxford Street.

Limitations related to the assessment of the outcome and design to address in the present project: Previous repeated measure studies of lung function relied on very low sample sizes, or when larger samples were available, only a limited number of indicators of lung function were measured.[4] Moreover, all previous

studies of air pollution and lung function have relied on spirometry (forced breathing), and none of them was based on the recently developed assessment of lung function from tidal breathing (breathing in daily lives)[19,20] with impedance pneumography (as will be incorporated in the present project[21,22]).

II.B – Cardiovascular health

II.B.1 – Blood pressure

II.B.1.a – Air pollution effects: Relatively few studies have investigated associations between the chronic exposure to air pollutants and blood pressure or the prevalence / incidence of hypertension. For example, in a US study, a higher exposure to nitrogen oxides (NO_x) but not to $PM_{2.5}$ was associated with a slight increase in the incidence of hypertension over 10 years.[23] Similarly, a German study of long-term effects reported that higher concentrations of $PM_{2.5}$ were associated with an increased blood pressure. Of interest for the present project focusing on multiple exposures, this association persisted after adjustment for road traffic noise.[24]

A larger number of studies were conducted on the effects of the short-term exposure to air pollutants on blood pressure. Assessing short-term effects is important since a transient elevation of blood pressure repeated over time could lead to a chronic increase in blood pressure, and because a transient increase in blood pressure is a trigger of cardiovascular events in vulnerable individuals[25] (as a potential explanation of the increased incidence of cardiovascular events during pollution episodes[26]). As an example, a US study reported that an increase of 10 $\mu g/m^3$ in the daily concentration of $PM_{2.5}$ was associated with a 3.2 mmHg higher systolic blood pressure, with still stronger effects in the area where the average concentration of $PM_{2.5}$ was the highest.[26] However, certain studies did not observe positive short-term effects of air pollution exposure on blood pressure, or even negative effects.[27] These incoherent patterns of findings may be attributable to the fact that blood pressure depends both on vascular resistance and on the cardiac output, while the main hypothesis for air pollution effects is related to the first aspect (air pollution may increase peripheral resistance and decrease the elasticity of arterial walls). These considerations suggest that it may be relevant, as in the present project, to focus on markers of arterial stiffness. The inconsistency in the associations documented may also be attributable to the varying sources and composition of suspended particles from one place to the other, to differences in the susceptibility of populations, etc.[27]

Of importance for the present project interested in environmental exposures during trips, two studies found that the positive relationship between the short-term exposure to $PM_{2.5}$ and blood pressure was stronger in areas where the road traffic was particularly dense.[26,28] An experimental study demonstrated that the effects documented on blood pressure were attributable to the organic carbon fraction of $PM_{2.5}$, mainly to fossil fuel combustion products of traffic sources.[29] Another study that relied on repeated measures did not find any association between the concentration of $PM_{2.5}$ and blood pressure but reported that a higher exposure to black carbon over the previous 7 days was related to an increased blood pressure.[30]

All the aforementioned studies on blood pressure have assessed air pollutant exposure based on measures from fixed monitoring stations, while very few studies were able to measure personal exposure.[31,32] One study that measured concentrations of $PM_{2.5}$, organic carbon, and black carbon directly outside the residence showed that the strongest positive associations with blood pressure measured in a repeated way were documented for organic carbon, and for periods where the participants were at home and where measurement error was consequently the weakest.[33] However, studies that relied on wearable monitors of $PM_{2.5}$ (carried in a backpack) did not permit to conclude that personal exposure was more strongly associated with blood pressure than background concentrations.[34,35] These counter-intuitive findings may be attributable to the fact that the successive measures from a personal monitoring of air pollutants are all influenced by background levels of air pollution; to the fact that the type of particles involved may differ between the background level measures and measures from personal monitors for the particular territories examined; to the limited number of air pollutants examined in protocols of personal follow-up; to the very weak sample sizes involved in these studies ($n < 20$); and, possibly, to the insufficient reliability of the personal measures of exposure derived from the miniaturised devices that were used. It must be emphasised, however, that one study[31] showed that the personal exposure to $PM_{2.5}$ measured with a wearable monitor was more strongly associated with blood pressure than the concentration of $PM_{2.5}$ measured outside each participant's residence; but that the concentration of black carbon outside the residence showed a still stronger association with blood pressure, leading to the conclusion that a priority for future research may be to perform a personal monitoring of black carbon through wearable sensors (which was not done in this study, as opposed to the present project).

II.B.1.b – Noise effects: Regarding long-term effects, according to the World Health Organisation,[36] associations were consistently documented between the residential exposure to road traffic noise and hypertension. Most studies relied on noise maps derived from noise dispersion models. For example, a Swedish study of 1953 participants that assessed road and railway traffic noise at the residence from noise maps showed a positive association between road traffic noise and self-reported physician-diagnosed

hypertension, with a stronger association documented with incidence than with prevalence (based on a retrospective questionnaire), and with a stronger association when the analyses were restricted to individuals who had lived for a long time at their residence.[37] A Swedish cross-sectional study of 667 subjects found that the adjusted odds of self-reported physician-diagnosed hypertension were 1.38 times larger for each 5 dB(A) increase in road traffic noise exposure (dispersion model and expert classification) at lower overall noise levels than in other studies.[38] Interestingly, the association was stronger among participants who had lived at the address for >10 years and among those not having triple-glazed windows, living in an old house, and having the bedroom facing a street. Other studies performed direct noise measurements in selected study sites to assess long-term exposures. For example, a cross-sectional study conducted in Taiwan among 321 males and 499 females residing nearby four main roads of Taichung along which measurements were performed reported an adjusted dose-response increase across noise exposure groups in the prevalence of self-reported physician-diagnosed hypertension.[39]

Regarding other sources than road traffic, certain studies have documented relationships between air traffic noise and hypertension or blood pressure,[40-42] while few were able to take into account railway traffic noise or the multi-exposure to noise of different transport modes. For example, a Swiss study of 6450 participants found that a cross-sectional measure of systolic blood pressure increased by 0.6 or 0.8 mmHg for each 10 dB(A) increase in daytime or night-time exposure to railway noise, while associations with road traffic noise were only documented among participants with diabetes.[43] Of interest for the present project interested in the multi-exposure to noise and air pollutants, the adjustment for outdoor annual concentrations of NO_2 and PM_{10} did not result in weaker associations of road or railway traffic noise with blood pressure. Also of interest for the innovative joint assessment of objective and subjective noise levels in the present project, the European HYENA study found that the positive association between aircraft noise and the prevalence of hypertension was stronger among participants who reported being annoyed by aircraft noise.[44]

