Noise and air pollution from road traffic: understanding their role in blood pressure

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Als meus pares

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„ Es ist nicht genug zu wissen, man muss auch anwenden; es ist nicht genug zu wollen, man muss auch tun”

“Knowing is not enough; we must apply. Willing is not enough; we must do.”
Johann Wolfgang von Goethe (1749-1832)

ABSTRACT

Epidemiological evidence is limited regarding the effects of long-term exposure to road traffic noise and traffic-related air pollution on the levels of blood pressure (BP) and hypertension. Moreover, whether the effects of the two environmental factors are mutually confounded and can be disentangled remains unknown. Understanding these associations is of high public health relevance, given (1) the ubiquitous exposure of the population to the noise and air pollution from traffic, (2) the fact that high BP has become the leading contributor to the burden of disease and mortality worldwide, and (3) the possibility to apply different abatement measures for each of these two environmental factors. This thesis aims at (a) exploring the long-term co-exposure to traffic-related air pollution and traffic noise of the study population and (b) evaluating and disentangling the association of long-term exposure to each of these two environmental factors with hypertension, systolic (SBP) and diastolic (DBP) BP in the adult population of the Mediterranean city of Girona (Catalonia, Spain).

We used data from the baseline examination (years 2003 to 2006) of one of the adult population-based cohorts of the REGICOR study (Girona Heart Registry). The study population consisted of 3836 randomly selected and non-institutionalized participants aged 35-84. BP was measured with standard protocols and the prevalence of hypertension was defined as having SBP $\geq$ 140 or DBP $\geq$ 90 mmHg or taking antihypertensive treatment. We used complementary residential information for those participants who attended the follow-up visit (years 2009-2011). To explore the spatial correlation, we performed 4-week measurements of nitrogen dioxide (NO_2) with passive samplers at 83 outdoor residential locations around the city of Girona and we derived their annual means. We estimated the long-term average levels of traffic noise for the 24 hours (L_{24h}) and for the nighttime (L_{night}) with a validated traffic noise model at the same locations. We assessed the main determinants of the spatial distribution of NO_2, L_{24h}, and L_{night} with linear regression models. To study the associations with blood pressure and hypertension, we assigned outdoor annual average levels of NO_2 and L_{night} at the residential postal addresses of each study participant. These estimations were derived with a NO_2 land-use

regression model and the traffic noise model. Individual indoor traffic L_{night} levels at the bedrooms were derived from the outdoor L_{night} levels after applying the noise attenuation factors provided by the reported window types, the opening frequencies and the bedroom orientation, according to literature. The cross-sectional association of each environmental factor with hypertension and BP was assessed with multivariate logistic and linear regression models, respectively and mutually adjusting for NO_2 or L_{night}. We also evaluated these associations controlling for BP-lowering medication with different techniques.

Our results showed that: 1) the spatial correlations of NO_2 with L_{24h} and L_{night} in Girona were 0.62 and 0.61, respectively (Spearman correlation), although they were city area-dependent. Traffic density in front of the measurement location, distance from the location to the street, and building density were common determinants of the spatial variability of NO_2 and noise levels. 2) A 10 $\mu g/m^3$ increase in NO_2 levels was associated with 1.34 mmHg (95%CI: 0.14, 2.55) higher SBP in those not taking BP-lowering medication. The association was similar in the entire population both after adjusting and not adjusting for BP-lowering medication. In contrast, it was weaker when using other techniques to deal with medication. The association between NO_2 and SBP was stronger in individuals living alone, in those exposed to high traffic density or to L_{night} levels $\geq$ 55 dB(A), and it was also stronger for both SBP and DBP in participants with CVD. No association was found for DBP or prevalence of hypertension in this population-based sample of 3700 individuals. 3) In a slightly healthier adult population, NO_2 was suggestively associated with BP, and outdoor traffic L_{night} with hypertension, when mutually adjusting for the other environmental factor. Associations were more consistent when we evaluated and adjusted for indoor traffic L_{night}. Namely we observed positive associations of NO_2 with prevalence of hypertension (OR=1.16, 95%CI: 0.99, 1.36), SBP (β=1.23, 95%CI: 0.21, 2.25), and DBP (β=0.56, 95%CI: -0.03, 1.14) per 10 $\mu g/m^3$ increase in NO_2 levels; and also of indoor traffic L_{night} with hypertension (OR=1.06, 95%CI: 0.99, 1.13) and SBP (β=0.72, 95%CI: 0.29, 1.15) per 5 dB(A) increase in L_{night}. The association between indoor traffic noise levels and hypertension was stronger among individuals with higher traffic noise annoyance and it was only present among those that did not take

anxiolytic treatment. The association between indoor traffic noise and SBP was suggestively stronger with a threshold at 30 dB(A).

This thesis shows the existence of a substantial but complex spatial correlation between traffic-related air pollution and traffic noise which calls for careful assessments of both environmental factors to investigate their common health endpoints. This thesis also adds to the limited evidence showing that the long-term exposure to traffic-related air pollution and the long-term exposure to traffic noise are associated (and independently associated) with both BP and hypertension. It also indicates the presence of potential susceptibility factors. Moreover, the results for noise are in line with the biological pathway model that relates noise-induced stress during the sleeping period with increased BP levels. This thesis has also conducted for the first time a comprehensive assessment of the different techniques to the control for BP-lowering medication, and suggests that all methods could bias the associations with BP in a certain degree. Finally, this thesis contributes to the characterization of indoor traffic noise levels at the bedroom and proposes its use to ascertain the effects of noise and to disentangle them from those of traffic-related air pollution.

Given the identified uncertainties on the studied associations, further studies are required to confirm these first results, including the use of personal markers of L_{night} levels at bedrooms and the longitudinal assessment of the change in BP levels.

RESUM

L'evidència epidemiològica és limitada en relació als efectes de l'exposició prolongada al soroll i la contaminació atmosfèrica provinents del trànsit amb els nivells de pressió arterial (PA) i la hipertensió. A més a més, es desconeix si els efectes dels dos factors ambientals estan mútuament confosos i si es poden separar. La comprensió d'aquestes associacions és d'alta rellevància per a la salut pública, donat (1) l'exposició ubiqua de la població al soroll i a la contaminació del trànsit, (2) el fet que la pressió arterial elevada s'ha convertit en el factor que més contribueix a la càrrega de malaltia i mortalitat a nivell mundial i (3) la possibilitat d'aplicar diferents mesures per al control de cadascun d'aquests dos factors ambientals. Aquest projecte de tesi té com a objectiu (a) explorar l'exposició conjunta de la població d'estudi a la contaminació atmosfèrica i al soroll del trànsit a llarg termini (b) avaluar i separar l'associació a llarg termini de cadascun d'aquests dos factors ambientals amb la hipertensió i la pressió sistòlica (PAS) i diastòlica (PAD) a la població adulta de la ciutat mediterrània de Girona (Catalunya, Espanya).

Vam utilitzar les dades de l'exploració basal (anys 2003-2006) d'una de les cohorts poblacionals d'adults de l'estudi REGICOR (Registre Gironí del Cor). La població d'estudi va consistir en 3836 participants de 35 a 84 anys seleccionats a l'atzar i no institucionalitzats. La PA es va mesurar amb protocols estàndards i la prevalença d'hipertensió es va definir com a una PAS $\geq$ 140 o PAD $\geq$ 90 mmHg o prendre tractament antihipertensiu. Vam utilitzar informació residencial complementària per a aquells participants que van assistir a la visita de seguiment (anys 2009-2011). Per explorar la correlació espacial, vam realitzar mesures de 4 setmanes de diòxid de nitrogen (NO_2) amb mostrejadors passius localitzats a l'exterior de 83 residències de la ciutat de Girona i vam calcular les seves mitjanes anuals. A les mateixes localitzacions, vam estimar els nivells mitjans a llarg termini del soroll del trànsit per a les 24 hores (L_{24h}) i per a la nit (L_{nit}) amb un model de soroll de trànsit validat. Es van avaluar els principals determinants de la distribució espacial del NO_2, L_{24h}, i L_{nit} amb models de regressió lineal. Per estudiar les associacions amb la pressió arterial i la hipertensió, es van assignar els nivells mitjans anuals exteriors de

NO_2 i L_{nit} a les adreces postals residencials de cada participant. Aquestes estimacions es van realitzar amb un model de regressió de l'ús del sòl d'NO_2 i el model de soroll de trànsit. Els nivells interiors de L_{nit} de trànsit als dormitoris es van derivar aplicant els factors d'atenuació al soroll del tipus de finestra, la freqüència d'obertura i l'orientació del dormitori reportats, d'acord a la literatura. L'associació transversal de cada factor ambiental amb la hipertensió i la PA es va avaluar amb models de regressió logística i lineal múltiple, respectivament, i ajustant mútuament per NO_2 o L_{nit}. Aquestes associacions també es van avaluar controlant per l'ús de medicació antihipertensiva amb diferents tècniques.

Els nostres resultats van mostrar que: 1) les correlacions espacials de NO_2 amb L_{24h} i L_{nit} a Girona eren de 0,62 i 0,61, respectivament (correlació de Spearman), tot i que depenien de l'àrea de la ciutat. La densitat del trànsit davant l'ubicació de mesura, la distància des de la ubicació al carrer, i la densitat d'edificació eren determinants comuns de la variabilitat espacial dels nivells de NO_2 i de soroll. 2) Un augment de 10 $\mu g/m^3$ en els nivells de NO_2 s'associava amb 1,34 mmHg (IC del 95%: 0,14; 2,55) més de PAS en els que no prenien medicaments antihipertensius. L'associació era similar en tota la població tant després d'ajustar com de no ajustar per l'ús de medicació antihipertensiva. En canvi, era més feble en utilitzar altres tècniques per tractar amb la medicació. L'associació entre NO_2 i PAS va ser major en les persones que vivien soles, en les persones exposades a l'alta densitat de trànsit o a nivells de $L_{nit} \geq 55$ dB (A), i també era major per a PAS i PAD en els participants amb malaltia cardiovascular. No es va trobar associació per a la PAD o la prevalença d'hipertensió en aquesta mostra poblacional de 3.700 individus. 3) En una població adulta lleugerament més saludable, el NO_2 estava suggestivament associat amb la PA, i el L_{nit} de trànsit a l'exterior amb la hipertensió, en ajustar mútuament per l'altre factor ambiental. Les associacions van ser més consistents en l'avaluar i ajustar per L_{nit} de trànsit interior. En concret vam observar associacions positives del NO_2 amb la prevalença d'hipertensió (OR = 1,16, IC del 95%: 0,99; 1,36), la PAS (β = 1,23, IC del 95%: 0,21; 2,25) i la PAD (β = 0,56, IC del 95%: -0,03; 1,14) per cada augment de 10 $\mu g/m^3$ en els nivells de NO_2, i també del L_{nit} de trànsit interior amb la hipertensió (OR = 1,06, IC del 95%: 0,99; 1,13) i la PAS (β = 0,72, IC del 95%: 0,29; 1,15) per

cada 5 dB(A) d'augment en els nivells de L_{nit}. L'associació entre els nivells de soroll de trànsit interiors i la hipertensió era major en els individus amb més molèstia al soroll de trànsit i només present entre els que no prenien tractament ansiolític. L'associació entre el soroll de trànsit interior i la PAS va ser suggestivament més forta amb un llindar d'efecte a 30 dB(A).

Aquesta tesi mostra l'existència d'una correlació espacial important però complexa entre la contaminació atmosfèrica i el soroll procedents del trànsit que suggereix una avaluació acurada dels dos factors per a investigar els seus efectes comuns sobre la salut. Aquesta tesi també incrementa l'escassa evidència sobre que l'exposició prolongada a la contaminació atmosfèrica i l'exposició prolongada al soroll del trànsit s'associen, i independentment, tant amb la pressió arterial com amb la hipertensió. També indica la presència de factors de susceptibilitat potencials. A més a més, els resultats pel soroll concorden amb el model del mecanisme biològic que relaciona l'augment dels nivells de pressió arterial amb l'estrès induït pel soroll durant el període de son. Aquesta tesi també ha realitzat per primer cop una avaluació exhaustiva de les diferents tècniques per controlar per la medicació antihipertensiva, i suggereix que tots els mètodes poden esbiaixar les associacions amb la PA en cert grau. Finalment, aquesta tesis contribueix a la caracterització dels nivells de soroll de trànsit a l'interior del dormitori i proposa el seu ús per determinar els efectes del soroll i per separar-los dels de la contaminació de l'aire relacionada amb el trànsit.

Donades les incerteses identificades en les associacions estudiades, es requereixen més estudis per confirmar aquests primers resultats, incloent l'ús de marcadors personals dels nivells de soroll al dormitori i l'avaluació longitudinal del canvi en la PA.

RESUMEN

La evidencia epidemiológica es limitada en relación a los efectos de la exposición prolongada al ruido y la contaminación atmosférica provenientes del tráfico con los niveles de presión arterial (PA) y la hipertensión. Además, se desconoce si los efectos de los dos factores ambientales están mutuamente confundidos y si se pueden separar. La comprensión de estas asociaciones es de alta relevancia para la salud pública, dado (1) la exposición ubicua de la población al ruido y la contaminación procedentes del tráfico, (2) el hecho que la presión arterial elevada se ha convertido en el factor que más contribuye a la carga de enfermedad y mortalidad a nivel mundial, y (3) la posibilidad de aplicar diferentes medidas para el control de cada uno de estos dos factores ambientales. Esta tesis tiene como objetivo (a) explorar la exposición conjunta de la población de estudio a la contaminación atmosférica y el ruido del tráfico a largo plazo (b) evaluar y separar la asociación a largo plazo de cada uno de estos dos factores ambientales con la hipertensión y la presión sistólica (PAS) y diastólica (PAD) en la población adulta de la ciudad mediterránea de Girona (Cataluña, España).

Utilizamos los datos de la exploración basal (años 2003 hasta 2006) de una de las cohortes poblacionales de adultos del estudio REGICOR (Registro Gerundense del Corazón). La población de estudio consistió en 3836 participantes de 35 a 84 años seleccionados al azar y no institucionalizados. La PA se midió con protocolos estándar y la prevalencia de hipertensión se definió como una PAS $\geq$ 140 o PAD $\geq$ 90 mmHg o tomar tratamiento antihipertensivo. Utilizamos información residencial complementaria para aquellos participantes que asistieron a la visita de seguimiento (años 2009-2011). Para explorar la correlación espacial, realizamos medidas de 4 semanas de dióxido de nitrógeno (NO_2) con muestreadores pasivos localizados en el exterior de 83 residencias de la ciudad de Girona y calculamos sus medias anuales. En las mismas localizaciones, estimamos los niveles medios a largo plazo del ruido del tráfico para las 24 horas (L_{24h}) y para la noche (L_{noche}) con un modelo de ruido de tráfico validado. Se evaluaron los principales determinantes de la distribución espacial del NO_2, L_{24h}, y L_{noche} con modelos de regresión lineal. Para estudiar las

asociaciones con la presión arterial y la hipertensión, se asignaron los niveles medios anuales exteriores de NO_2 y L_{noche} en las direcciones postales residenciales de cada participante. Estas estimaciones se realizaron con un modelo de regresión del uso del suelo para NO_2 y el modelo de ruido de tráfico. Los niveles interiores de L_{noche} de tráfico en los dormitorios se derivaron aplicando los factores de atenuación al ruido del tipo de ventana, la frecuencia de apertura y la orientación del dormitorio reportados, de acuerdo a la literatura. La asociación transversal de cada factor ambiental con la hipertensión y la PA se evaluó con modelos de regresión logística y lineal múltiple, respectivamente, y ajustando mutuamente por NO_2 o L_{noche}, entre otros factores. Estas asociaciones también se evaluaron controlando por el uso de medicación antihipertensiva con diferentes técnicas.

Nuestros resultados mostraron que: 1) las correlaciones espaciales de NO_2 con L_{24h} y L_{noche} en Girona eran de 0,62 y 0,61, respectivamente (correlación de Spearman), aunque dependían del área de la ciudad. La densidad del tráfico enfrente de la ubicación de medida, la distancia desde la ubicación a la calle, y la densidad de edificación eran determinantes comunes de la variabilidad espacial de los niveles de NO_2 y de ruido. 2) Un aumento de 10 $\mu g/m^3$ en los niveles de NO_2 se asociaba con 1,34 mmHg (IC del 95%: 0,14; 2,55) más de PAS en los que no tomaban medicamentos antihipertensivos. La asociación era similar en toda la población tanto después de ajustar como de no ajustar por el uso de medicación antihipertensiva. En cambio, era más débil al utilizar otras técnicas para tratar con la medicación. La asociación entre NO_2 y PAS era mayor en las personas que vivían solas, en las personas expuestas a una densidad alta de tráfico o a niveles de $L_{noche} \geq 55$ dB (A), y también era mayor para PAS y PAD en los participantes con enfermedad cardiovascular. No se encontró asociación para la PAD o la prevalencia de hipertensión en esta muestra poblacional de 3.700 individuos. 3) En una población adulta ligeramente más saludable, el NO_2 estaba sugestivamente asociado con la PA, y el L_{noche} de tráfico en el exterior con la hipertensión, al ajustar mutuamente por el otro factor ambiental. Las asociaciones resultaron ser más consistentes al evaluar y ajustar por L_{noche} de tráfico interior. En concreto, observamos asociaciones positivas del NO_2 con la prevalencia de hipertensión (OR = 1,16, IC del 95%: 0,99; 1,36), la PAS (β = 1,23, IC del 95%: 0,21; 2,25) y la PAD (β = 0,56, IC del

95%: -0,03; 1,14) por cada aumento de 10 μg/m^3 en los niveles de NO_2, y también del L_{noche} de tráfico interior con la hipertensión (OR = 1,06, IC del 95%: 0,99; 1,13) y la PAS (β = 0,72, IC del 95%: 0,29; 1,15) por cada 5 dB(A) de aumento en los niveles de L_{noche}. La asociación entre los niveles de ruido de tráfico interiores y la hipertensión fue mayor en los individuos con más molestia al ruido de tráfico y sólo presente entre los que no tomaban tratamiento ansiolítico. La asociación entre el ruido de tráfico interior y la PAS era sugestivamente más fuerte con un umbral de efecto a 30 dB(A).

Esta tesis muestra la existencia de una correlación espacial importante pero compleja entre la contaminación atmosférica y el ruido procedentes del tráfico que sugiere una evaluación cuidadosa de los dos factores para investigar sus efectos comunes sobre la salud. Esta tesis también incrementa la escasa evidencia acerca de que la exposición prolongada a la contaminación atmosférica y la exposición prolongada al ruido del tráfico se asocian (e independientemente) tanto a la presión arterial como a la hipertensión. También indica la presencia de factores de susceptibilidad potenciales. Además, los resultados para ruido concuerdan con el modelo del mecanismo biológico que relaciona el aumento de los niveles de presión arterial con el estrés inducido por el ruido durante el período de sueño. Esta tesis también ha realizado por primera vez una evaluación exhaustiva de las diferentes técnicas para controlar por la medicación antihipertensiva, y sugiere que todos los métodos pueden sesgar las asociaciones con la PA en cierto grado. Finalmente, esta tesis contribuye a la caracterización de los niveles de ruido de tráfico en el interior del dormitorio y propone su uso para determinar los efectos del ruido y para separarlos de los de la contaminación del aire relacionada con el tráfico.

Dadas las incertidumbres identificadas en las asociaciones estudiadas, se requieren más estudios para confirmar estos primeros resultados, incluyendo el uso de marcadores personales de los niveles de ruido en el dormitorio y la evaluación longitudinal del cambio en la PA.

PREFACE

The evidence suggests that both traffic-related noise and air pollution may contribute to cardiovascular disease (CVD), a main cause of worldwide morbidity and mortality. Part of the impact of both factors may be mediated by hypertension, a major determinant of CVD. In addition, the main underlying source of both noise and air pollution is traffic, and the question remains whether their cardiovascular effects are partly or totally explained by the other traffic-related stressor. This project aimed at assessing exposure to both traffic noise and air pollution and evaluating their independent associations on hypertension, systolic and diastolic blood pressure. This is the first project comprehensively analyzing both traffic-related noise and air pollution and aiming at disentangling their effects.

This thesis has been developed between 2009 and 2013 at the Centre for Research in Environmental Epidemiology (Barcelona, Spain) and partly at the Swiss Tropical and Public Health Institute (Basel, Switzerland), under the supervision of Prof. Nino Künzli and Dr. Xavier Basagaña. The results are based on the collaboration with the REGICOR project (Girona's Heart Registry), a set of cohorts investigating cardiovascular risk factors since 35 years ago. This thesis is in accordance to the regulations of the Doctoral Program in Biomedicine of the Experimental and Health Sciences' Department at the Pompeu Fabra University and includes an abstract, a general introduction and state of the art, a rationale, the objectives, the hypotheses, the methods, the results (a compilation of the scientific publications), an overall discussion, and final conclusions.

The original publications are:

I. Local determinants of traffic noise levels versus determinants of air pollution levels in a Mediterranean city.

II. Long-term exposure to traffic-related air pollution, blood pressure and hypertension in an adult population-based cohort.
III. High blood pressure and long-term exposure to indoor noise and air pollution from traffic.

This thesis contributed to: 1) The understanding of the long-term outdoor spatial correlation between nitrogen dioxide and traffic noise, 2) the characterization of those urban factors that explain the spatial distribution of outdoor traffic noise and nitrogen dioxide and ultimately determine their correlation, 3) the understanding of the biases introduced by antihypertensive medication and the inclusion of two correlated variables (noise and air pollution) in statistical models, 4) the estimation of indoor noise exposure at the bedroom through extensive questionnaire information for the first time, 5) the identification of potential susceptibility factors contributing to stronger associations between the studied exposures, blood pressure, and hypertension, and 6) the identification of independent associations of long-term exposure to traffic noise and air pollution with hypertension and blood pressure when assessing indoor instead of outdoor traffic noise levels.

The PhD student contribution included the noise questionnaire design and assessment of its performance through a pilot study, the participation in fieldwork, estimation of noise levels and of annual averages of NO_2, data collection and entry, geocoding of addresses and validation, and the elaboration of the analyses planning, data cleaning, management, statistical analyses, and writing of the articles. It also included participation in project meetings, writing of project and fellowship applications and reports, coordination and participation at local and international workshops, and communication of results locally, at international conferences (contributed and invited), and to the community. The student had a main contribution in other national and international projects related to noise and air pollution during the development of the thesis.

CONTENTS

1 INTRODUCTION

The environment plays an important role in human health. Two prevalent and ubiquitous ambient factors to which most of the population is exposed to on a daily basis are air pollution and noise, particularly from traffic (European Environment Agency, 2009). Compared to air pollution, noise has been less studied, partly because of social acceptance and lack of knowledge about its potential health effects, but also because of the complexity and lack of standardization for its assessment in epidemiological studies.

Interestingly, plausible associations have been established for the long-term exposure to both traffic noise and air pollution levels with cardiovascular diseases (CVDs) (Babisch, 2006; Brook et al., 2010; Ising and Kruppa, 2004), a major cause of morbidity and mortality worldwide. These environmental stressors may also impact hypertension, a very prevalent cardiovascular condition and major determinant of CVDs.

Considering that traffic is a main source of both environmental stressors, findings for traffic noise may be partly or totally explained by traffic-related air pollution, and vice-versa. Adequate assessment is necessary to identify their independent effects.

This introduction gives background about the main topics of this thesis within the framework of epidemiology and public health, namely: traffic noise, traffic-related air pollution, and hypertension; and finishes with the evidence and gaps regarding their association.

1.1 Traffic noise

Road traffic noise (or traffic noise) has always been an issue for the human being. In ancient Rome and in the Medieval Europe, rules existed to control noise from carriages and horses to allow good sleep (World Health Organization, 1999). Environmental noise includes noise from road, rail and aircraft transportation, and industrial activities. Nowadays, traffic noise is the most prevalent source of environmental noise in urban areas (European Environment Agency, 2009). Data from the European Commission indicates that around a 40% of the European and 50% of the Spanish populations living in agglomerations larger than 250,000 inhabitants (a total of 110 million inhabitants) are exposed to nighttime traffic noise levels higher than 50 dB(A) http://noise.eionet.europa.eu/, NOISE: Noise Observation and Information Service for Europe, 2012). These levels are above the guideline values for outdoor noise levels during the nighttime (40 dB(A)) **(See Appendix I. Environmental noise guidelines)**. Current concepts indicate that noise may particularly impact health at night, by impairing the restorative processes of the sleeping period (World Health Organization, 2009) **(See section 1.4.2, p. 19)**.

It is well established that transportation noise, which is defined as an unwanted sound, produces annoyance and sleep disturbance, and that it affects cognitive and emotional responses (Muzet 2007). In addition, the still small but growing field of noise epidemiology supports the long-term effects of traffic noise on CVDs (Babisch, 2011, 2006).

1.1.1 Noise concepts and human hearing

Sound (or **noise)** is a sensory perception as a consequence of the vibration of an elastic media (e.g. the air).

Generally, noise is measured according to the sound pressure created by the sound waves on the air. Since the range of sound pressures captured by the human ear is very wide, noise is generally calculated in **decibels** (**dB**) or sound pressure level, a logarithmic transformation of the sound pressure which enables the use of smaller numbers. The minimum value of dB is 0, and corresponds to the minimal pressure perceptible to the human ear, whereas the theoretic upper limit of the sound pressure is set by atmospheric pressure, i.e. 191dB. In practice, this level is physically not reached. A more interesting value is the threshold of hearing pain which starts around 125dB (World Health Organization, 1999) **(See Appendix II. Noise levels from common sources)**.

The **logarithmic scale** also simulates the logarithmic behavior of the human hearing. For instance, a doubling in traffic flow (e.g. from 100 to 200 cars) will have double sound energy but it will only increase the sound pressure level by 3dB (e.g. from 40 dB(A) to 43 dB(A)), i.e. the sound pressure is not doubled (multiplicative scale) but suffers and additive increase. Thus, dB cannot be added arithmetically (Rossing, 2007; World Health Organization, 1999).

It should be also emphasized that most sounds are a combination of many frequencies. The frequency refers to the number of vibrations per second generated by a sound and it is measured in Hertz (**Hz**). The young **human ear responds to a range from 20 Hz to 20 kHz**, **but it is more sensitive to high frequencies (high-pitched sounds)**, particularly between 1 kHz and 4 kHz. This means that not all frequencies are heard as equally "loud" at the same sound pressure level. Thus, to refer to the human hearing perception,

sound pressure levels are corrected, giving less weight to low frequencies (low-pitched sounds).

This filter is called **A-weighting** and the units are normally expressed as **dB(A)**. Another common filter is C-weighting, which gives more weight to low frequencies. Z-weighting refers to the dB without filter (Rossing, 2007), (**Figure 1**). The frequency spectra of traffic normally ranges from 100Hz to 5kHz with peaks at 1kHz (Buratti and Moretti, 2010).

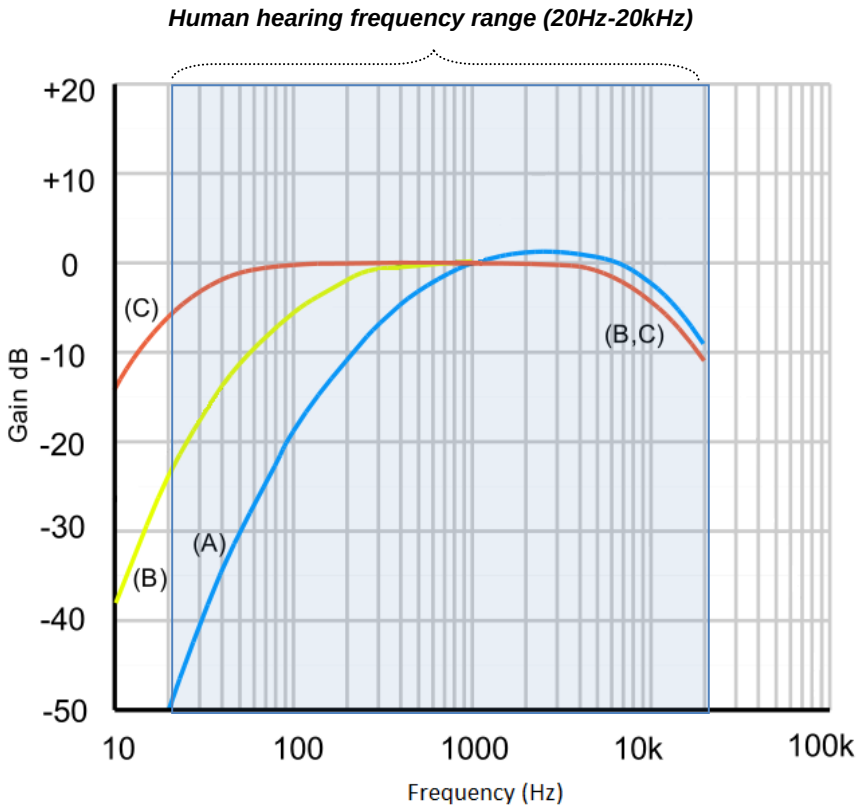

Figure 1. (A) A-weighting (blue), (B) Z-weighting, (C) C-weighting (Adapted from Wikimedia Commons, 2005).

1.1.2 Noise indicators

Different noise indicators are used depending on the outcome, noise source and time window of exposure relevant for the noise effects. To assess long-term exposure to traffic noise, a rather constant fluctuating sound, we use **daily annual averages**, expressed as the equivalent continuous sound pressure level in dB(A), and determined over all days of a year ($LAeq,_{24h}$). This 24h-average can be divided into different time periods: day (L_{day}), evening ($L_{evening}$), or night (L_{night}). L_{den} is a subjective 24h-average of the three periods above, with a weight given to the most annoying periods $L_{evening}$ (+ 5 dB) and L_{night} (+ 10 dB), (*Directive 2002/49/EC*, 2002).

1.1.3 Noise exposure assessment

The characterization of long-term noise exposure for each participant is needed in order to assess chronic effects. Measuring personal noise exposure for each individual and for a specific source is inefficient, as the extreme amount of resources required would generally not compensate the added value of more precise measurements. For this reason, modeling techniques are used that estimate outdoor traffic noise exposure at the residences of each participant.

Every 5 years and since 2002, the European member states have to produce, among others, traffic **noise maps** of large agglomerations at the most exposed façade of buildings and using harmonized noise indicators, namely L_{den}, L_{day}, $L_{evening}$, and L_{night} **(See Section 1.1.2, p.5)**. These maps have to follow the European Noise Directive guidelines (*Directive 2002/49/EC*, 2002). Although this has increased the availability of noise data in many countries and has standardized the noise indicators used, allowing comparisons, noise estimates from these noise maps might not always be reliable for health assessment. Indeed, these maps are intended to detect noisy

areas, thus they do not require high-resolution estimations, particularly in quieter zones. Actually, maps may well differ, since the guidelines for the first round (the current maps) allowed the development of maps either with standard street measurements or with models, and the noise exposure assessment could be more or less refined in both cases based on the European recommendations (WG-AEN, 2003). Thus, the reliability of each map will ultimately depend on the resources and data available at each EU city. These maps should therefore be carefully evaluated before being used for epidemiological purposes and according to the requirements of each study. Epidemiological studies may have access to the maps, or to the actual measurements, or to the models used to produce this information.