Only few studies in real-life, non-occupational settings have relied on wearable noise sensors to investigate short-term effects on blood pressure. Pointing to the limitations of resting blood pressure, a study of 60 young adults in Taiwan that simultaneously measured ambulatory blood pressure and personal noise exposure over 24 hours found that each 5 dB(A) increase in noise exposure was associated with a transient increase of 1.15 and 1.16 mmHg in systolic and diastolic blood pressure during daytime and of 0.74 and 0.77 mmHg during night-time.[45] A German study of 632 adolescents and 482 adults documented an association between night-time noise exposure (personal dosimetry over 24 hours) and hypertension (measured blood pressure), but did not report any association with the subjective assessment of noise from a diary (the study, however, did not examine interactions between objective and subjective noise assessments).[46]

Limitations related to the assessment of the outcome and design to address in the present project: First, most studies of long-term effects of noise have used a cross-sectional design (no incidence data on hypertension) and relied on self-reports of physician-diagnosed hypertension. Second, relatively few studies of air pollution effects were based on repeated measures of resting blood pressure,[47] and repeated measure studies have either recruited a small number of participants (much smaller than 100) or collected a limited number of measures per individual ($n \approx 3$[26,30]). Third, among repeated measure studies, extremely few have relied on an ambulatory monitoring of blood pressure,[33,45,48] and none has examined both resting and ambulatory blood pressure as we plan to do (each assessment having its own strengths). Fourth, extremely few studies have examined pulse pressure, central rather than brachial blood pressure (as more predictive of target organ damage and morbidity / mortality), and aortic pulse wave velocity or the augmentation index (as markers of arterial stiffness[49]) in relation to air pollutants.[27,50] Finally, the air pollution and noise studies that compared participants with each other (rather than repeated measures with each other) have insufficiently controlled for confounding factors related to individual and environmental characteristics[51] (our analyses of longer-term effects will have to address this concern).

II.B.2 – Heart rate variability

Researchers have focused on heart rate variability to investigate how the sympathetic and parasympathetic branches of the autonomous nervous system modulate heart rate. An alteration of the autonomous regulation of heart rate may be one of the pathophysiological mechanisms through which air pollution increases cardiovascular mortality,[52,53] as also confirmed by toxicological studies.[54] Such a mechanism may also contribute to the increased incidence of ischemic heart disease associated with long-term noise exposure.[55,56] Indeed, studies have shown that reduced heart rate variability may be associated with an increased incidence of myocardial infarction in the general population, and with a poor prognosis in heart disease patients.[57-59]

II.B.2.a – Air pollution effects: The strongest evidence for a relationship between an increased exposure to air pollutants and reduced heart rate variability has been reported for particulate matter.[47] A meta-analysis (18667 participants from 29 studies) of the relationship between particulate matter and heart rate variability suggests that an increased concentration of $PM_{2.5}$ is associated with a reduced heart rate variability, as

demonstrated by indicators of both the time domain and the frequency domain.[60] Even if certain studies have reported stronger air pollution effects among people with cardiovascular diseases,[61] this meta-analysis did not observe that the association became weaker when studies with cardiovascular disease patients were excluded. Studies have often measured air pollutant exposure over 24 hours. For example, a work that assessed the concentration of $PM_{2.5}$ from a fixed monitoring station reported that considering exposure windows of 1 hour to 4 hours did not yield a stronger association than an exposure window of 24 hours.[62] It should be noted, however, that certain studies did not identify associations between an increased exposure to air pollutants and reduced heart rate variability, or even reported associations in the opposite direction.[63-65]

Regarding air pollutants from traffic sources, a study of 28 elderly subjects reported that a high concentration of $PM_{2.5}$ (assessed from fixed monitoring stations) was associated with reduced heart rate variability, but that the concentration of black carbon resulted in stronger associations and with a larger number of indicators of heart rate variability.[66] A high concentration of carbon monoxide (CO) was also associated with reduced heart rate variability, but the association with CO had entirely disappeared after adjustment for black carbon, a marker of particles from road traffic.

II.B.2.b – Noise effects: The literature on the effects of noise on heart rate variability is much scarcer than that available on the effects of air pollutants. A German study of 110 individuals (326 electrocardiogram recordings) observed that increases in sound pressure below 65 dB(A) were associated with changes in heart rate variability suggestive of an elevation in sympathetic tone and parasympathetic withdrawal, while elevations in sound pressure above 65 dB(A) were primarily associated with increased sympathetic activity.[55] Of relevance for the present project is a Chinese randomised crossover study of participants successively spending time in a traffic centre and in a park who underwent personal monitoring of noise and traffic-related air pollutants ($PM_{2.5}$, CO, and black carbon).[56] This study found that higher noise levels were associated with reduced heart rate variability, resulting from an increased sympathetic activation and a decreased parasympathetic modulation. It also reported that noise levels modified the relationships between air pollutants and heart rate variability.

Limitations related to the assessment of the outcome and design to address in the present project: First, previous repeated measure studies of heart rate variability have relied on small sample sizes. For example, of the 25 repeated measure studies identified in the aforementioned meta-analysis of air pollution effects,[60] one study included 100 participants, 3 studies between 50 and 100 participants, and 21 studies less than 50 participants. Second, a number of studies did not combine indicators of heart rate variability from both the time domain and the frequency domain, although certain did.[60,67]

II.C – Assessment of environmental exposures

A major challenge of studies on environmental effects is to assign an individual exposure to the participants while minimising the associated error. It has been shown for long that the environmental exposure measures used in the analyses can have a significant influence on the associations estimated with health outcomes.[68] Regarding air pollution, a large proportion of studies have assigned to each participant the background concentrations of pollutants measured at the closest monitoring station, or have averaged or interpolated measures at different stations.[16] Other studies have relied on estimations of outdoor concentrations at the residence from air dispersion models.[10,11] Regarding noise, studies have also often relied on the noise value from modelled maps at the residential location.[37] Assessing individual environmental exposures with these approaches has a limited validity[34,69]: (i) because the exposure data either ignore proximity sources (background concentrations of air pollutants), or only imperfectly account for the effects of these proximity sources on the exposure (air dispersion models), or ignore the circumstances of exposure (e.g., noise assessed on the most exposed façade of buildings[70]); (ii) because people spend a different fraction of their time at their residence (where the exposure is estimated) rather than at other places visited during their daily activities; and (iii) because people spend a different amount of time inside rather than outside buildings (while the estimation approaches often use outdoor exposure data). As a consequence, a study found that concentrations of pollutants measured at fixed monitoring stations did not permit to assess in a valid way personal exposures during trips.[71] Due to the aforementioned sources of measurement error, the magnitude of misclassification resulting from the use of residential estimates of exposure likely varies according to individual profiles. Combining precise locational information obtained from GPS tracking with maps of pollutants, as few studies have done but often without the concomitant measurement of health outcomes,[72] only partially addresses these limitations.