Traffic **noise modeling techniques** account for: traffic flow, speed, heavy vehicles, nature of the pavement, and for other land-use information. For refined exposure assessment, information about traffic flow in small streets and the three-dimension geometry of buildings is relevant. Knowing the geometry permits accounting for the distance to and the height of the residences, and for the reflection and absorption of sound on surfaces. This information is then implemented in specific noise software to obtain outdoor noise levels (L_{day}, L_{night} and $L_{evening}$) at the most exposed façade or the postal address (WG-AEN, 2003). These models are complex, and require expertise and substantial resources.

1.2 Traffic-related air pollution

The effects of ambient air pollution on human health have been studied during decades (ATS, 1996) and related to cardiovascular and respiratory outcomes (Brunekreef and Holgate, 2002; Curtis et al., 2006; Künzli et al., 2010b). Ambient particulate matter (PM) was also located among the 10 leading risk factors contributing to the Global Burden of Disease in 2010 (Institute for Health Metrics and Evaluation, 2013), **(Figure 2)**. Moreover, it is suggested that the toxicological properties of the combustion-related pollution may particularly impact health (Brook et al., 2010; Schlesinger et al., 2006). Despite efforts to decrease emissions from vehicles, limit values are yet exceeded in many European Countries and levels below the actual standard limits may also cause adverse health effects (European Environment Agency, 2012) **(See Appendix III. Air quality criteria for Europe)**.

1.2.1 Indicators of traffic-related pollution

Traffic-related pollution consists of a complex mixture of pollutants mainly emitted through the motor-vehicle combustion process (primary pollutants). These include carbon dioxide (CO_2), carbon monoxide (CO), nitrogen oxides (NO_x, i.e. nitrogen monoxide –NO – and nitrogen dioxide – NO_2 –), particulate matter (PM), sulphur dioxide (SO_2), among others. In turn, these emissions contribute to the production of secondary pollutants, depending on the meteorological conditions, geography, and pollutant sources. Traffic-related pollution is also generated through resuspension of road dust, tire and brake wear (Health Effects Institute, 2010). Because of the complexity of measuring all components of this mixture, exposure to traffic-related pollution is commonly measured with surrogates of the traffic emissions.

A common surrogate of traffic-related pollution is **NO_2**. Most NO emitted by traffic is rapidly transformed to NO_2, and NO_2 decreases exponentially with distance to the source (here traffic) (Singer et al., 2004). In turn, NO_2 together with sunlight contribute to the generation of tropospheric ozone concentrations. As it happens with other surrogates, other sources (such industrial and indoor cooking combustion processes) contribute to ambient NO_2 levels and final exposure, thus, limiting the specificity of NO_2 as a marker of traffic-related pollution. Nonetheless, the characterization of its temporal and spatial gradients is feasible thanks to its control by legislation and the availability of inexpensive samplers that can provide fine spatial resolution of traffic-related NO_2 levels. According to the Health Effects Institute Panel on the Health Effects of Traffic-related Air Pollution (2010), using ambient NO_2 concentrations in combination with indicators of traffic or traffic models can provide promising surrogates of traffic-related NO_2 levels.

PM is a mix of suspended solid and liquid particles of different size and chemical composition. Identifying traffic-related PM is difficult since direct traffic emissions of PM generally represent a small share of all its sources. PM sources include fuel combustion, road dust resuspension, construction, and pollens, among others. In addition, secondary PM is also formed by reaction with primary gaseous emissions, mixing with primary PM and making it difficult to assess the local traffic contribution of PM (European Environment Agency, 2012; Health Effects Institute, 2010). PM is classified according to the aerodynamic diameter of the particle and considering that particles of less than 10 μm can penetrate deep into the lung. They range from PM_{10} (< 10 μm) to ultrafine particles – UFP or $PM_{0.1}$– (< 0.1 μm). The UFP fraction relates to fresh fuel combustion, industrial processes and ambient chemistry and given their small size, they may be the most threatening to health (Mills et al., 2008). While UFP levels are high near traffic, characterizing UFP is yet a challenge for epidemiological studies, given that they

have a short lifetime and decay rapidly with distance to the source (Health Effects Institute, 2010).

Traffic itself (e.g. proximity of the residence to the nearest road, or traffic volume at different distances or buffers) has also been used as a marker of traffic-related pollution. However, proximity to traffic accounts for other factors such as noise, and thus, results could be confounded by these factors (Brook et al., 2010).

1.2.2 Air pollution exposure assessment

As explained for noise, directly measuring personal exposure is not feasible for studies analyzing long-term exposures and measurements are not specific for a single source of pollution (here traffic-related air pollution). Some modeling techniques can provide informative outdoor estimates of long-term exposure to selected pollutants based on spatial concentration contrasts. As it is known that people spend most of their time at home, it is assumed that assigning outdoor pollution estimates at the residences of each person captures a relevant part of the individuals' total exposure.

The most common modeling techniques include geostatistical interpolation of monitor data, land-use regression, dispersion modeling, and hybrid models (Jerrett et al., 2005). These models use different parameters related to meteorology, land use data, traffic data, monitor data, or emission rates (Health Effects Institute, 2010). The selection of the model depends on the relevant time window of exposure for the studied effect, the pollutant to be characterized and its distribution, the geographical area, the data availability, and the resources (Rivera, 2012).

For instance, to study hypertension, a disease that develops progressively, average levels of air pollution over one or several years are used. Moreover, small scale spatial contrasts need to be

captured to assess exposure to traffic-related pollution among participants. Land-use regression models are a practical approach that can be used to evaluate exposure to traffic-related pollution (Jerrett et al., 2005), and that can offer high resolution area-specific models if enough measurements are available and if input data accounts for traffic and spatial factors relevant to the individual's exposure (Hoek et al., 2008). A high number of measurements is also needed to obtain robust models (Basagaña et al., 2012; Rivera, 2012).

1.3 Hypertension and cardiovascular diseases

Cardiovascular diseases (CVDs) are a group of conditions of the cardiovascular (CV) system and include diseases of the heart, vascular diseases of the brain, and diseases of the blood vessels (World Health Organization et al., 2011).

Hypertension is a silent and multifactorial CV condition. The chronic increased pressure exerted on vessels, the pulsatile force, and the excessive velocity of the blood, slowly progresses into the damage of many organs, particularly leading to renal and vision impairment, and CVDs. Regarding CVDs, excessive blood pressure (BP) promotes the thickening of the artery walls and the damage of the vessels. This contributes to the progression of atherosclerosis, the ultimate cause of most CVDs. In addition, high BP leads to thickening of the heart muscle, contributing to heart failure, and it can also trigger acute CV events (Khan, 2006).

It has been observed that the risk of CVDs progressively increases with increasing BP levels. For every 20 mmHg of systolic or 10 mmHg of diastolic BP increase, there is a doubling of mortality from both ischemic heart disease (IHD) and stroke in individuals from 40 to 89 years old. The presence of other risk factors is though common, and the number of cardiovascular risk factors compounds the final cardiovascular risk (Chobanian et al., 2003; REGICOR, 2013). Yet, hypertension is a major risk factor of most CVDs, namely IHD, cerebrovascular disease (ischemic and hemorrhagic strokes), peripheral vascular disease, and heart failure (World Health Organization et al., 2011).

1.3.1 Prevalence and burden of disease

CVDs are the leading cause of death and disability worldwide, accounting for 30% of all-cause mortality in 2010 (Lozano et al., 2012), and amounting to 295 million Disability Adjusted Life Years (DALYs), which means 12% of the total estimated years of healthy life lost worldwide in 2010 (Murray et al., 2012). Most of this burden is due to IHD. In Spain, CVDs are also the leading causes of death, representing 31% of overall mortality in 2011 (INE, 2011).

In turn, high BP is the leading individual contributor to the Global Burden of Disease, accounting for 9.4 million (18%) of overall deaths and 7% of total DALYs in 2010 **(Figure 2)**. High BP also accounts for 53% of the DALYs for IHD (Lim et al., 2012), which illustrates the importance of hypertension as a risk factor for CVDs.

The burden of high BP increased 30% from 1990 to 2010. This is determined by the growing prevalence of hypertension, which reached 40% in 2008 among adults aged 25 or older, similarly to Spain (Banegas, 2005). This increment was greater in middle- and low-income countries, and attributed to urbanization and aging of the population (World Health Organization et al., 2011).

A relevant part of the burden of high BP impacts middle age groups, the population with prehypertension **(See point 1.3.2)**, and those with uncontrolled hypertension (i.e. with BP levels above the threshold for hypertension) (Lawes et al., 2008). However, it is estimated that less than a third of individuals are protected from IHD and strokes (Chobanian, 2009; Kaplan and Opie, 2006) even with controlled hypertension (i.e. with DBP and SBP levels below 90 and 140 mmHg, respectively, thanks to therapeutic measures), High BP is therefore a major public health problem that requires primary population-based prevention (Chobanian et al., 2003).

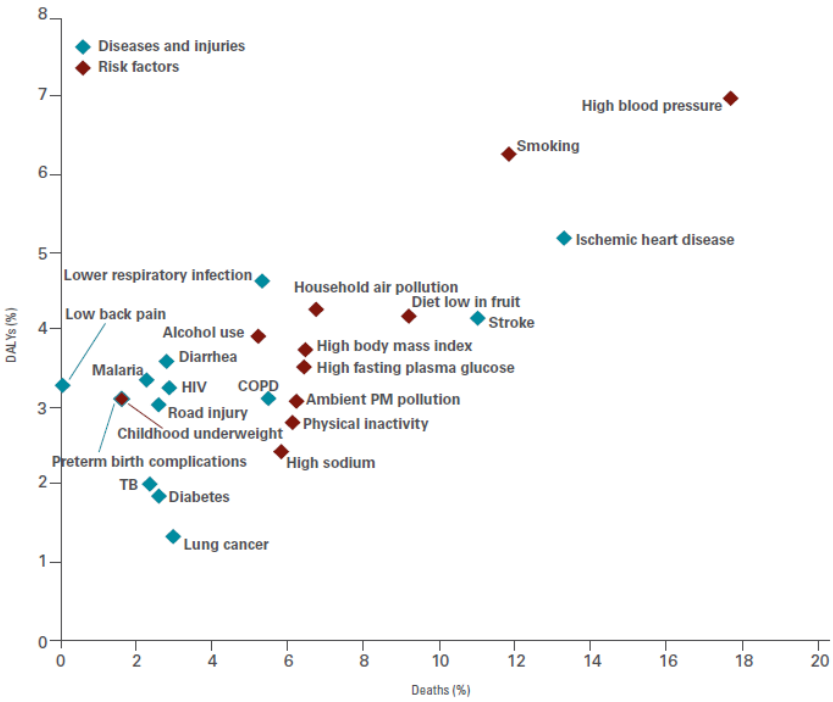

Figure 2. The 10 leading diseases and injuries and 10 leading risk factors based on percentage of global deaths and DALYs, 2010. Figure from the Global Burden of Disease Report, 2010 (Institute for Health Metrics and Evaluation 2013).

1.3.2 Classification of blood pressure

Systemic arterial BP is the physical pressure exerted by blood flow against the arterial vessels. For each heartbeat, this pressure has a maximum and a minimum value, namely **systolic BP (SBP)** and **diastolic BP (DBP)**, respectively. The maximum corresponds to the systole or contraction of the left ventricle and subsequent pumping of blood to the arteries, and the minimum corresponds to the diastole or heart relaxation (Khan, 2006). BP is measured at the brachial artery following standard procedures, and the measure is expressed in millimeters of mercury (mmHg). **BP is classified according to Table 1** (Chobanian et al., 2003).

The **prehypertension** category was introduced after the observation that the risk of IHD and stroke mortality increased continuously with higher BP, and particularly, that having BP levels between 130-139/85-89 mmHg (SBP/DBP, respectively), doubled the relative risk of CVD, compared to levels < 120/80 mmHg (Chobanian et al., 2003). Prehypertensive individuals with no other conditions are not treated but advised to practice healthy lifestyles.

Defining **hypertension** is helpful for clinical practice. However, analyzing **BP** continuously is important given that complications increase in a linear fashion with higher BP.

Table 1. Classification of blood pressure according to the Joint National Committee 7 recommendations

JNC 7 Category	SBP/DBP (mmHg)
Normal	< 120/80
Prehypertension	120–139/80–89
Hypertension	≥ 140/90
STAGE 1	140–159/90–99
STAGE 2	≥ 160/100

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure

1.3.3 Determinants and mechanisms of hypertension

Systemic hypertension is a multifactorial disease and its etiology cannot be established in most cases. This type of hypertension is called primary or essential hypertension. Secondary hypertension is caused by underlying medical conditions, e.g. diabetes or kidney disease, or medications. Primary hypertension represents more than 90% of all cases (Black and Elliott, 2013).

The underlying **biological mechanisms** leading to hypertension relate to cardiac output, blood volume, and vascular resistance, which determine final pressure. Multiple systems are involved in the adequate regulation of these factors. The most common pathways include contractile processes in the vasculature, activation of the central and autonomous nervous system, and sodium excretion processes in the kidney. New pathways also include inflammatory processes and immune reactions. However, the specific roles of each of the systems has not been elucidated yet (Coffman, 2011; Kaplan and Opie, 2006) **(Figure 3)**.

The evidence suggests that the elevation of BP is driven by genetic and environmental **risk factors**, the latter being mainly high dietary sodium intake, overweight, ethnicity, physical inactivity, excessive alcohol intake, and stress. The strongest non-modifiable determinant of hypertension is age, which can lead to a prevalence of hypertension above 75% already at age 70. On the other hand, women have a lower prevalence of hypertension than men, but the inverse pattern is observed after menopause (Black and Elliott, 2013; Chobanian et al., 2003; Kaplan and Opie, 2006).

Overall, several modifiable risk factors of hypertension exist. Exposure to these risk factors increases with urbanization, which partly explains the rise of high BP and CVDs worldwide (World Health Organization et al., 2011).

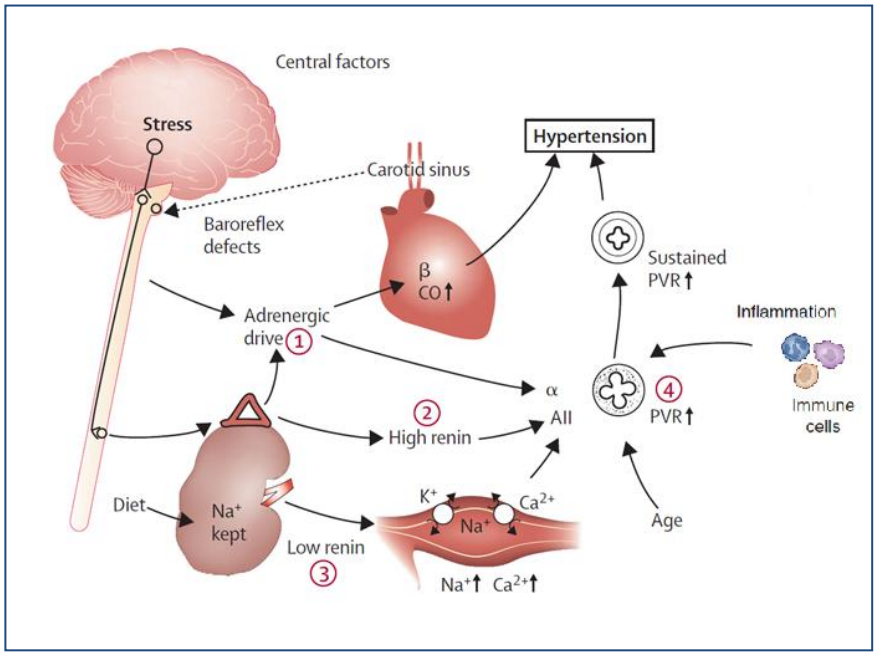

Figure 3. Major mechanisms: 1) increased adrenergic drive, as often found in young adults (30-49 years); 2) high-renin hypertension, as found in individuals with renal dysfunction; 3) low-renin hypertension, as found in individuals with inherently raised aldosterone concentrations; 4) increased peripheral vascular resistance (PVR), as seen in elderly patients. CO=cardiac output. β=beta-adrenergic stimulation. α=alpha-adrenergic stimulation. All=angiotensin II. New identified pathways: inflammation and immune system. (Adapted from Coffman 2011 and Kaplan and Opie 2006).

1.4 Traffic-related air pollution, traffic noise and hypertension

1.4.1 Evidence for traffic noise and hypertension

Long-term exposure to outdoor traffic noise has been associated with CVD (Babisch, 2011, 2006), particularly with ischemic heart disease. A few recent studies, some of which are contemporaneous to this thesis, have also provided new evidence on the association with hypertension. Those are summarized in a meta-analysis of 24 cross-sectional studies published in late 2012. This meta-analysis reported a statistically significant association between day-time traffic noise levels (LAeq, 16h) (range 45-75 dB(A)) and prevalence of hypertension with an odds ratio (OR) of 1.034 (95% CI: 1.011, 1.056) for a 5 dB(A) exposure contrast (van Kempen and Babisch, 2012). However, SBP and DBP levels have been less studied in relation to traffic noise and results have been heterogeneous (Babisch, 2006; Dratva et al., 2012; Sørensen et al., 2011).

The above-mentioned meta-analysis identified important sources of heterogeneity. First of all, no associations were found between traffic noise and hypertension in studies analyzing older populations or women. This is in line with some studies that only observed associations or reported stronger associations between traffic noise and hypertension in middle-aged groups (Bodin et al., 2009; de Kluizenaar et al., 2007) or in men (Barregard et al., 2009; Jarup et al., 2008). Secondly, the meta-analysis also suggested that those studies with supposedly better noise exposure assessment, those studying larger exposure contrasts, and those treating noise as a continuous variable observed stronger associations. Finally, although some previous studies only observed relationships above 55 dB(A) or higher values (Barregard et al., 2009; Bodin et al., 2009; de Kluizenaar et al., 2007), the meta-analysis conducted by

van Kempen and Babisch (2012) could not determine a threshold of effect for traffic noise, due to the different treatment of the noise variable across studies.

These inconsistencies agree with recent expert reviews (Babisch, 2011; Belojevic et al., 2011; Bluhm and Eriksson, 2011; Kempen, 2011; Lercher et al., 2011; Stansfeld and Crombie, 2011) which suggested further assessments of the effect modification by age and gender, and the study of threshold effects.

Other issues have to be considered. Current studies rely on outdoor noise estimates at the most exposed façade of dwellings, although it is often argued that the actual traffic noise levels indoors may differ. Babisch et al. (2011) suggested that noise exposure assessment could be improved with information on shielding, room orientation and also by analyzing coping behaviors. Special emphasis was given to the fact that noise effects could be more relevant during sleeping hours at night and thus, that bedroom orientation should be considered. This question has been little assessed, generally testing the effect modification of some (Barregard et al., 2009; Bluhm et al., 2007; Lercher et al., 2011) or many (Babisch et al., 2012) of these factors by means of stratification or interaction analysis. However, results have been inconsistent. Besides, one study in 1999 changed participants to quieter noise categories if their bedroom did not face the postal address or if they always closed windows (Babisch et al., 1999). Based only on these two corrections this study observed an increase in risk of IHD for subjects in the highest noise category. Estimating traffic noise levels indoors and at the bedroom might be essential to improve the assessment of noise effects on health.

Finally, whether the indirect biological pathway (annoyance) interacts with the direct pathway (objective noise exposure) leading to stronger associations between traffic noise and hypertension is unclear (Babisch et al., 2013) **(See section 1.4.2, p.19)**.

1.4.2 Biological mechanisms of traffic noise

The non-auditory effects of noise have been related to the stress concept (Babisch, 2002). Two principal pathways are proposed: the direct and the indirect. The direct pathway involves unconscious physiological reactions, i.e. direct interactions between the acoustic nerve and the central nervous system. In turn, the indirect pathway relates to the conscious perception of the sound made by each individual, and his/her emotional response through cortical arousal (Babisch et al., 2013). The first can be investigated with objective noise indicators, whereas the second requires subjective indicators of annoyance.

Overall, stress activates the hypothalamus-pituitary-adrenal axis and limbic system, which in turn activates the sympathetic autonomous nervous and endocrine systems. This agrees with wide evidence from experimental studies that show increased BP, heart rate, serum lipids, glucose, and corticosteroid levels with increasing noise exposure. Moreover, the cardiovascular responses remain sustained over time. Thus chronic exposure to noise could lead to chronic deregulations, and promote hypertension, atherosclerosis, and CVDs (Ising and Kruppa, 2004).

It should be noted that non-auditory noise effects are not necessarily a result of the cumulative addition of noise exposure, i.e. they do not follow the concept of dose, but depend on the disturbed activity. It is therefore hypothesized that the restorative period of sleep, which modulates the cardiovascular function, is a particularly important period for the development of noise-related cardiovascular disorders. Actually, exposure to noise leads to cardiovascular arousal also while sleeping and unconscious, even without awakenings (Babisch, 2011; Muzet, 2007). This also suggests that the direct unconscious pathway may be the primary source of noise effects at night (Babisch et al., 2013).

1.4.3 Evidence for traffic-related air pollution and hypertension

The American Heart Association recently established that there is a causal relationship between short- and long-term exposure to $PM_{2.5}$ (including combustion-related, or traffic-related ambient air pollution) and cardiovascular morbidity and mortality (Brook et al., 2010). Regarding long-term exposure, epidemiological evidence was strong for an association with ischemic heart disease and for all-cause cardiovascular mortality. In the recent years, evidence has also increased for atherosclerosis, the main underlying cause of CVD (Adar et al., 2013; Künzli et al., 2011; Rivera et al., 2013).

Hypertension is another main risk factor of CVD and it is classified as a disease itself. In 2010 there was moderate epidemiological evidence supporting acute elevations of BP with short-term exposure to air pollution (i.e. days to months). The evidence kept growing (Auchincloss et al., 2008; Brook et al., 2011; Chuang et al., 2010; Delfino et al., 2010; Dvonch et al., 2009; Zanobetti et al., 2004), although some studies reported inverse (Ebelt et al., 2005; Hampel et al., 2011; Harrabi et al., 2006; Ibald-Mulli et al., 2004) or null associations (Madsen and Nafstad, 2006).

In contrast, no evidence about the long-term effects of air pollution on high BP was available when initiating this thesis. To date little is yet known about its association with BP (SBP and DBP), and less is even known about its effects on hypertension.

Four cross-sectional studies found significant positive associations between annual average home outdoor concentrations of different pollutants ($PM_{2.5}$, PM_{10}, NO_2, SO_2, ozone, and/or black carbon) and BP in an elderly population in Taiwan (Chuang et al., 2011), in a population-based sample in the Ruhr area, Germany (Fuks et al., 2011), in elderly men in Boston, USA (Schwartz et al., 2012), and in men in China (Dong et al., 2013). In contrast, higher

concentrations of NO_x were inversely associated with SBP in Denmark (Sørensen et al., 2012).

As already mentioned, evidence for hypertension is even more limited. In Germany, no associations were found between $PM_{2.5}$ and prevalence of hypertension (Fuks et al., 2011), whereas in Sweden there was a protective effect of NO_x and NO_2 on prevalence but no association on incidence of self-reported hypertension (Sørensen et al., 2012). Only Dong et al. (2013) observed increased prevalence of hypertension with increased exposure to long-term estimates of PM_{10}, SO_2, and ozone, particularly in men; and only one study observed increased risk of incidence of hypertension for 1-year average NO_x concentrations in Los Angeles, USA (Coogan et al., 2012).

Finally, no conclusions can be drawn yet about any susceptible groups to the effects of air pollution on high BP.

1.4.4 Biological mechanisms of traffic-related air pollution

Different interrelated biological mechanisms have been proposed for the long-term effects of air pollution on cardiovascular diseases. These pathways are based on experimental and epidemiological evidence that has been extensively revised (Brook et al., 2010; Künzli et al., 2011; Mills et al., 2008; Simkhovich et al., 2008).

Inhalation of PM components – particularly those derived from combustion which carry ultrafine particles, transition metals, organic compounds (Mills et al., 2008) – and maybe gaseous pollutants (Brook et al., 2010), promote pulmonary inflammation and oxidative stress. This pulmonary reaction leads to the release of systemic proinflammatory markers such as cytokines, monocites and neutrophils, or platelets; vasculoactive molecules such as endothelin, and reactive oxygen species (Brook et al., 2010; Mills et

al., 2008) that affect the vascular system. In the long-term, this systemic reaction promotes endothelial vascular dysfunction, and the progression of atherosclerosis, the main underlying process of CVDs. Endothelial vascular dysfunction could in turn contribute to hypertension (Brook et al., 2009), which may partly mediate the progression of atherosclerosis and explain part of the CVD burden.

Another hypothesis suggests direct and rapid translocation of ultrafine particles and soluble compounds from the alveoli to the capillary circulation. Particles could infiltrate in arterial walls, and contribute to inflammation and oxidative processes in the long-term, or destabilize atherosclerotic plaques and lead to acute CV events (Mills et al., 2008; Simkhovich et al., 2008).

Immediate vascular responses to air pollution may be also mediated by the autonomic nervous system (ANS) imbalance due to pulmonary neural reflexes in lung receptors (Brook et al., 2010; Künzli and Tager, 2005). Acute reactions lead to reduced heart rate variability, vasoconstriction, and increased BP levels which could trigger CV events.

1.4.5 Disentangling the effects of traffic-related air pollution and traffic noise on high blood pressure

Traffic is a major source of both noise and air pollution and both factors have been associated with high BP (i.e. high systolic or diastolic BP, or hypertension). Therefore, in areas where the correlation between traffic-related air pollution and noise levels is high, the association between long-term exposure to traffic-related air pollution and high BP may be confounded by traffic noise, and vice-versa.

Most epidemiological studies have focused either on the long-term effects of air pollution or noise, and few studies analyzing high BP

have mutually adjusted for these environmental stressors (Coogan et al., 2012; de Kluizenaar et al., 2007; Dratva et al., 2012; Fuks et al., 2011; Schwartz et al., 2012; Sørensen et al., 2012, 2011). Whether this adjustment is sufficient to evaluate the independent effects of each of these environmental stressors depends on the markers of traffic-related air pollution used, which were not always specific, and the quality of the traffic noise data. Moreover, epidemiological studies generally rely on outdoor modeled estimates of both noise and air pollution which may have similar input variables, thus correlations derived from modeled estimates may be biased.

Furthermore, few studies have described the spatial distribution of these two factors in order to understand their correlation (Allen et al., 2009; Davies et al., 2009; Gan et al., 2012; Kim et al., 2012; Tang and Wang, 2007; Weber and Litschke, 2008). Different correlations were observed across the different cities studies, which suggest correlations to be area-dependent. Kim et al. (2012) also observed the strongest correlations at traffic sites and during the nighttime. Therefore, characterizing this correlation and the determinants contributing to the residential exposure of participants to both traffic noise and air pollution may help understand the degree of confounding and ability to disentangle the effects of the two stressors.

Finally, it should be borne in mind that epidemiological studies generally rely on outdoor environmental estimates, thus it is important to assess this correlation outdoors. However, the correlation between traffic noise and air pollution may be smaller for the true co-exposure indoors. Therefore, the latter assessment may help disentangle the effects of both environmental factors.

1.4.6 BP-lowering medication

The above-mentioned studies aimed at investigating whether traffic-related noise or air pollution increased BP levels. Under the assumption of a causal association, the environmental factor would lead to higher BP, and thus, to medication, which in turn would decrease BP levels. Since the latter is the only measurable level, those individuals affected by the environmental factor would more likely be treated and would show decreased, and not increased, BP levels.

To overcome this problem, studies generally adjust for medication. However, treatment is not a confounder of the association between air pollution or noise and the measured (tested) BP levels, but more likely a mediator. A simulation study observed that adjusting and not adjusting for medication may introduce bias (Tobin et al., 2005) and proposed other methodological approaches. Although all proposed methodologies had limitations, results can be compared across the different approaches to see the impact of medication on associations.

2 RATIONALE

Little is known whether long-term exposure to traffic noise and to air pollution leads to higher BP levels and to hypertension. Moreover, indoor traffic noise levels may particularly differ from outdoor levels, thus knowing indoor traffic noise levels might be essential to ascertain noise effects. Studying both hypertension and BP is also relevant to assess the robustness of results and to capture any relationships with BP that do not reach the clinical definition of hypertension but might be important **(See section 1.3.2, p.14)**.

Furthermore, it should be elucidated whether the observed long-term cardiovascular effects of near-road markers of traffic-related air pollution may be partly explained by other traffic-generated stressors such as noise, and vice-versa. Identifying the responsible factors is crucial to implement specific abatement policies for each of them. Few efforts have been done to understand their correlation and to disentangle their effects.

Given the substantial proportion of the population exposed to traffic and the leading worldwide burden of death and morbidity of hypertension and CVDs, identifying the effects of traffic-related air pollution and traffic noise on these diseases is of high public health relevance. Abatement policies for the responsible factor may help reduce hypertension and CVDs in a greater extent than treatment of hypertension **(See section 1.3.1, p.12)**.

This investigation is conducted in the framework of the REGICOR study, a set of population-based cohorts investigating cardiovascular risk factors in the province of Girona, Spain. There is a high interest in investigating this Mediterranean population, which is characterized by low cardiovascular mortality despite the high number of traditional cardiovascular risk factors (Masiá et al., 1998). In turn, traffic is particularly prevalent in Spanish urban areas.

3 OBJECTIVES

General objectives:

a) To explore the long-term co-exposure to traffic-related air pollution and traffic noise of the population living in Girona city.

b) To evaluate the association of long-term exposure to traffic-related air pollution and long-term exposure to traffic noise with hypertension, systolic and diastolic blood pressure in the adult population of Girona city in Spain.

Specific objectives:

1. To evaluate the spatial correlation between the annual average levels of measured NO_2 and of modeled traffic noise taken outdoors at several residences in the city of Girona.
2. To explore the local determinants of the spatial distribution of NO_2 and traffic noise levels in Girona city, and the factors determining the correlation between the two.
3. To evaluate the cross-sectional association of long-term exposure to NO_2 levels at home with the prevalence of hypertension, and levels of systolic and diastolic blood pressure; adjusting for traffic noise.
4. To test different statistical methods to control for blood pressure-lowering medication in the analysis on the association of long-term exposure to NO_2 with systolic and diastolic blood pressure.
5. To evaluate the cross-sectional association of long-term exposure to traffic noise levels at home with the prevalence of hypertension and the levels of systolic and diastolic blood pressure; adjusting for NO_2.
6. To disentangle the associations of long-term exposure to traffic noise and NO_2 levels with prevalence of hypertension and blood pressure levels using indoor estimates of traffic noise at bedrooms at night.

4 HYPOTHESES

I. The spatial correlation between long-term residential outdoor levels of traffic noise and traffic-related air pollution levels, such as NO_2, varies across Girona city.

II. Long-term exposure to higher traffic-related air pollution levels is associated with a higher prevalence of hypertension and increased blood pressure levels.

III. Long-term exposure to higher traffic noise levels is associated with a higher prevalence of hypertension and increased blood pressure.

5 METHODS

This section gives an overall view of the study population and the exposure assessment used in this thesis. Details on the methods for each of the analyses are given in each of the Papers ***(Section 6, p. 37)***.