Even if certain studies could not demonstrate that personal measures of air pollutants are more strongly associated with health than concentrations from fixed monitoring stations,[7] there is a large consensus that the use of wearable monitors is key to improve the assessment of personal exposures.[31] Studies have shown that the personal exposure to suspended particles measured by wearable sensors had a weak spatial correlation with background concentrations from fixed monitoring stations.[73] Moreover, even if longitudinal studies

have usually reported stronger correlations between personal measures of exposure to particulate matter and background concentrations,[73,74] they also suggest that these correlations are relatively weak for a number of individuals, thus emphasising the benefits of personal monitoring.[74,75]

Another important aspect is that most studies captured the exposure (either air pollution or noise) aggregated for entire periods without discriminating between subperiods of space-time budgets (for example over 24 hours in analyses of short-term effects). As recently emphasised,[76,77] very few studies have determined real-life exposures related to the personal transport habits of people. Regarding air pollution, the preliminary evidence available suggests that many people receive a significant fraction of their exposure to certain pollutants when commuting to work,[78] and that the time spent in traffic contributes significantly to the personal exposure to these pollutants.[12,79,80] Accurately quantifying levels of exposure to air pollutants and noise in the multiple microenvironments, especially in the different transport modes, would represent a significant advance, as a study for example showed that the exposure to $PM_{2.5}$ was particularly associated with mortality when the primary source of exposure was motor vehicle exhaust.[81] The very few studies[71,76] that compared exposure levels between the different transport modes, mostly related to air pollution rather than to noise, were often based on small samples and often compared two predefined itineraries (thus were poorly generalisable) and a limited number of alternative modes. Even if their findings will have to be confirmed with more robust and generalisable designs, these studies suggest that the itinerary and the transport mode selected influence the personal exposure level. Overall, while few studies of air pollution effects and still less studies of noise effects[55] have used wearable monitors, the use of such air pollution and noise sensors should permit to better characterise personal exposures and reduce the misclassification of exposures.[55,77,78] Moreover, personal monitoring will be particularly useful to investigate exposures related to personal transport habits, if and only if we are able to deploy it together with novel methodologies from Transport sciences allowing us to accurately apprehend participants' transport habits and use of modes.

In addition to this overall challenge, there are specific challenges related to the assessment of air pollutants and noise. Regarding air pollution, first, only very few studies to date have performed a personal monitoring of black carbon, which is a priority for at least two reasons in the present project: (i) because black carbon is seen as an excellent marker of particulate pollution related to road traffic (tire wear particles, diesel vehicle exhaust),[82] a recent study demonstrating that transport episodes represented 6% of the participants' time but 21% of their exposure to black carbon and 30% of inhaled doses[77]; and (ii) because our literature review reported evidence that black carbon was more strongly associated (e.g., than $PM_{2.5}$) with the respiratory and cardiovascular outcomes examined in the present project. Second, only a limited number of studies of short-term effects of air pollutants have accounted for estimates of inhaled doses[71,77] as we plan to do. Regarding noise exposure, first, a considerable number of studies have investigated how objective noise influences self-reported annoyance due to noise[83]; however, even if individuals may evaluate a given sound level as annoying or even pleasant depending on the source and behavioral context,[46] very few studies were able to account for subjective annoyance as a modifier of noise effects on cardiovascular outcomes.[44] Second, studies relying on noise maps (imprecise for assessing personal exposure) were able to distinguish between road, air, and rail traffic noise,[41,43] but studies that relied on personal noise dosimeters were often unable to distinguish between sources of noise,[46] i.e., did not use some of the recently developed procedures of recognition of sources of noise as we plan to do. Third, studies related to cardiovascular outcomes have assessed the average overall sound pressure in dB but have never, especially in real-life settings as opposed to laboratory environments, examined impulsive noise, or distinguished between noise frequency components[84] (e.g., low and high pitch sounds) through frequency spectrum analysis (a considerable limitation because the different organs are susceptible to different acoustic frequencies).

Finally, very few cardiovascular studies developed a multi-exposure perspective considering both air pollutants and noise,[24] and extremely few based on personal monitors. Two studies used personal monitors to perform a simultaneous assessment of noise and particle number concentration,[55] and of noise, $PM_{2.5}$, CO, and black carbon.[56] Both were related to heart rate variability, and we are not aware of any such study for blood pressure. Such strategies of simultaneous monitoring thus need to be further developed, (i) because road traffic is a shared source of air pollutants and noise and provides potential for reciprocal confounding,[55,56] and (ii) in order to investigate amplification effects (interaction between these exposures).

III – OBJECTIVES AND GROUND-BREAKING NATURE OF THE PROJECT

III.A – Objectives

III.A.1 – Overall orientation of the project

Building on data collection and analytic methods from Epidemiology, Geography, and Transport sciences, the present project aims to develop a comprehensive assessment of the relationships between transport-related exposures and health based on a representative sample of 1000 participants followed over two years, to support European and national policies. Its objectives are to address a gap in knowledge: (i) by focusing

on both short-term and longer-term effects of personal transport behaviour on health, based on a repeated assessment of transport behaviour and health over two years (to allow for differential health changes); (ii) by considering two distinct environmental exposures (air pollution and noise) related to the transport activity that have often been investigated separately; (iii) by assessing a wide range of health outcomes related to respiratory and cardiovascular health; (iv) by deriving reliable measures of exposures, confounders, and outcomes using a number of passive and active sensors and innovative electronic survey methods; and (v) by using simulations to evaluate the health impacts of scenarios of change of personal transport behaviour and of reduction of exposures during transport, as a tool for decision-makers to orientate public policies.

III.A.2 – Empirical objectives

(i) We will assess the contribution of personal transport behaviour to the overall air pollution ($PM_{2.5}$, black carbon, NO_2, and O_3) and noise exposure of individuals; we will compare the air pollution and noise exposure in the different transport modes (walking, biking, 2-wheel or 4-wheel personal motorised vehicle, public transport modes); and we will examine the extent to which transport-related exposures contribute to differences in air pollution and noise exposure between socioeconomic groups.

(ii) We will investigate whether (a) profiles of transport behaviour, (b) total personal exposure to selected air pollutants and noise, (c) transport-related personal exposure to selected air pollutants and noise are associated with short term respiratory and cardiovascular outcomes and with longer-term (two-year) changes in respiratory and cardiovascular outcomes (as summarised in the Table below).