5.1 Study population

REGICOR (Registre Gironí del Cor – Girona's Heart Registry) is an epidemiological study running since 1978. It consists of a set of population-based cohort studies that aim at investigating the distribution of ischemic heart disease and its risk factors in the adult population of Girona province, and at improving the prevention tools and strategies to reduce the burden of cardiovascular diseases (www.regicor.org, REGICOR, 2013). This thesis has been developed within the framework of the REGICOR2000-Air study and the MARATÓ-funded study *"Life-style and environmental determinants of cardiovascular diseases in a Spanish cohort study"* that evaluated the effects of long-term exposure to traffic-related air pollution and traffic noise on several cardiovascular endpoints, including hypertension.

This thesis used data from the baseline recruitment of the cohort study conducted during years 2003-2005, a cohort with a large recruitment of randomly selected inhabitants of Girona city. The follow-up of this cohort started in 2009 and consisted of a detailed health reassessment, collection of the participants' residential address history during the last 10 years, and of questionnaire data about room orientation, window opening habits, and protections and remedies against noise at home.

5.2 Noise exposure assessment

To characterize the long-term exposure to outdoor levels of traffic noise at home, we used **Girona city's traffic noise model** built by University of Girona engineering researchers in year 2005 (Deltell, 2005). This model followed the European Noise Directive Guidelines (*Directive 2002/49/EC*, 2002) and was based on the interim French noise modeling method (CERTU/CSTB/LCPC/ SETRA, 1997). The model accounted for the local traffic noise contribution, as it considered traffic intensities in small streets. These data was obtained from existing city records, traffic counts, and the estimations proposed in the Good Practice Guideline for Noise Mapping (WG-AEN, 2003). It also accounted for the height of buildings, among other factors, as described in the Papers **(Section 6, p.37)**. The model was validated with 119 street noise measurements and had a coefficient of determination (R^2) of 0.93.

Since the sound pressure levels of a moving source decrease 3dB per doubling of distance, considering the perpendicular distances to the source (axis of the street) is relevant for the precision of the noise estimates. We derived traffic noise estimates at the precise postal addresses of all participants (i.e. receptor points), 2 m away from façades and at the dwelling's height above ground, in a semi-automatic process. To check the precision, we built a vector that accounted for the distance between the original postal address' geocode and the façade's geocode. The vectors were small, with only 2% of the geocodes moved 20 m or more. These larger distances mainly occurred in squares, round-abouts, and avenues. Findings in this thesis were robust to the exclusion of individuals for which geocodes did not fall in front of the postal address or those with vectors greater than 20 m.

The noise estimates were derived with Cadna-A© software, using a 1000 m radius buffer and first order reflections, and had a resolution of 0.1 dB. The noise estimates corresponded to the long-term

average traffic noise levels for the daytime (L_{day}) and nighttime (L_{night}). A map of the L_{day} and L_{night} noise levels in Girona city is given in **Figure 4.** (Note that, for this thesis, the noise estimates were directly derived from the model described above, not from these maps – **See section 1.1.3, p. 5**).

We also elaborated a **noise questionnaire** based on a selection of standardized questions previously used within the European multicentre HYENA study (Jarup et al., 2005). We collected information on: dwellings' noise insulation, shift-work, room orientation, hearing impairment, window types, window-closing habits, coping behaviors against noise at night (e.g. wearing ear plugs), source-specific noise annoyance (Fields et al., 2001), and noise sensitivity (Weinstein, 1978).

Upon translation into Catalan and adaptation of some questions to the purpose of our study, we conducted a pilot study with 30 participants (mainly with high educational level – university degree –). We addressed the following questionnaire criteria: clarity of each question, space to answer, tediousness-length, coherence, and distribution of answers according to the self-reported traffic density at the residential area. The response rate was of 100%, and the average response time was 6 minutes. The questionnaire was generally clear, with some remarks in specific questions, and coherently answered across questions. We improved the wording, the description of the window types, underscored that answers should be given for the bedroom during the sleeping period, and asked for the frequency of closing windows independently of the purpose (in the HYENA study it referred to closing windows against noise). We also gave space to report other types of windows, shielding elements, and remedies against noise. A description of the participants' opinion is given in **Appendix IV.**

Paper III **(p.109)** describes the method to derive traffic noise levels at the bedroom façade and indoors based on the noise questionnaire.

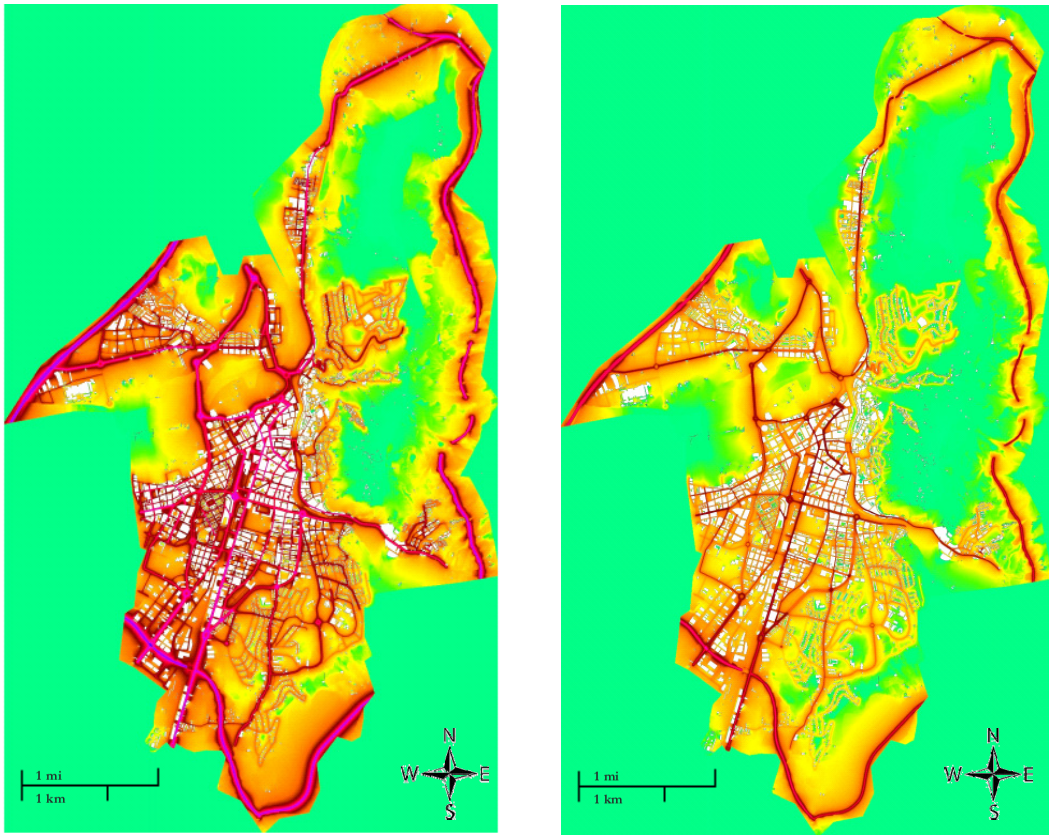

Figure 4. Daytime, $L_{day,\ 7am\text{-}11pm}$, (left) and nighttime, $L_{night,\ 11pm\text{-}7am}$, road traffic noise maps of Girona city (year 2005).
Levels reported as A-weighted equivalent noise levels.
Adapted from Deltell, 2005, unpublished.

5.3 Air pollution exposure assessment

To describe the long-term exposure to local concentrations of traffic-related air pollution, we performed a dense campaign of monthly measurements of NO_2 that captured the traffic contrasts at each of the towns participating in REGICOR2000-Air, including Girona city. Palmes tubes were deployed for one month at 562 balconies of several REGICOR participants from June 2007 to July 2009. Based on the monthly NO_2 measurements and continuous monitor data, we derived temporally-corrected annual means, and used them for the general objective "a)" of this thesis. Paper I **(p. 44)** describes this process in detail for the campaigns performed in Girona city.

Thereafter, we completed the existing data on daily traffic intensities by counting the number of light and heavy vehicles passing by in both directions during 15 minutes using manual counters. These data was scaled to daily traffic intensities, and a traffic network was built. More information can be found elsewhere (Rivera, 2012). This information was used, together with land-use data, to build the NO_2 city-specific land-use regression models (LUR) (year 2010), (Rivera et al., 2013). The main predictor variables of Girona city's model were the height of the sampler and traffic-related variables at different radius buffers around the sampling locations. The model's coefficient of determination (R^2) was 0.63.

We finally used Girona's LUR model to assign outdoor levels of annual average NO_2 at the postal address of each study participant.

6 RESULTS

6.1 Paper I: Local determinants of road traffic noise levels versus determinants of air pollution levels in a mediterranean city

Foraster, M., Deltell, A., Basagaña, X., Medina-Ramón, M., Aguilera, I., Bouso, L., Grau, M., Phuleria, H.C., Rivera, M., Slama, R., Sunyer, J., Targa, J., Künzli, N., 2011. Local determinants of road traffic noise levels versus determinants of air pollution levels in a Mediterranean city. Environ. Res. 2011; 111(1): 177–183.*

* *This paper is reproduced according to the original print version. References of this paper are included in the references' section of the thesis.*

6.2 Paper II: Long-term exposure to traffic-related air pollution, blood pressure and hypertension in an adult population-based cohort

Foraster, M., Basagaña, X., Aguilera, A., Rivera M., Agis D., Bouso, L., Deltell A., Marrugat J., Ramos R., Sunyer, J., Vila J., Elosua R., Künzli, N., 2011.

Environmental Health Perspectives [Under review]

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* *This paper is reproduced according to the revised version submitted. References of this paper are included in the references' section of the thesis.*

LONG-TERM EXPOSURE TO TRAFFIC-RELATED AIR POLLUTION, BLOOD PRESSURE AND HYPERTENSION IN AN ADULT POPULATION-BASED COHORT

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Running title: Air pollution and blood pressure

Keyword list: NO_2, air pollution, blood pressure, hypertension, noise, traffic

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There are no competing financial interests.

Abbreviations:
BP: Blood pressure; DBP: Diastolic blood pressure;
L_{night}: A-weighted long-term average sound level (dB(A)); NO_2: Nitrogen dioxide ($\mu g/m^3$); SBP: Systolic blood pressure.

Abstract

Background: Long-term exposure to traffic-related air pollution may increase blood pressure (BP) levels and induce hypertension; however evidence is yet limited and this association may be confounded by traffic noise, and biased due to inappropriate control for BP-lowering medications.

Objectives: We evaluated the association between long-term traffic-related air pollution, BP and hypertension, adjusting for transportation noise and short-term air pollution, and assessing different methodologies to control for BP-lowering medications in the city of Girona (Spain).

Methods: We measured systolic BP (SBP), diastolic BP (DBP) and socio-demographic and lifestyle factors at baseline (years 2003-2006) in 3700 participants, aged 35-84, from a population-based cohort. We estimated home outdoor annual average concentrations of nitrogen dioxide (NO_2) – a marker for local traffic-related pollution – with a land-use regression model. Associations with BP and hypertension were assessed using linear and logistic regression, respectively.

Results: A 10 $\mu g/m^3$ increase in NO_2 levels was associated with a 1.34 mmHg (95%CI: 0.14, 2.55) higher SBP in those not taking BP-lowering medication, after adjusting for transportation noise. Results were similar in the entire population after adjusting for BP-lowering medication, as commonly done in previous studies, but weaker when using other methodologies to take medication into account. No association was found for DBP or hypertension. The association was stronger for BP in participants with cardiovascular disease and present for SBP in those exposed to high traffic density, and nighttime traffic noise levels $\geq$ 55dB(A).

Conclusions: We observed a positive association between long-term exposure to home outdoor NO_2 concentrations and SBP, after adjustment for transportation noise. High BP might be a pathway through which air pollution may impact atherosclerosis and cause cardiovascular diseases.

1. Introduction

Air pollution may not only trigger cardiovascular events but promote chronic pathologies and subsequent cardiovascular disease (CVD) (Pope and Dockery, 2006), which would further contribute to cardiovascular mortality (Brook et al., 2010). This is supported by animal studies (Brook et al., 2010) and associations between long-term exposure to air pollutants and markers of atherosclerosis (Künzli et al., 2011). Long-term exposure to air pollution may also contribute to CVD through high blood pressure (BP), an established determinant of atherogenesis and CVD, and a leading cause of death (Lopez et al., 2006). Given the ubiquity of air pollution, identifying the association with high BP is of high relevance for public health.

There is increasing evidence that short-term exposure to air pollution (i.e. hours to months) is associated with high systolic BP (SBP) and/or diastolic BP (DBP) levels, although there exists some heterogeneity in previous studies (Brook et al., 2011, 2010; Chuang et al., 2010; Delfino et al., 2010). Less is known about long-term exposure. Four cross-sectional studies found significant positive associations between annual average home outdoor concentrations of different pollutants with BP in population-based samples, the elderly, or men (Chuang et al., 2011; Dong et al., 2013; Fuks et al., 2011; Schwartz et al., 2012). In contrast, one study reported inverse associations with SBP (Sørensen et al., 2012). Evidence for increased prevalence or incidence of hypertension is still more limited (Coogan et al., 2012; Dong et al., 2013). Plausible biological pathways involve autonomic nervous system imbalance, oxidative stress and systemic inflammation, and subsequent endothelial dysfunction (Brook et al., 2009; Mills et al., 2008).

Several studies suggest that near-road traffic-related air pollution – indicated with residential proximity to traffic – could be particularly important for CVD (Brook et al., 2009; Hoffmann et al., 2007;

Künzli et al., 2010a). Traffic-related air pollution could also be relevant for BP (Schwartz et al., 2012). Traffic is also a main source of noise, which has been associated with hypertension in the long-term (van Kempen and Babisch, 2012), and may potentially confound or modify the effects of air pollution on BP. However, few studies have adjusted for it (Fuks et al., 2011; Sørensen et al., 2012).

A particular challenge and weakness of previous publications relates to dealing with BP-lowering medication. Conceptually, air pollution would lead to high BP, and treatment, which would then decrease BP levels. Thus, treatment would be a mediator, not a confounder, of the final measured BP levels. Therefore, the common procedure of adjusting for medication may introduce bias, as suggested before (Fuks et al., 2011; Schwartz et al., 2012; Tobin et al., 2005)

The purpose of this cross-sectional study was to evaluate the association between home outdoor estimates of annual average concentrations of NO_2, a marker of traffic-related air pollution, and both BP levels and prevalence of hypertension, adjusting for traffic-related noise, and particularly evaluating different procedures to account for BP-lowering medication. Furthermore, we investigated whether residential proximity to main roads, high traffic noise levels, and different population characteristics modified the association between pollution and BP. We capitalize on the large and well defined adult population of the REGICOR cohort studies conducted in Girona (Spain).

2. Methods

2.1. Study population

The study population consisted of 3,836 individuals, aged 35–83 who participated at baseline (years 2003 to 2006) in one of the population-based cohorts of the REGICOR project, described elsewhere (Grau et al., 2007). Briefly, we selected subjects randomly from all non-institutionalized inhabitants of the city of Girona. The response rate was 73.8%. Girona is a typical mid-sized Mediterranean urban area of 96,722 inhabitants (Idescat, 2011) in the north-east of Spain with a densely populated centre where traffic is expected to be the main contributor to air pollution levels. The study was approved by Hospital del Mar Research Institute ethics committee and participants signed written informed consent.

2.2. Outcomes and health assessment

Participants fasted for 10h previous to examination. Trained nurses performed the examinations from 8 to 11am, and measured BP at the beginning, following the Joint National Committee (JNC) VII recommendations (Chobanian et al., 2003), in sitting position, and with a calibrated automatic device (OMRON 711). The first and second measurements were done after at least 10 and 3 minutes of rest, respectively. If measurements differed by 5 mmHg or more, a third one was taken. To avoid white coat effect, we used the last measurement available. Afterwards, the nurses withdrew blood to obtain cholesterol, triglyceride and fasting glucose levels.