(iii) We will investigate whether transport behaviour, air pollution exposure, and noise exposure mediate socioeconomic disparities in short-term and longer-term changes in respiratory and cardiovascular outcomes.

(iv) As a tool for decision-makers to orientate policies to mitigate the detrimental health effects of transport-related exposures, we will perform simulations on the basis of the empirical associations estimated to assess the extent to which individual changes in transport habits (scenarios of behavioural change) or changes in exposure levels during transport (scenarios of environmental change) would decrease the time of exposure to air pollution and noise levels above those recommended, and subsequently affect respiratory and cardiovascular health. We will deliver a flexible and easily usable simulation tool for policy-makers.

Summary of short-term and longer-term associations examined between transport behaviour, related exposures, and respiratory and cardiovascular health

Main outcome variables / Main exposure variables	Spirometry (peak expiratory flow, FEV_1, FVC, etc.)	Impedance pneumography (ratio of volume at peak expiratory flow to total expired volume, entropy of breathing, etc.)	Respiratory symptoms (cough, shortness of breath, wheezing, etc.)	Blood pressure at rest, pulse pressure	Ambulatory blood pressure (brachial and central blood pressure, pulse pressure, pulse wave velocity, augmentation index)	Heart rate variability (indicators from the time and frequency domains, nonlinear parameters)
Transport behaviour Time spent in transport, modes used	×	×	×	×	×	×
Total or transport-related personal exposure to air pollutants Concentrations, inhaled doses	×	×	×	×	×	×
Total or transport-related personal exposure to noise Overall sound pressure, impulsive noise, frequency components, source-specific noise, interaction with annoyance				×	×	×

III.A.3 – Methodological challenges

To adequately address the empirical objectives, the project will have to focus on methodological challenges related to the assessment of environmental exposures and to the investigation of their effects:

(i) We will test the validity of different personal and easily wearable monitors of air pollutants (black carbon, $PM_{2.5}$, and NO_2) that provide regular timestamped information and are sufficiently miniaturised to not interfere with behaviour. The aim will be to evaluate these sensors prior to their inclusion in the study in the typical conditions of the territory: streets of Paris, underground public transport modes, etc.

(ii) We will test innovative approaches allowing us to investigate whether the health effects of noise: (a) are stronger when the subject is annoyed by the source of noise; (b) are stronger for impulsive noise (sound pressure peaks); (c) are particularly attributable to specific noise frequency components (e.g., low or high pitch sounds) or to noise containing discrete frequencies or marked tones; and (d) are particularly attributable to specific (automatically identified) sources of noise.

(iii) We will compare the exposure to different air pollutants and noise: (a) measured by personal sensors worn by the subject; (b) estimated by combining the participants' GPS tracks (itineraries of trips and stays at activity places collected by GPS receivers and validated / corrected through the electronic mobility survey)

with information from the model-based maps of noise and hourly air pollutant concentrations; and (c) estimated at the residence as commonly done with modelled maps. We will examine the extent to which measuring exposures with personal sensors allows us to better capture the exposure–health associations.

(iv) We will test innovative modelling approaches allowing an improved characterisation of the relationships between air pollution and noise exposure and health: (a) we will assess the time size of the exposure window and the lag to incorporate between the exposure window and the health outcome to best capture the relationships between environmental exposures and health; and (b) we will systematically examine, beyond the average associations, the heterogeneity in the exposure–health relationships: according to health and sociodemographic characteristics; according to the geographic location of the residence or of the activity places; according to the level of the exposure; and according to the level of the outcome itself.

III.B – Ground-breaking nature of the project

To contribute to strengthen the partnership at the local, national, and European levels between Public health and Urban planning decision-makers and inform European and national policies designed to mitigate the environmental hazards associated with motorised transport, our project aims to provide a more comprehensive evaluation of the health effects of exposures related to personal transport behaviour than previous studies, by building on innovative data collection and analytic methods from Epidemiology and Social epidemiology, Geography, and Transport sciences.

Regarding measurement strategies, a key strength of the project is that it systematically relies on objective measurement approaches for the assessment of exposures, confounders, and health outcomes. The protocol will use passive sensors of location, behaviour, environmental conditions, and health (GPS receivers, accelerometers, air pollution and noise sensors, heart rate monitors, ambulatory blood pressure monitors, and impedance pneumography) and active sensors, i.e., devices requiring an action of the subject for measurement (blood pressure at rest and spirometry). The use of some of these sensors / monitors is extremely innovative: the recently developed ambulatory blood pressure monitor that will be used (TensioMed Arteriograph 24) measures central blood pressure (which is more predictive of target organ damage than brachial blood pressure) and aortic pulse wave velocity and the augmentation index as markers of arterial stiffness[49], as very rarely examined in relation to air pollution and noise; the BioPatch that will be worn to assess heart rate variability (and accelerometry and the respiratory rate) has recently received its certification from the US FDA; impedance pneumography is very novel and has never been used to investigate air pollution effects on respiratory health; and no study has ever relied on a repeated smartphone survey to assess respiratory symptoms as close as possible from their onset.

A second measurement strength of the project, integrating methodologies from Public health / Nutrition and Transport sciences,[85,86] is related to the precise measurement of personal transport behaviour over 8 days using GPS receivers and a GPS data-based electronic survey of activities and transport modes. Our RECORD MultiSensor Study was the first ever in the world to combine GPS tracking, such an advanced algorithm-based processing of GPS data, and a full electronic mobility survey over 8 days based on a web application relying on this pre-processed information. This approach allows us to decompose in a precise way the 8-day follow-up period into time spent at the different activity places and trips and trip stages (segments of trips with a unique mode), permitting to ascribe the data collected with the behavioural, environmental, and health sensors to each trip or activity place time segment of the mobility survey. Moreover, based on the repeated assessment of 8-day transport behaviour at baseline and after two years and on a systematic survey assessment of whether people regularly go to the places visited, we will develop a methodology to distinguish between *casual* transport behaviour over 8 days and *regular* transport behaviour (over a longer period), as needed to investigate short-term and longer-term effects of transport on health.

Other measurement strengths of the project include, as very few studies have done,[55,56] the simultaneous monitoring of air pollution and noise with personal monitors, and the comparison of exposure measures based on personal sensors and GPS tracks (Geographic methodology). Finally, the project will promote ground-breaking strategies to investigate noise health effects allowing us to assess: whether smartphone-evaluated noise annoyance modifies the effects of objective noise; the effects of impulsive noise (sound pressure peaks); whether accounting for noise frequency components determined by frequency spectrum analysis in addition to the overall sound pressure permits to better describe health effects; and whether specific sources of noise (e.g., road traffic) automatically identified based on predefined noise patterns are particularly associated with cardiovascular health.

The innovative analytical strengths of the project are the following: (i) it relies on a *momentary perspective*, i.e., analyses repeated measures of health for each individual in function of the exposures and circumstances preceding measurement; (ii) various strategies to account for the otherwise biasing influence of residual spatial and temporal autocorrelation in the data will be explored; (iii) Random forest approaches[87]

will be used to compare the importance of the multiple versions of the exposure measures; (iv) the project will rely on a complex regression model to perform a joint analysis of the *short-term effects* and *longer-term effects* of exposures based on longitudinal data; and (v) we will apply mediation analyses involving a primary exposure (socioeconomic status), intermediary exposures (air pollution and noise), and health endpoints, as a potential mechanism contributing to socioeconomic disparities in health.

As important information for the development of European and national policies, these ground-breaking innovations will permit, compared to previous research, (i) to precisely quantify the percentage of exposure to various air pollutants and noise that is attributable to the transport activity; (ii) to establish a more precise link between the use of each transport mode and the exposure to air pollutants and noise as a way to better understand source-specific impacts as recently recommended[88]; and (iii) to assess the health impacts of scenarios of changes both in personal transport behaviour and in exposure levels during transport.

Section b. Methodology

I – DATA COLLECTION AND PROCESSING

I.A – Sampling and recruitment

A Gantt Chart of the project tasks is reported in Extra Annex 6. The participants will be recruited through a three-stage stratified sampling design. The neighbourhood sampling phase will involve the random selection of local neighbourhoods (average number of residents = 2000) in the Paris city and first crown of counties around Paris, stratified by area-level socioeconomic status and road traffic density. Socioeconomic status will be assessed with a composite index (education, occupation, income) based on the 2011 Census and Tax registry, and traffic density with the regional traffic model of the Ministry of Infrastructures. Neighbourhoods will be categorised according to the quartile of socioeconomic status and to the quartile of traffic density to which they belong. To maximise disparities in exposure to air pollutants and noise, within each socioeconomic stratum, we will randomly select five neighbourhoods in each of the two extreme quartiles of traffic density (10 neighbourhoods in each socioeconomic quartile, i.e., 40 neighbourhoods).

At the second stage, the exhaustive land and real estate property file from the Tax administration will be used to sample dwelling units in each of the selected neighbourhoods. We will perform a systematic, without-replacement probability sampling of dwelling units in each neighbourhood. Each selected dwelling will be contacted by telephone, and if not reachable after five calls, will be visited at least five times at different times of the day. Technicians will derive an exhaustive list of household members between 30 and 64 years of age, speaking French, and free of cardiovascular or cerebrovascular diseases, and will divide them into three groups: hypertensive individuals; individuals with self-reported chronic bronchitis, chronic cough or sputum production, or asthma; and others. At the third stage, within each household, eligible individuals within each of these three strata will be selected for participation according to a stratum-specific sampling rate (clustered stratified sampling). Based on realistic hypotheses on household sizes, on the prevalence of the different health conditions in the age group, on the proportion of households that will not be reached, and on the probability of acceptance to participate in the study, and based on the target sample size of 250 hypertensive participants, 250 individuals with respiratory problems, and 500 participants free of these conditions (n = 1000 overall), (i) the sampling probability will be equal to 0.40 for hypertensive individuals, equal to 1 for eligible individuals with respiratory problems, and equal to 0.60 for individuals free of these conditions; and (ii) the initial sample drawn from the Tax registry will comprise 8000 dwellings, i.e., 200 per neighbourhood. Reserve samples of 80 dwelling units (2 per neighbourhood) will be drawn, and will be used progressively if the initial sample does not allow us to reach the desired sample size.

There will be absolutely no problem of statistical power to investigate short-term effects, given that the individual-level sample size of our repeated measure study is 10 times larger than that of most of the comparable repeated measure studies published so far. This large sample size, however, will be useful to investigate effects on changes in health over two years (and beyond): assuming a Type 1 error rate of 5%, a power of 80%, a given variance for the outcome and a correlation of 0.9 between the measures aggregated over several days at baseline and at year 2 (tested in our RECORD Study), a set of determinants of the outcome accounted for in the analyses, and an attrition of 20% over two years (considering that only participants who agree to perform the follow-up will be recruited and that participants will receive a gift card of 30 € at each collection wave), a baseline sample size of 1000 participants will allow us to detect differences in the change in, for example, systolic blood pressure between baseline and follow-up of slightly less than 1 mmHg between the two contrasted neighbourhood exposure groups. Considering outdoor residential exposures, the average difference in exposure between the two contrasted groups of neighbourhoods is expected to be, for example, of more than 30 $\mu g/m^3$ for NO_2 and of more than 25 dB(A) in A-weighted day-evening-night equivalent sound level (Lden). Given the contrasted exposure groups selected, the reliable health variables that will be used (averaging measures over 8 days), and the two-year

follow-up (to allow differential changes to occur), the sample size will allow us to detect the expected longer-term effects.

The participants will be recruited at home. The participants will fill out questionnaires on the following dimensions: socioeconomic status, health related behaviour (physical activity, food frequency questionnaire, smoking, alcohol consumption), perception of their residential environment, resources for transport (driving licence, bike or vehicle ownership, public transport pass, gasoline or diesel engine of vehicle), cooking and heating equipment, environmental tobacco smoke, double / triple-glazed windows in the dwelling, etc.

Over the 8 days, the participants will alternate between a "cardiovascular health" configuration of sensors and a "respiratory health" configuration of sensors. The "cardiovascular health" configuration will apply to days 1, 3, 5, and 7, and the "respiratory configuration" will apply to days 2, 4, 6, and 8. In both configurations, participants will carry a GPS receiver, an accelerometer, and an air pollution monitor. In the "cardiovascular health" configuration, they will additionally carry a noise sensor; they will undergo ambulatory blood pressure monitoring for 24 hours; they will then measure their blood pressure at rest in the morning and in the evening on days 3, 5, and 7 (day 1 devoted to ambulatory monitoring); their heart rate will be measured continuously on days 3, 5, and 7; and they will be surveyed on their annoyance related to noise with a smartphone. In the "respiratory health" configuration, they will instead wear a second air pollution monitor and the impedance pneumography (IP) recorder; they will perform a spirometry test in the morning and in the evening; and they will be surveyed on their respiratory symptoms with a smartphone. Participants will wear all the devices from wakeup to bedtime and will be instructed to recharge the devices as appropriate. Participants will receive a gift card of 30 €, a strong support during the follow-up, and detailed reports on their health status. Our accumulated experience in pilot studies since 2012 (in which participants receiving no gift card wore as much as five sensors) suggests that we will be able to recruit participants.