We collected questionnaire information on co-morbidities, life-styles and socio-economic factors (SES) such as smoking, weekly leisure time physical activity, daily alcohol intake, Mediterranean diet, and educational level, and assessed deprivation index at the census track level. Diabetes was defined based on fasting glucose

blood levels and height and weight were measured to derive the body mass index as weight/height^2 (kg/m^2). Details on definitions and measurements are given in the Supplement (See Supplemental Material, **p.92**).

We defined hypertension as having SBP or DBP ≥ 140/90 mmHg (Chobanian et al., 2003), respectively, or as a positive response to the question "Do you take or have you taken any doctor prescribed medication to reduce blood pressure in the last two weeks?". For BP analysis, we accounted for any "BP-lowering medication". It included antihypertensive treatment as defined with the question above, or the use of any treatment from the medication list provided by participants and coded by a physician into "antihypertensive" or "beta-blocker" (i.e. diuretics, ACE inhibitors, alpha or beta-blockers, angiotensin receptor II blockers, and calcium channel blockers).

2.3. Exposure assessment

We geocoded participants' residential addresses at enrollment. We estimated annual average outdoor NO_2 (μg/m^3) at the residences with a city-specific land-use regression (LUR) model (R^2=0.63) based on a dense network of residential outdoor NO_2 measurements (years 2007-2009), as described elsewhere (Rivera et al., 2013). The main predictor variables were the height of the sampler and traffic-related variables at different radius buffers (from 25 to 1000 m) around the sampling locations.

To control for acute effects of short-term air pollution and temperature on measured BP, we obtained daily means of temperature and of NO_2 concentrations at an urban background station from the regional air quality monitoring network. Season was categorized as winter (January-March), spring (April-June), summer (July-September) and autumn (October-December).

We also derived long-term average traffic noise levels (dB(A)) at the residences' façade with a detailed city-specific noise model (year 2005), which complies with the European Noise Directive 2002/49/EC (END). The main input variables were: street slopes, type of asphalt, urban topography, and traffic density (See Supplemental material, **p.93**). Since railway noise has also been associated with BP (Dratva et al., 2012), and a single North-South rail bridge crosses dense traffic areas in the city, we also derived residential railway noise estimates from an END-based model (See Supplemental material, **p.93**). Since it is suggested that transportation noise may particularly impact cardiovascular health during the restorative sleep processes at nighttime (Jarup et al., 2008), we used the nighttime (11pm-7am) noise indicators (L_{night}). A small airport is located outside the city and did not affect our study population.

Traffic markers (traffic intensity at the nearest road and traffic load within a 500m buffer) were collected using the city road network with linked traffic intensities from local registries and traffic (Rivera et al., 2012).

2.4. Statistical analyses

Analyses were performed with complete cases, i.e. excluding missing observations (n=101) on the outcomes, exposure and covariates of the main models. We used multivariable linear regression models for BP and logistic regression for hypertension and performed regression diagnostics. Linearity of the crude and adjusted associations was assessed with generalized additive models and covariates were transformed or categorized accordingly. Inclusion of covariates in models was based on the hypothesized causal pathway of long-term effects of NO_2 on BP and current evidence (Fuks et al., 2011). We also built saturated models with all covariates univariately associated with the outcome and exposure (p-value < 0.2) and performed backward regression, manually

removing the variables with the highest p-value one-by-one, if estimates changed by less than 20% and keeping p-values < 0.1. Finally, we assessed the inclusion of potential intermediate variables, co-morbidities, and use of different lags for daily temperature and NO_2 levels prior to examination (lags: 1, 2, 3 and the average from 0 to 3 days), compared to lag 0 (used by default). Temporal trend (day of examination) was also examined to control for potential decreasing trends in BP levels over the study period due to improved BP management. As the different model specifications gave similar results, we present final estimates with the most parsimonious adjustment set of variables, to avoid overadjustment and variance inflation. All evaluated variables are described in **Table 1** and in the Supplemental Material, **Table S1**.

A main objective of this study was to rigorously investigate potential biases related to different methodologies used or proposed to control for BP-lowering medication. Thus, we studied the effects of NO_2 on BP: a) restricting analysis to participants not taking any BP-lowering medication i.e. in "non-medicated"; b) restricting analysis to "medicated" participants; c) ignoring treatment; d) adjusting for treatment; e) adding a fixed value of mmHg for SBP (+10, 15 and 20) and DBP (+5, 10, 15) to those treated; f) using censored regression, which assumes that had medicated participants not been treated, they would have BP levels at least as high as the measured levels. Methodologies from a) to d) were used for comparison with previous literature. Methodologies e) and f) were favored in a comprehensive simulation study, but rely on non-measurable assumptions that might be violated in our study population (Tobin et al., 2005). For extended analysis we selected model a). To test the hypothesis of air pollution affecting BP, subjects not taking any BP lowering drugs are of prime interest as this is the only group where the main outcome was measured without bias. Although there might be some degree of selection bias in this group, we believe its impact might be limited, as subsequently explained in the discussion section.

We assessed effect modification of the association between NO_2 and BP among non-medicated by traffic L_{night} (< 55 dB(A) versus ≥ 55 dB(A)), traffic intensity at the nearest road, and traffic load in 500m as binary variables with a cut-off at the median. We also tested age, sex, educational level, smoking, Mediterranean diet, living alone (a marker of uncontrolled hypertension (Morgado et al., 2010)), diabetes, CVD, and season of examination (given possibly larger effects in summer (Fuks et al., 2011; Sørensen et al., 2012).

We also tested different time windows of exposure, 1) using the average NO_2 exposure of the last 10 years for 2402 individuals which already attended the follow-up and had information on residential history, and 2) restricting analyses to subjects not moving in the last 2, 5 and 10 years.

Effects on BP and hypertension are expressed per 10 $\mu g/m^3$ increase in NO_2 unless differently specified.

Analyses were done using Stata 12.0 (StataCorp, College Station, TX) and R 2.12.

3. Results

The final sample size consisted of 3700 individuals. Participants excluded from the study had slightly higher SBP levels, less healthy life-style, more co-morbidities, and lower transportation (i.e. traffic and railway) L_{night} levels (data not shown).

The characteristics of the study population included in the final models are summarized in **Table 1** and in the Supplemental Material, **Table S1**. A 72.6% of all participants did not take any BP-lowering medication (i.e. non-medicated group). Non-medicated differed from medicated participants in being younger on average (53 vs. 68 years old, respectively) but with similar age ranges (35-

83 versus 35-82, respectively), having lower BP, higher educational level, less co-morbidities, including a greater proportion of women, and smoking and drinking more.

The median of the home outdoor estimates of annual average NO_2, long-term railway L_{night} and traffic intensity at the nearest road were 26.4 $\mu g/m^3$, 41.4 dB(A), and 1400 vehicles/day, respectively. Non-medicated participants had slightly lower traffic L_{night} levels compared to medicated participants (56.5 dB(A) versus 56.9 dB(A), respectively).

The highest correlations (Spearman rank) of annual mean NO_2 concentrations were with traffic L_{night} (r=0.74) and traffic load in a 500m buffer (r=0.91) (See Supplemental Material, **Table S2**).

A 10 $\mu g/m^3$ increase in annual average NO_2 (from now onwards, NO_2) was associated with a statistically significant increase of 1.15 mmHg (95%CI: 0.34, 1.95) in SBP in non-medicated in univariate analysis, and of 1.34 mmHg (95%CI: 0.14, 2.55) after full adjustment (**Table 2**). This association was less precise in the group of medicated participants (β=1.19, 95%CI: -1.37, 3.75). The association between NO_2 and SBP in the entire population (with and without adjustment for BP-lowering treatment) yielded similar results (β=1.11, 95%CI: -0.03, 2.24 and β=1.35, 95%CI: 0.23, 2.47, respectively). Models adding a fixed value of SBP to medicated participants showed smaller effects, steadily shrinking to the null with increasing fixed values. No association between NO_2 and SBP was observed with censored regression. The main confounders of the association between NO_2 and SBP were age, transportation noise (both traffic and railway), and daily temperature. Not adjusting for transportation noise resulted in a smaller coefficient for NO_2 (β=0.59, 95%CI: -0.15, 1.34) as observed in **Table 2**. In fact, the associations of traffic and railway L_{night} with SBP in the model for non-medicated participants were β=-0.94 (95%CI: -2.53, 0.64), p-value=0.244, and β=-0.21 (95%CI: -0.63, 0.21), p-

value=0.326, respectively, per 10 dB(A) change in L_{night}. The addition of heart rate, CVD, hyperlipidemia, Mediterranean diet, exercise, day of examination, daily temperature, or daily NO_2 levels at lags different than 0, did not affect results. No effects of NO_2 on DBP (β=0.15, 95%CI: -0.57, 0.88) or hypertension (OR=0.93, 95%CI: 0.79, 1.1) were identified (see Supplemental Material, **Tables S3 and S4**).

Figure 1 and Supplemental Material (**Figure S1**) show the interaction analysis for the association between NO_2 and SBP and DBP, respectively, in non-medicated participants. NO_2 was more strongly associated with SBP among individuals with CVD (β=5.96, 95%CI: 1.85, 10.08) than among individuals without (β=1.17, 95%CI: -0.04, 2.38), and associated with DBP among individuals with CVD (β=2.71, 95%CI: 0.23, 5.18), (p-values of interaction < 0.031). A stronger effect of NO_2 on SBP was also found in those living alone. NO_2 was associated with SBP in participants exposed to traffic, particularly with traffic loads above the median in a 500 m buffer (β=2.28 mmHg, 95%CI: 0.58, 3.97) and individuals exposed to traffic $L_{night} \geq 55$ dB(A) (β=1.82, 95%CI: 0.56, 3.07), (p-values of interaction < 0.028). Larger effects in SBP were suggestive in those getting BP measured in summer. This seasonal interaction was statistically significant for DBP. Gender, educational level, diabetes, age, smoking, and Mediterranean diet did not modify the main associations (**Figure 1**). Finally, neither the use of BP-lowering medication nor of antihypertensive treatment interacted with the observed associations (p-values of interaction > 0.472), (results not shown).

Restricting the sample to non-movers or using 10-year average NO_2 levels yielded similar or smaller increases in BP compared to findings with the annual average NO_2 levels at the current address in non-medicated participants (see Supplemental Material, **Table S5**). Furthermore, in comparison to findings in the entire sample, the associations in the sub-sample of participants with residential

history were more robust to the use of different modeling strategies to correct for BP-lowering medication (see Supplemental Material, **Table S6**).

4. Discussion

This is one of the only studies to analyze the association between near-road traffic-related air pollution and both blood pressure (BP) and hypertension, and to control for detailed transportation noise information. Moreover, this study evaluates in detail the influence on findings of using different methodologies to control for BP-lowering medications.

This cross-sectional population-based study showed a statistically significant association between increased long-term exposure to home outdoor nitrogen dioxide (NO_2) concentrations, a widely used marker of near-road traffic-related air pollution, and increased systolic blood pressure (SBP), among participants not taking BP-lowering medication (non-medicated). This association was similar in the entire population no matter whether models were adjusted or not for medication. However, the relationship was weaker or diluted when using methods proposed to be less biased in a simulation study (Tobin et al., 2005). Results were controlled for exposure to transportation noise, short-term air pollution levels and temperature and robust to the inclusion of several co-factors. No significant associations were found for hypertension or diastolic blood pressure.

4.1. Blood pressure

The main results for SBP are consistent with most of the few studies available (Chuang et al., 2011; Dong et al., 2013; Fuks et al., 2011; Schwartz et al., 2012).

Fuks et al. (2011) reported similar effect sizes to ours. However they analyzed urban background particulate matter of an aerodynamic diameter ≤ 2.5 $\mu g/m^3$ and not NO_2. Regarding NO_2, one study found inverse associations between nitrogen oxides (NO_x, NO and NO_2) and SBP (Sørensen et al., 2012), a study in China found no association (Dong et al., 2013), and a survey of elderly in Taiwan (Chuang et al., 2011) found stronger effects than ours (namely a 11.22 mmHg increase in SBP (95%CI: 8.56, 13.89) per 10 $\mu g/m^3$ in NO_2). The different effect sizes may originate from different population characteristics (age, ethnicity, life-style, etc.) or residual confounding due to the lack of information on SES in Taiwan. Moreover, to the extent that NO_2 may serve as a marker, differences in the air pollution mixtures between the study areas may also explain the discrepancies.

As reported in two previous epidemiological studies, there was no association between NO_2 and DBP (Auchincloss et al., 2008; Sørensen et al., 2012). Animal and human experimental studies suggest that BP responses to long-term exposure to air pollution may be mediated by sustained systemic inflammation and/or oxidative stress, impairing endothelial function and increasing BP (Brook et al., 2009; Mills et al., 2008). As discussed by Auchincloss et al. (2008), endothelial dysfunction and subsequent stiffening of the aorta would result in increased SBP but lower DBP, i.e. increased pulse pressure, and subsequent isolated systolic hypertension after age 60 (Franklin, 2006).

4.2. Effect of BP-lowering treatment

One of the difficulties in studying BP is that antihypertensive medication is a potential mediator between air pollution and measured BP levels, and not a confounder of the studied association. Consequently, the common procedures of adjustment for medication may introduce bias. Previous studies either analyzed non-medicated participants (Sørensen et al., 2012), did not adjust

for medication (Chuang et al., 2011), adjusted for medication (Schwartz et al., 2012), or compared models with an without adjustment (Fuks et al., 2011). To overcome this problem, some methodologies have been proposed (Tobin et al., 2005). However, as discussed below, the latter also rely on non-measurable assumptions that may be violated in some populations.

BP levels are not modified by medication in the non-medicated group. In this subgroup, we observed a statistically significant positive association between NO_2 and SBP. Our analyses do not support strong biases due to self-selection of non-medicated participants. Firstly, the main determinants of being non-medicated with high BP were being younger and healthier, thus we expect findings to be conservative under this least severe case scenario. Secondly, as suggested by Fuks et al. 2011, if air pollution would lead to high BP, medication intake and subsequent decrease in the measured BP levels, and if this would be the only mechanism in place, then we should observe an inverse association between air pollution and measured BP for medicated participants. However, point estimates were positive but less precise in treated participants, and similar to point estimates in non-medicated. This suggests a heterogeneous effect of treatment, leading to more variability in the measured BP levels and thus imprecise results. This heterogeneity is likely to occur, given the wide range of the population studied, different treatments potentially used, and likely diverse compliance to treatments. This heterogeneity would also result in less systematic bias when adjusting for medication, which agrees with the similar positive findings that we observed either adjusting or not for treatment.

Using a fixed correction of +10 mmHg in SBP for those treated led to weaker although suggestive results, whereas larger corrections showed a steady shrinkage of results towards the null. This also suggests that the effects of treatment were heterogeneous in the population, as this method relies on the assumption that the

magnitude of the effect of medication can be quantified, i.e. that medication introduces a systematic error. Regarding censored regression, one of the assumptions of this model is that the distribution of underlying BP in treated subjects is the same as the distribution of observed BP in untreated subjects, which might be often wrong (Tobin et al., 2005), and not necessarily true in our sample.

In summary these observations likely indicate that the effect of treatment was very heterogeneous in the entire population, preventing an accurate use of proposed methodologies such as the fixed correction (particularly large corrections), whereas probably biasing results in a lesser extent in commonly used procedures. In fact, in extensive analyses in a younger subgroup, with less hypertension and potentially less heterogeneous effects of treatment, all methods converged into statistically significant positive associations between NO_2 and SBP (see Supplemental Material, **Table S6**). Whereas a systematic bias on measured BP would lead to shrinkage of results against our hypothesis in commonly used methodologies, as suggested by Tobin et al. (2005), we expect heterogeneity to increase random error with less precise estimates biased towards the null, particularly in the fixed correction method.