Over the 8-day period of the baseline wave, participants will provide 12000 respiratory questionnaires, 8000 measures of spirometry, 4000 days of follow-up of tidal breathing, 3000 days of follow-up of heart rate, 49500 measures of ambulatory blood pressure, and 8000 measures of resting blood pressure. The literature review above shows that it is a very large sample size for a repeated measure study. The devices will be recovered during face-to-face appointments.

I.B – Mobility and transport assessment

Participants will be surveyed with the VERITAS web mapping application that we have developed with the University of Montreal,[89] to geocode the regular places where they perform a list of predefined activities.

Participants will wear a BT-Q1000XT GPS receiver and a wGT3X+ accelerometer at the belt for 8 days. Relying on the most advanced survey strategies in Transport sciences (that were further developed for the present project[85,86]), the GPS data will be downloaded and automatically analysed with algorithms integrated to the TripBuilder application. On the basis of the GPS data (locations, speeds, and accelerations) and external sources of data (survey questions on transport resources, VERITAS data on regular activity places, geographic information system data on points of interest and public transport stations), these algorithms identify the activity places (stops) and the trips (and their unimodal components) between these places, and automatically impute information on certain of the activities performed at the different places and on the transport modes used in each trip. The pre-processed GPS tracks and the imputed information will be automatically uploaded in the web mapping interface of the TripBuilder application that has been optimised for the study. Presenting the GPS tracks and related information on an electronic map, this application will allow us to survey the participants on their activities and transport modes in each trip (validate, correct, or complement the imputed information). The application also permits to edit the GPS tracks, by eliminating the artefacts and by graphically reporting missing trips or portions of trips. The final output over 8 days comprises the cleaned GPS tracks; the location of, the arrival time to, and the departure time from each activity place; and the location and time of each point of change of mode during trips. The survey technicians will also ask to the participants how often they went to each of the activity places (per week, month, or year) over the previous year, overall and with the same transport mode (this information will be used to assess the regular transport behaviour of participants, see below).

I.C – Smartphone survey

On the "cardiovascular health" days of the protocol, the detection of a certain noise level (to be determined in the final pilot tests) with the smartphone sensor will trigger a survey on the smartphone asking to the participants to describe the source of noise and to rate the degree pleasantness / unpleasantness of the sound and related annoyance. On the "respiratory health" days of the protocol, participants will be surveyed on their respiratory symptoms, and will have to indicate whether the symptom was absent, mild, or severe over the last hour: asthma attack, loose or hacking cough, shortness of breath, wheezing, phlegm, runny nose, and

stuffed nose (adapted from the European Community Respiratory Health Survey). Participants will receive an alert at a random time three times per day on the Samsung Galaxy S4 smartphone provided for the study, prompting them to answer to this very short survey. The smartphone survey system from our colleagues in Minnesota (MEI Research) that we currently test permits a real-time follow-up of the response rate of each participant from the web platform, and thereby to intervene in order to encourage participation if needed.

I.D – Spirometry

On the "respiratory health" days of the protocol, a spirometry test will be performed by the participants before taking their medications each morning and each evening using SmartSpiro (for which the participants will receive a training), a device that meets the ATS and ISO standards. SmartSpiro measures the following indicators: peak expiratory flow (PEF), FEV_1, FVC, the forced expiratory flow between 25% and 75% of vital capacity, and the forced expiratory volume in 6 seconds. The device has been designed to reject the maneuvers that are incorrectly performed and to provide explanatory feedback to the participants to improve the measure. The participants will not have to write down the measures, as SmartSpiro will automatically send the information to the study server through a connection to the Samsung smartphone provided to the participants. The lung function indices will also be expressed as percentages of the values predicted from the age, sex, height, and weight of the participants.[13,90] Moreover, following Hoek, we will determine dummy variables indicating whether each particular measure is 10% or 20% below the median value of the personal set of morning or evening measures.[91]

I.E – Impedance pneumography

Impedance pneumography measures changes in the electrical resistivity of the thorax when air enters and leaves the lungs while breathing. Recent developments of this technique conducted by colleagues from the Tampere University of Technology[21,22,92] will enable for the first time in an air pollution study the continuous monitoring of lung function and of its time variations by considering tidal breathing during normal daily life (as opposed to spirometry that only provides a momentary snapshot of lung function in a rather artificial setting). It has been shown that the shape of the tidal breathing flow curve and the time variations of the tidal breathing flow yield information on an individual's respiratory state, including the presence of airway obstruction.[19,20] On the "respiratory health" days of the protocol (days 2, 4, 6, and 8), we will use the miniaturised IP recorder (4 electrodes) to collect impedance pneumography data. The processing of these data implies (i) to select the data segments that are not distorted by excessive movements of the subject; (ii) to run a filter algorithm allowing to clean out cardiogenic distortions[93]; and (iii) to derive indicators that reflect the degree of airway obstruction based on the shape of the tidal breathing flow curve and on the time variations of the tidal breathing flow.

I.F – Ambulatory and resting blood pressure

On day 1 (the day after the recruitment day), participants will wear a "TensioMed Arteriograph 24" ambulatory blood pressure monitor for 24 hours, including day and night. Participants will be equipped after waking up at their residence by a trained technician. The device will allow us to measure, as extremely few studies have done, in addition to brachial (peripheral) systolic and diastolic blood pressure and pulse pressure, central systolic blood pressure and pulse pressure, and aortic pulse wave velocity and the so-called augmentation index as markers of arterial stiffness.[49] The device will take a measure every 20 minutes during the day and every 45 minutes during the night.

Starting in the morning of day 3, participants will be asked to measure their blood pressure at rest in the morning and in the evening 3 successive times, while sitting and relaxing, with their non-dominant arm resting on a table (according to the self-measurement protocol of the European Society of Hypertension). Participants will be asked to perform the morning measure before taking their medications. Self-measurement of blood pressure, especially for several days, is thought to be as reliable as measurement at the physician's office.[94] Participants will use the certified Withings blood pressure monitor that will permit the real-time transmission of the measures to the study server through a connection to the Samsung smartphone provided to the participants. The participants will answer each morning and each evening on the smartphone to a very short survey on the circumstances of measurement of blood pressure (medications taken, time spent at rest, social interactions, ambient noise). The average of the second and third measures will be used in the analyses. Pulse pressure will be determined as the difference between systolic and diastolic blood pressure.

I.G – Heart rate variability

On days 3, 5, and 7, a monitoring of heart rate will be performed from wakeup to bedtime with the Zephyr BioPatch worn on the left below the pectoral muscle. The RR interval file will be determined from an electrocardiogram sampled at 250 Hz. The raw ECG data in mV will be stored at 250 Hz. In close collaboration with a start-up company related to the Tampere University of Technology, the Kubios software

will be used to determine heart rate variability parameters related to the time domain and to the frequency domain. While the former do not allow one to distinguish between the sympathetic and the parasympathetic modulations of the central nervous system, the latter decompose the periodical oscillations of heart rate at different frequencies. We will also apply nonlinear methods. Indicators of heart rate variability will be determined for 5 minute, 1 hour, and 24 hour intervals.

I.H – Follow-up after two years

Participants will be invited to perform the same data collection (locational, behavioural, environmental, and health sensors) after two years (allowing for differential changes between exposure groups to occur). They will be recruited only if they intend to participate in the two study waves. They will also receive a gift card of 30 € for the second data collection. Our plan is to pursue the follow-up after two years with complementary sources of funding.

I.I – Air pollution and noise exposure

I.I.1 – Short-term exposures from personal monitors

Air pollution exposure: Through a service provision contract, we will ask the Ile-de-France region Air quality monitoring network (AIRPARIF) to evaluate for the measurement of personal exposure to air pollutants: the Aethalometer AE51 (black carbon), the Sidepak AM510 and the CairSol ($PM_{2.5}$), and the Aeroqual S300 (NO_2). AIRPARIF will test the reproducibility of the measures with different devices of the same type, will compare the measures with those obtained from already validated devices, will assess pollutant levels in different microenvironments, and will examine the impact of different interfering factors (including temperature and humidity). The recent experience of AIRPARIF shows that the presence of a miniaturised monitor of air pollution on the market offers no guarantee of its reliability for ambulatory monitoring, a limitation that has been seriously underestimated in recent epidemiological studies and that we intend to overcome through the collaboration between epidemiologists (Inserm) and metrologists (AIRPARIF). For example, tests have shown that the CairSens does not permit a reliable ambulatory monitoring of NO_2 due to the presence of artefacts resulting from variations in humidity from one microenvironment to the other. However, we are confident that the Aeroqual S300 to be tested in the project will provide more reliable measures because it incorporates a humidity sensor. It is important to emphasise that we will be able to conduct the project in any case as we will rely on the Aethalometer AE51 (in addition to one other air pollutant monitor that the tests will identify, to improve the characterisation of exposure). The Aethalometer AE51, yielding measures of black carbon whose significance for health has been emphasised in the review above, has been already successfully used in a small number of studies.[76,77,95]

Two approaches will be used to estimate the inhaled doses of pollutants. In both approaches, we will multiply the inhaled volume of air estimated for each minute of the follow-up by the corresponding exposure concentrations. This one-minute inhaled volume of air will be calculated for each subject: (i) using a series of stochastic equations, according to the age, sex, and weight, and to the corresponding one-minute energy expenditure estimated from the accelerometer[72,96]; or (ii) by multiplying the respiratory rate measured continuously with the BioPatch by an estimate of the average volume in one breath from the IP recorder.

Noise exposure: On the "cardiovascular health" days, the Svantek SV 102+ dosimeter fixed at the belt, with a microphone attached to the participant's collar close to the ear, will be used for a personal monitoring of noise. First, in addition to the average overall sound pressure in dB(A), we will assess impulsive noise (sound pressure peaks). Second, this dosimeter integrates a one-third octave band filter, permitting to divide noise into its frequency components (frequency spectrum analysis). Dummy variables will be determined to identify the octave bands that contain the majority of the total sound power. It will allow us to assess in a very innovative way[84] the effects of noise frequency components, and of noise containing discrete frequencies or marked tones (higher level in a one-third octave band than in the adjacent frequency bands, more likely to be perceived as a nuisance), on blood pressure and heart rate variability. Third, we will rely on the Orelia ACE-plugin software enabling the automatic recognition of sources of noise (road traffic, aircraft traffic, railway traffic, industries, social interactions, music, etc.) based on the search of specific patterns of noise. A fourth innovation related to noise exposure assessment will be to perform surveys of noise annoyance with the smartphone triggered by the detection of high noise levels (see above).

The participants will be instructed to place the air pollution and noise monitors as close as possible from them when they do not wear them (e.g., when sleeping or bathing).

I.I.2 – Estimation from exposure maps

For comparative purposes, we will also approximate the air pollution and noise exposure with model-based maps of air pollutants and noise, both (i) at the residence as commonly done in the literature and (ii) along the GPS tracks over 8 days (corrected and complemented during the survey). In the second approach,

building on Geographic methods, we will extract the air pollutant or noise exposure value from the model-based map at each GPS point and aggregate the information at the level of relevant periods (see below).

The hourly maps of pollutants used for these approaches of estimation of individual exposures will be made by AIRPARIF. The modelled maps of $PM_{2.5}$, black carbon, NO_2, and O_3 are based, for background pollution levels, on the CHIMERE model that is grounded on an emission inventory and corrected using measures from the network of background monitoring stations, and for the proximity to sources, on the ADMS software (except for O_3) that relies on a traffic / emission model corrected with the real counting of traffic.

Regarding noise, we will employ the strategic noise maps elaborated by Bruitparif in accordance with the Environmental Noise Directive, as described in our previous work.[97,98]

In the estimation of exposure based on GPS tracks, adjustments will be made for indoor and underground locations (as confirmed during the mobility survey): an average coefficient related to the impermeability of the buildings to air or to acoustic insulation will be applied for indoor locations, while average values from previous measurement campaigns will be used for underground transport stages.

Based on the literature review for each health outcome, we will calculate air pollution / noise exposures in windows of different time sizes (30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 1 day, and 2 days).[30,33,55] To assess transport-related exposures, we will determine variables aggregating the exposure data only for the time slots related to trips between activity places (known from the mobility survey) within these exposure windows. We will also apply different lags between the end time of the exposure window assigned to each health measure and the corresponding measure (between 0 and 48 hours).

I.I.3 – Estimation of longer-term exposures

A basic approach would be to assume that the exposures measured / estimated over 8 days reflect regular exposures over a longer period. As a way to refine this crude approach, during the mobility survey, participants will be asked for each place visited their frequency of visit to that place over the previous year, overall and with the same transport mode (number of times per week / month / year over the previous year or over a shorter period if applicable). We will approximate exposure levels over one year by reweighting the average exposure at each activity place and during the trip(s) to that activity place according to the corresponding frequencies reported over the previous year. This one-year estimated exposure will be calculated by reweighting the exposures measured with the personal sensors, but will be also determined from the exposures estimated by combining the GPS tracks with annual exposure maps (to address the problem that the measured exposure in a trip / place may not correspond to the average yearly exposure at that location). The calculation will be performed separately for the first and for the second data collection period. We will also cumulate the estimated exposures for the two one-year exposure periods.