4.3. Hypertension

Prevalence of hypertension was not associated with annual average NO_2 concentrations in our study. The few previous studies found inconsistent results for prevalence of hypertension with different pollutants (Dong et al., 2013; Fuks et al., 2011; Johnson and Parker, 2009; Sørensen et al., 2012). Regarding incidence of hypertension, no association was found in Denmark (Sørensen et al., 2012), whereas another study found statistically increased risk of hypertension with long-term NO_2 and a positive tendency for $PM_{2.5}$ (Coogan et al., 2012).

We hypothesized the differences to be due to misclassification of hypertensive cases, as proposed before (Fuks et al., 2011). However, the different definitions of hypertension yielded all null results (see Supplemental Material, **Table S4**), except for a non-significant increase in hypertension in non-medicated, which agrees with our results on BP. Non-medicated hypertensive participants were characterized by being younger. Alternatively, the null associations may relate to a loss in statistical power and information when using a binary variable.

4.4. Transportation noise

As emphasized by others (van Kempen and Babisch, 2012), we considered transportation noise as a potential confounder in our analyses. Although traffic noise and NO_2 were highly correlated (r=0.74), the negative confounding of transportation noise on the studied association with SBP was not explained by collinearity among these factors (mean variance inflation factor (VIF) for the model=1.45, VIF for NO_2=3.2, individual VIF for road L_{night}=2.25). We hypothesized that the negative confounding might in part be explained by use of protections and coping behavior against noise among participants more exposed to noise. Thus, the estimates of outdoor may not be sufficient to investigate the independent effects of this stressor on BP. We consider better noise exposure assessment a crucial next step to elucidate the role of noise. Thus, we currently develop models to individually estimate home indoor noise levels from traffic.

4.5. Effect modification

We observed a stronger positive association between NO_2 on BP in participants with CVD, similarly to Sorensen et al. 2012, who reported this interaction between long-term residential NO_x and

DBP. However, given the small numbers in both cases, further studies are needed to investigate this interaction. We also found a stronger association for participants living alone. Living alone was strongly correlated with being older and exposed to slightly higher NO_2 levels in our population, and Morgado et al. (2010) identified it as a marker of uncontrolled hypertension (Morgado et al., 2010).

Besides, we found a statistically significant association between NO_2 and SBP only in those with traffic loads in a 500 m buffer above the median (which was suggestive with traffic at the nearest road), and those with high road traffic noise (≥ 55 dB(A)). This may suggest that at higher traffic levels, NO_2 may be more representative of near-road traffic related pollutants, which were particularly associated with CVD (Auchincloss et al., 2008; Brook et al., 2009; Hoffmann et al., 2007; Künzli et al., 2010a). Thus, depending on the location, NO_2 may be a marker of different types of pollutants. It could also be due to a non-linearity in the effects of NO_2 on BP. Indeed, we observed a suggestive non-linearity of the effects of NO_2 on BP, consisting of a null to negative association at very low NO_2 levels (compared to levels in larger Spanish and European cities) and a clear positive trend from 20 $\mu g/m^3$ onwards (Supplement, **Figure S2**). Our results did not change by the use of a quadratic term, given that the non-linearity was observed at very low levels and given that our population was exposed to a large range of NO_2 concentrations. However, the observation of a non-linearity may confirm the hypothesis of near-road traffic-related pollution being particularly relevant. In our study areas, low levels of NO_2 reflect sites with little traffic, thus, exposure is mostly related to urban background pollution whereas in other urban areas, NO_2 is clearly a marker for near-road traffic-related pollutants. Similar reasons may explain the negative associations observed between SBP and NO_x in Denmark (Sørensen et al., 2012), where NO_2 levels were particularly low (median=16.3, 5%-95% percentile:12.0-32.6, at baseline). In addition, the adjustment for traffic intensity or traffic load in 500m diluted the effects of NO_2 on

SBP (results not shown); which also indicates that we are observing traffic-related air pollution effects on SBP, but not background pollution effects.

4.6. Strengths and limitations

The main inferential limitation of this study was its cross-sectional design. Our results should be confirmed in longitudinal analysis with repeated measures of blood pressure and incidence of hypertension.

As in many epidemiological studies, BP was measured with standard protocols, consisting in repeated measures taken during one single exam, not following clinical procedures to diagnose hypertension. Although results were robust to different definitions of hypertension and we selected the last BP measurement available to minimize the "white-coat" effect, the lower precision of the outcome could lead to a non-differential misclassification, biasing results towards the null.

Regarding exposure misclassification, we assessed individual residential outdoor exposure, not personal exposure. Although people spend a relevant part of their time at home (Leech et al., 2002), we cannot conclude whether time-activity patterns in this population would affect our findings. To the extent that people living in pristine areas are likely to commute to less clean areas for work, lack of data on exposure during work may bias results towards the null. Although our LUR model was developed after examination, no major changes in traffic and the monitored background NO_2 levels occurred from 2003 to 2009. Thus, we expect spatial gradients of NO_2 to be stable over time, as reported before (Eeftens et al., 2011). Finally we did not observe biases due to past residential mobility or time window of exposure.

Another limitation was the lack of information on lead exposure from leaded gasoline used before year 2000 in Spain. Long-term cumulative exposure, reflected by bone lead levels, could remain high in this adult population and potentially interact with or confound the association between NO_2 and high BP (Schwartz et al., 2011).

As an important strength, we evaluated a population-based cohort, thus results in the entire population can be generalized, and a wider age range compared to previous studies, some of which were only in elderly participants (Chuang et al., 2011; Schwartz et al., 2012). Additional strengths include the comprehensive analysis of BP-lowering medication, the use of a LUR model that captured the intraurban variability in NO_2 levels, and the control for detailed transportation noise data, which has rarely been taken into account in previous literature (Fuks et al., 2011; Sørensen et al., 2012). This is relevant, as road traffic and railway noise have been associated with high BP and hypertension (Dratva et al., 2012; van Kempen and Babisch, 2012).

5. Conclusions

We observed a positive association between long-term exposure to NO_2 and SBP in a population-based cohort in Girona, which was stronger among participants with CVD, those living alone, and those exposed to more traffic and road traffic noise. These results suggest specific effects of near-road traffic-related pollutants on BP and were observed after a detailed assessment of BP-lowering medication and control for transportation noise. High BP might be a pathway through which air pollution causes CVD. Although the effect size was small, these findings are of high public health relevance, given the ubiquity of air pollution, affecting a high proportion of the population. Indeed, a "small" reduction of 2 mmHg in the population mean SBP translated into a 25% reduction in stroke events (Girerd and Giral, 2004).

Table 1. Main characteristics of the study population (N=3700) with and without stratification by use of blood pressure (BP)-lowering medication.

	Blood pressure-lowering medication			
	Total N=3700	No N=2685	Yes N=1015	
	N (%)	N (%)	N (%)	p-value [a]
Hypertension, Yes	1478 (39.9)	565 (21.0)	913 (90.0)	< 0.001
Gender, Male	1720 (46.5)	1203 (44.8)	517 (50.9)	0.001
Body mass index, < 20	135 (3.60)	124 (4.60)	11 (1.10)	< 0.001
0-25	1110 (30.0)	939 (35.0)	171 (16.8)	
25.1-30	1618 (43.7)	1168 (43.5)	450 (44.3)	
> 30	837 (22.6)	454 (16.9)	383 (37.7)	
Living alone, Yes	413 (11.2)	265 (9.90)	148 (14.6)	< 0.001
Educational level, University or similar	1050 (28.4)	853 (31.8)	197 (19.4)	< 0.001
Secondary	1110 (30.0)	878 (32.7)	232 (22.9)	
Primary	1432 (38.7)	902 (33.6)	530 (52.2)	
Illiterate	108 (2.90)	52 (1.90)	56 (5.50)	
Smoking, Never smokers	1881 (50.8)	1329 (49.5)	552 (54.4)	< 0.001
Smokers	811 (21.9)	677 (25.2)	134 (13.2)	
Former smokers	1008 (27.2)	679 (25.3)	329 (32.4)	
Diabetes, Yes	580 (15.7)	265 (9.90)	315 (31.0)	< 0.001
Daily alcohol intake (g/l), No alcohol	956 (25.8)	630 (23.5)	326 (32.1)	< 0.001
Little (< 20)	2237 (60.5)	1672 (62.3)	565 (55.7)	
Moderate (20.1–39.9)	390 (10.5)	292 (10.9)	98 (9.70)	
Excessive (≥ 40)	117 (3.20)	91 (3.40)	26 (2.60)	
Cardiovascular disease [b,c], Yes	269 (7.30)	83 (3.10)	186 (18.5)	< 0.001

Table 1 (continued)

Variable	Total N=3700 Median (IQR)	Blood pressure-lowering medication: No N=2685 Median (IQR)	Blood pressure-lowering medication: Yes N=1015 Median (IQR)	p-value[a]
Systolic blood pressure (mmHg)	125 (26.0)	120 (22.0)	139 (27.0)	< 0.001
Diastolic blood pressure (mmHg)	78.0 (13.0)	77.0 (12.0)	81.0 (14.0)	< 0.001
Age (years)	57.0 (20.0)	53.0 (17.0)	68.0 (15.0)	< 0.001
Deprivation index [d]	-1.82 (1.28)	-1.82 (1.22)	-1.81 (1.37)	< 0.001
Annual average NO_2 levels ($\mu g/m^3$)	26.6 (11.7)	26.4 (11.6)	26.8 (11.9)	0.837
Traffic L_{night} (dB(A)), 11pm-7am	56.6 (7.00)	56.5 (7.00)	56.9 (7.10)	0.022
Railway L_{night} (dB(A)), 11pm-7am	41.2 (15.2)	41.4 (15.0)	41.0 (15.2)	0.056
Daily mean NO_2 levels at lag 0 ($\mu g/m^3$)	32.0 (11.9)	32.0 (11.7)	31.7 (12.6)	0.362
Daily mean temperature at lag 0 (ºC)	14.5 (12.4)	14.3 (12.8)	15.0 (11.7)	0.021

NO_2: Nitrogen dioxide

L_{night}: Long-term average nighttime noise levels

[a] χ^2 test and Kruskal-Wallis test for strata of BP-lowering drugs with categorical variables or continuous variables, respectively.

[b] Myocardial infarction, ictus, or any cardiovascular surgical intervention

[c] N below 3700 (< 1% missing observations)

[d] High deprivation corresponds to high values

Table 2. Multivariate linear regression for the effect of a 10 µg/m^3 increase in annual average home outdoor NO_2 concentrations and 95% confidence intervals on systolic blood pressure (SBP, mmHg).

Models for SBP	N	beta (95%CI) [a]	beta (95%CI) [b]
Non medicated	2685	1.34 (0.14, 2.55)	0.59 (-0.15, 1.34)
Medicated	1015	1.19 (-1.37, 3.75)	0.68 (-1.09, 2.44)
Without adjustment for medication	3700	1.11 (-0.03, 2.24)	0.56 (-0.17, 1.28)
With adjustment for medication	3700	1.35 (0.23, 2.47)	0.67 (-0.04, 1.38)
+10 mmHg [c]	3700	0.78 (-0.43, 2.00)	0.41 (-0.36, 1.18)
+15 mmHg [c]	3700	0.62 (-0.65, 1.89)	0.33 (-0.47, 1.14)
+20 mmHg [c]	3700	0.46 (-0.88, 1.80)	0.26 (-0.59, 1.11)
Censored regression	3700	0.38 (-0.98, 1.73)	0.12 (-0.73, 0.97)

[a] Fully adjusted models, adjusted for: age, age squared, sex, living alone, education, diabetes, BMI, nighttime railway noise, nighttime traffic noise, smoking, alcohol consumption, deprivation, daily NO_2 and temperature (lag 0).
[b] Models adjusted for covariates in fully adjusted model except for nighttime railway and traffic noise.

Adjusted for blood pressure-lowering medication if specified in table.

[c] Correction to SBP for participants with BP-lowering medications

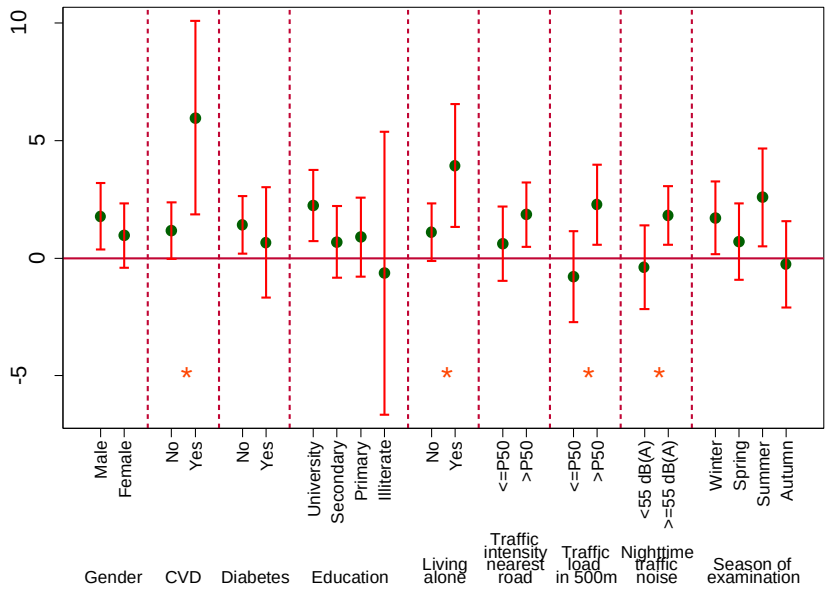

Figure 1. Adjusted beta coefficients for a 10 µg/m^3 increase in annual average home outdoor NO_2 concentrations and 95% confidence intervals on systolic blood pressure (mmHg) by subgroups of the population (N=2685, non-medicated participants). Each multivariate linear regression model was adjusted for the corresponding interaction-term, one at a time, and age, age squared, sex, living alone, education, diabetes, BMI, nighttime railway noise, nighttime traffic noise, smoking, alcohol consumption, deprivation, daily NO_2 and temperature (lag 0). *indicates p-value of interaction < 0.05.

Supplemental material

Long-Term Exposure to Traffic-Related Air Pollution, Blood Pressure and Hypertension in an Adult Population-Based Cohort

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1. Questionnaire data and health assessment

We collected questionnaire information on: smoking (smoker/ex-smoker of more than one year/never smoker), weekly leisure time physical activity (in metabolic equivalents based on Minnesotta's questionnaire) (Elosua et al. 2000), daily alcohol intake (g/l) (no alcohol/little (< 20) / moderate (20.1-40) / excessive (> 40)), living alone (no/yes), and family history of cardiovascular deaths. Mediterranean diet was based on the REGICOR adherence score, being 10 the lowest and 30 the highest adherence (Schröder et al. 2004). Socio-economic status (SES) was assessed individually with the reported level of education and occupational status, and at the area-level with the deprivation index, calculated at the census track level of the baseline residential address (Domínguez-Berjón and Borrell 2005). We defined diabetes as fasting blood glucose levels ≥ 126 mg/dl or reported treatment with antidiabetic drugs, body mass index (BMI) as weight/height^2 (kg/m^2) (< 20 / 20-25 / 25.1-30 / > 30), and cardiovascular disease as having ever had a cardiovascular event (myocardial infarction or stroke) or cardiovascular-related surgery intervention. We measured heart rate during the blood pressure (BP) measurement, with the same automatic device (OMRON 711).

2. Noise exposure assessment

Long-term average traffic noise levels (dB(A)) were derived at the geocoded residences, 2m from the façades and at the floors' height of each dwelling, with a detailed and validated city-specific traffic noise model (year 2005), described elsewhere (Foraster et al. 2011). This model complies with the European Noise Directive 2002/49/EC (END), and applies the interim European model for road traffic, NMPB routes-96 (CERTU/CSTB/LCPC/SETRA 1997). Estimates were computed by numerical calculations in Cadna-A software. The main input variables were: street slopes, type of asphalt, urban topography (including building heights), and traffic density.