II - ANALYSES

II.A – Descriptive analyses

The Gantt Chart of the project (Extra Annex 6) also provides the schedule of the analyses. Taking into account the exact time segments devoted to trips in the 8-day mobility data, we will compare the exposure to air pollutants and noise between the different transport modes (walking, cycling, 2-wheel motor vehicle, car, and the different public transport modes). This comparison will be made both at the trip level (overall trip from one destination to the next one including walk segments) and at the trip stage level (portion of a trip with a unique mode). Because we segment the 8-day period into time segments at activity places and during trips, we will be able to determine the percentage of exposure to air pollutants and noise that is attributable to the transport activity.

II.B – Analyses of short-term effects

The health outcomes will be log transformed if needed. Design and non-response weights will be used in the analyses. For each outcome variable, analyses of short-term effects of exposures on health will be based on a repeated measure framework. The regression models will incorporate a random effect at the individual level and a temporal autocorrelation structure (e.g., autoregressive-1, etc.).[67,99] As an alternative modelling approach, we will also include in the model the average exposure of each participant over the observation period and the difference between her / his momentary exposure (for a given measure at a given time) and this average exposure.[6,33] Based on our previous work,[100] we will also explore different strategies to account for a possible residual spatial autocorrelation. Finally, we will specify random slopes to allow the relationships between air pollution / noise exposure and health to vary between individuals, in order to determine whether an observed effect of this exposure is only documented in few susceptible individuals or among most of the participants[66] (random slope analysis to assess between-individual heterogeneity in the associations as a preliminary step to the examination of factors modifying the effects of exposures). As the

participants will wear several air pollution monitors on some days and an air pollution monitor and a noise dosimeter on other days, and because the exposure to several air pollutants and noise will be also determined at the level of the GPS tracks, we will be able to estimate multi-exposure models.

On the basis of our precise literature review for each exposure–outcome relationship, we will take into account – to adjust for confounding or as modifying factors – the following variables into the models (varying or not over time; list of factors to be adapted to the exposure and health variables examined): demographic characteristics (age, sex, country of birth, cohabitation, etc.); socioeconomic characteristics (education, employment status, occupation, income, wealth, etc.); health characteristics (health variable used for the stratification, body mass index, waist circumference, heart rate,[55,101] personal history of diseases, medication use,[26] etc.); health behaviour (physical activity and body posture assessed with accelerometry,[33,55,101] tobacco and alcohol consumption, score of dietary consumption,[102] etc.); contextual characteristics defined at the residence, at the different activity places visited over the observation period, and along the trip itineraries (socioeconomic level, building density, population density, traffic density,[26,28] etc.); temperature, relative humidity or apparent temperature,[27] and atmospheric pressure[62,67]; estimated incidence of influenza or influenza-like illness[4]; pollen and mould in the air (French Aerobiology Network); hour, day of the week, and season of the measurement; and conditions of measurement of blood pressure at rest. Quadratic or cubic terms, piecewise regression analyses,[55] or smoothing terms (for example splines) will be used to take into account humidity or temperature in the models for air pollution effects,[27] and to test the hypothesis of nonlinear associations between air pollutants or noise and health.[66] Interactions between the effects of air pollutants and noise will be tested for the cardiovascular outcomes.[56] In addition to classical sensitivity analyses comparing the strength of associations, we will use a Random forest algorithm,[87] a machine learning approach that operates by constructing a multitude of decision trees in bootstrap samples of the original sample, to rank the different versions of the air pollution and noise exposure variables according to their predictive contribution.

II.C – Analyses of longer-term effects

Analyses of longer-term effects of air pollution or noise exposures on changes in respiratory and cardiovascular outcomes could be conducted by considering as the outcome the average of the measures in the second wave minus this average in the first wave. However, short-term effects and seasonal variations would introduce noise in the assessment of longer-term changes. To remedy the problem, a two-stage model will be used. Stage 1 will model the short-term effect of the exposure on the repeated outcome measure, as described in the previous section. Pooling the data of the two different waves (baseline and after two years), we will add to the model: a dummy variable for the second wave (as opposed to the first); an interaction between this dummy and the short-term exposure effect; and an individual-level random slope for this dummy variable. Overall, the effects of short-term exposures may increase / decrease from the first to the second wave, and the extent of the increase / decrease may vary between individuals. Based on this model, a prediction of the outcome will be derived for each of the two measurement waves for each participant, considering an average level of the short-term exposure and fixing the other time-varying covariates to a given level. The second stage of the model will estimate the effect of the longer-term exposures on the change in the predicted level of the outcome between waves 1 and 2. The two stages of the model will be estimated jointly through a Markov chain Monte Carlo approach to account for the uncertainty in the predictions in the estimation of longer-term effects. A model will also assess the potential effect of longer-term exposures on a change in the susceptibility to short-term exposures between the two waves.

Beyond average associations, we will investigate the heterogeneity in the estimated health effects of air pollution and noise: according to the characteristics of individuals (interaction terms); according to the geographic location (random effect approach); according to the exposure level (interactions between categorical and continuous exposure variables); and according to the level of the outcome (quantile regression). Finally, relying on recent statistical developments,[103] we will calculate total and direct effects to determine the percentage of socioeconomic differences in respiratory and cardiovascular health that would be eliminated by fixing the exposure to air pollutants and noise at an acceptable level.

II.D – Simulations of scenarios of behavioural and / or environmental change

The simulations will test scenarios of pseudo-interventions changing in a probabilistic way the transport behaviour of individuals (number, length, destination, and transport modes of trips) and / or the level of environmental exposure during trips. Changes in transport behaviour will be implemented by replacing the observed exposure in a trip by the exposure level predicted from a regression model for the new characteristics of the trip. We will test the impact of these probabilistic changes in specific trips on the average individual exposure over 8 days, on the distribution of this exposure across individuals, and on the resulting health effects. Each scenario will be tested across 10000 probabilistic realisations, allowing us to

report posterior distributions as estimates of the effect of the scenario. We will also examine whether each scenario of transport behaviour change and / or of environmental change tends to increase or decrease socioeconomic disparities in environmental exposures and in the resulting health effects. The method to perform flexible simulations of scenarios, as useful to orientate policies, will be packaged in a tool for decision-makers, and will be released as a deliverable of the project.

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