Residential railway noise estimates were derived from a propagation model, based on ISO 96/13 and accepted by the European Noise Directive 2002/49/EC. The propagation model was built upon source identification of railway noise. This consisted of day-time and nighttime measurements of the spectra (i.e. noise frequency in 1/3 octave bands) and noise equivalent levels (in dB(A)) of freight and normal trains (a total of 72 measurements). Measurements were taken with a SC-30 sound level meter and CB-5 calibrator (CESVA, inc.).

Supplemental Material, Table S1. Extension of characteristics of the study population (N=3700) reported in Table 1, with and without stratification by use of blood pressure (BP)-lowering medication.

	Blood pressure-lowering medication			
	Total	No	Yes	
	N=3700	N=2685	N=1015	
Variable	Median (IQR)	Median (IQR)	Median (IQR)	p-value[a]
Weekly physical activity (MET)	1519 (1886)	1491 (1828)	1575 (1952)	0.218
Mediterranean diet adherence score[b]	20.0 (4.00)	20.0 (4.00)	20.0 (4.00)	0.136
Traffic intensity in nearest road (veh/day)	1459 (5674)	1400 (5662)	1459 (5466)	0.192
Traffic load in 500 m buffer/10000 (veh·m/day)	8043 (6539)	8014 (6461)	8125 (6653)	0.807
	N (%)	N (%)	N (%)	p-value[a]
Occupational Status[c], Working	2003 (54.4)	1721 (64.4)	282 (27.9)	< 0.001
Homemaker and economically inactive	479 (13.0)	319 (11.9)	160 (15.8)	
Retired	1117 (30.3)	560 (21.0)	557 (55.1)	
Unemployed	84 (2.30)	73 (2.70)	11 (1.10)	
Heart rate[c], < 60	626 (16.9)	432 (16.1)	194 (19.2)	< 0.001
60-80	2584 (69.9)	1922 (71.7)	662 (65.4)	
80.1-100	459 (12.4)	317 (11.8)	142 (14.0)	
> 100	26 (0.70)	11 (0.40)	15 (1.50)	
Direct relative died for cardiac reasons[c], Yes	366 (10.0)	251 (9.40)	115 (11.5)	0.064
Hyperlipidemia[c,d], Yes	1067 (28.9)	661 (24.6)	406 (40.0)	< 0.001
Season, Winter	1065 (28.8)	810 (30.2)	255 (25.1)	0.025
Spring	1242 (33.6)	886 (33.0)	356 (35.1)	
Summer	664 (17.9)	475 (17.7)	189 (18.6)	
Autumn	729 (19.7)	514 (19.1)	215 (21.2)	

[a] χ^2 test and Kruskal-Wallis test for strata of BP-lowering drugs with categorical variables or continuous variables, respectively.

[b] 10 (lowest) and 30 (highest) adherence to diet

[c] N below 3700 (< 1% missing observations)

[d] Hyperlipidemia defined as having total cholesterol > 250 mg/dl or taking statins or any treatment to decrease cholesterol levels

Supplemental Material, Table S2. Spearman's correlation between the long-term and short-term environmental factors. N=3700.

Variables	Annual NO_2	Traffic L_{night}	Railway L_{night}	Daily NO_2, lag 0	Daily temperature, lag 0	Traffic intensity
Annual NO_2 ($\mu g/m^3$)	1.00					
Traffic L_{night} (dB(A))	0.74*	1.00				
Railway L_{night} (dB(A))	0.66*	0.48*	1.00			
Daily NO_2, lag 0	0.02	-0.02	0.03*	1.00		
Daily temperature, lag 0	0.02	-0.04*	-0.10*	-0.20*	1.00	
Traffic intensity nearest road (veh/day)	0.62*	0.76*	0.37*	-0.03	-0.04*	1.00
Traffic load in 500m buffer (veh·m/day)	0.91*	0.59*	0.71*	0.02	0.02	0.49*

NO_2: Nitrogen dioxide, L_{night}: Long-term average nighttime noise levels.
*p-value < 0.05

Supplemental Material, Table S3. Effect of a 10 $\mu g/m^3$ increase in annual average home outdoor NO_2 concentrations and 95% confidence intervals on diastolic blood pressure (DBP).

Models for DBP	N	beta (95%CI)[a]	beta (95%CI)[b]
Non medicated	2685	0.15 (-0.57, 0.88)	0.12 (-0.33, 0.57)
Medicated	1015	0.66 (-0.67, 1.99)	0.53 (-0.39, 1.44)
Without adjustment for medication	3700	0.22 (-0.43, 0.87)	0.23 (-0.18, 0.64)
With adjustment for medication	3700	0.33 (-0.32, 0.97)	0.28 (-0.13, 0.69)
+5 mmHg[c]	3700	0.06 (-0.62, 0.74)	0.15 (-0.28, 0.59)
+10 mmHg[c]	3700	-0.10 (-0.83, 0.64)	0.08 (-0.39, 0.55)
+15 mmHg[c]	3700	-0.26 (-1.07, 0.55)	0.004 (-0.51, 0.52)
Censored regression	3700	-0.29 (-1.07, 0.48)	-0.08 (-0.56, 0.41)

[a] Fully adjusted multivariate linear regression models, adjusted for: age, age squared, sex, living alone, education, diabetes, BMI, nighttime railway noise, nighttime traffic noise, smoking, alcohol consumption, deprivation, daily NO_2 and temperature (lag 0)
[b] Multivariate linear regression models adjusted for covariates in [a] except for nighttime railway and traffic noise.
Adjusted for blood pressure-lowering medication if specified in table.
[c] Correction to DBP for participants with BP-lowering medications

Supplemental Material, Table S4. Effect of a 10 μg/m^3 increase in annual average home outdoor NO_2 concentrations and 95% confidence intervals on the prevalence of hypertension.

Models for hypertension (HT)	N	OR (95%CI)[a]	OR (95%CI)[b]
HT main outcome [c]	3700	0.93 (0.79, 1.10)	1.00 (0.90, 1.11)
HT alternative outcome [d]	3700	0.98 (0.83, 1.15)	1.00 (0.90, 1.11)
HT extremes [e]	3101	0.91 (0.75, 1.09)	0.95 (0.84, 1.07)
HT only among non-medicated [f]	2685	1.12 (0.90, 1.38)	1.06 (0.93, 1.22)

[a] Fully adjusted multivariate linear regression models, adjusted for: age centered, sex, living alone, education, diabetes, BMI, deprivation, daily NO_2 and temperature (lag 0), nighttime traffic noise, nighttime railway noise.

[b] Multivariate linear regression models adjusted for covariates in [a] except for nighttime railway and traffic noise.

[c] Hypertension defined as having SBP or DBP ≥140/90 mmHg, respectively, or as a positive response to the question "Do you take or have you taken any doctor prescribed medication to reduce blood pressure in the last two weeks?"

[d] Hypertension defined as having SBP or DBP ≥140/90 mmHg, respectively, or reporting antihypertensive-like treatment in the medication list provided by participants and coded by a physician into "antihypertensive" or "beta-blocker" (i.e. diuretics, ACE inhibitors, alpha or beta-blockers, angiotensin receptor II blockers, and calcium channel blockers).

[e] Same definition as [c] excluding participants with borderline BP levels and not reporting use of antihypertensive treatment. I.e. with SBP and DBP ≥ 135/85 mmHg and < 150/95 mmHg.

[f] Same definition as [c] but only among participants not taking any BP-lowering treatment.

Supplemental Material, Table S5. Effect of a 10 µg/m^3 increase in annual average home outdoor NO_2 concentrations and 95% confidence intervals at the current address, for non-movers and for 10-year average home outdoor NO_2 concentrations on systolic (SBP) and diastolic (DBP) blood pressure. Non-medicated population with residential history (N=1843).

		SBP	DBP
Model	**N**	**beta (95%CI)[a]**	**beta (95%CI)[a]**
Annual NO_2 at current address	1843	2.11 (0.66, 3.57)	0.72 (-0.16, 1.61)
10-y average NO_2	1843	1.51 (0.14, 2.88)	0.40 (-0.43, 1.23)
Non-movers 2 years	1754	1.98 (0.48, 3.47)	0.73 (-0.18, 1.63)
Non-movers 5 years	1575	2.02 (0.43, 3.61)	0.89 (-0.06, 1.83)
Non-movers 10 years	1219	1.93 (0.02, 3.84)	0.90 (-0.21, 2.00)

[a] Multivariate linear regression models adjusted for: age, age squared, sex, living alone, education, diabetes, BMI, nighttime railway noise, nighttime traffic noise, smoking, alcohol consumption, deprivation, daily $NO_2$and temperature (lag 0).

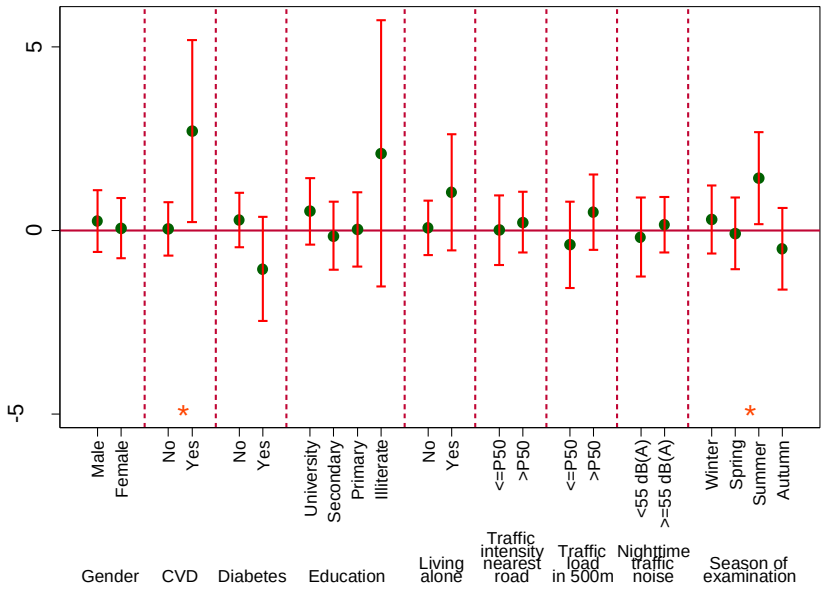
Supplemental Material, Table S6. Effect of a 10 µg/m^3 increase in annual average home outdoor NO_2 concentrations on systolic blood pressure (SBP) and diastolic blood pressure (DBP) for the group of participants with residential history (N=2402). Each model uses a different methodology to evaluate blood pressure-lowering medication.

		SBP	DBP
Model	**N**	**beta (95%CI)[a]**	**beta (95%CI)[a]**
Non medicated	1843	2.11 (0.66, 3.57)	0.72 (-0.16, 1.61)
Medicated	559	3.27 (-0.09, 6.63)	0.63 (-1.17, 2.43)
Without adjustment for medication	2402	2.20 (0.82, 3.59)	0.68 (-0.13, 1.48)
With adjustment for medication	2402	2.33 (0.96, 3.69)	0.74 (-0.06, 1.54)
+10 mmHg (SBP)/+5 mmHg (DBP)[b]	2402	2.04 (0.57, 3.52)	0.60 (-0.25, 1.44)
+15 mmHg (SBP)/+10 mmHg (DBP)[b]	2402	1.96 (0.41, 3.51)	0.51 (-0.40, 1.43)
+20 mmHg (SBP)/+15 mmHg (DBP)[b]	2402	1.88 (0.25, 3.51)	0.43 (-0.57, 1.44)
Censored regression[b]	2402	1.86 (0.26, 3.47)	0.47 (-0.47, 1.41)

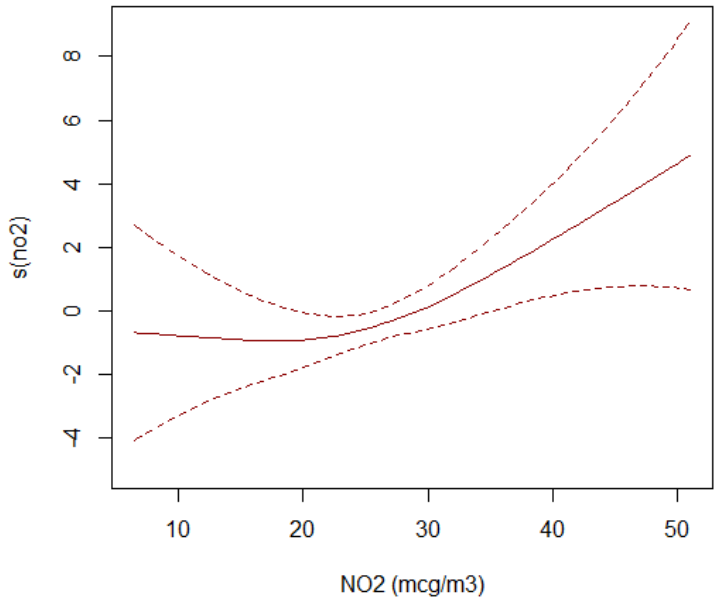
[a] Multivariate linear regression models adjusted for: age, age squared, sex, living alone, education, diabetes, BMI, nighttime railway noise, nighttime traffic noise, smoking, alcohol consumption, deprivation, daily NO_2 and temperature (lag 0).

Adjustment for blood pressure-lowering medication if specified in table.

[b] Correction to SBP or DBP, respectively, for participants with BP-lowering medications



Supplemental Material, Figure S1. Adjusted beta coefficients for a 10 µg/m^3 increase in annual average home outdoor NO_2 levels and 95% confidence intervals on diastolic blood pressure (mmHg) by subgroups of the population (N=2685, non-medicated participants). Each multivariate linear regression model was adjusted for the corresponding interaction-term, one at a time, and age, age squared, sex, living alone, education, diabetes, BMI, nighttime railway noise, nighttime traffic noise, smoking, alcohol consumption, deprivation, daily NO_2 and temperature (lag 0). * indicates p-value of interaction < 0.05.



Supplemental Material, Figure S2. Smooth spline for the effect of a 1 µg/m^3 increase in annual average home outdoor NO_2 levels (µg/m^3) and 95% confidence intervals in a generalized additive model for systolic blood pressure (mmHg). Model adjusted for: age, age squared, sex, living alone, education, diabetes, BMI, nighttime railway noise, nighttime traffic noise, smoking, alcohol consumption, deprivation, daily NO_2 and temperature (lag 0).

6.3 Paper III: High blood pressure and long-term exposure to indoor noise and air pollution from traffic.

Foraster, M., Künzli, N., Aguilera, A., Rivera M., Agis D., Vila J., Bouso, L., Deltell A., Marrugat J., Ramos R., Sunyer, J., Elosua R., Basagaña, X., 2011.

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HIGH BLOOD PRESSURE AND LONG-TERM EXPOSURE TO INDOOR NOISE AND AIR POLLUTION FROM ROAD TRAFFIC

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Keyword list: indoor, noise, air pollution, NO_2, blood pressure, hypertension, traffic

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There are no competing financial interests.

Abbreviations:
BP: Blood pressure
dB(A): A-weighted decibels
DBP: Diastolic blood pressure
L_{night}: A-weighted long-term average sound level (dB(A))
mmHg: millimeters of mercury
NO_2: Nitrogen dioxide ($\mu g/m^3$)
SBP: Systolic blood pressure

Abstract

Background: Traffic noise has been associated with prevalence of hypertension, but reports are inconsistent for blood pressure (BP). People's noise exposure indoors might be essential to ascertain effects and disentangle them from those suspected for traffic-related air pollution.

Objectives: We analyzed associations of long-term exposure to indoor traffic noise levels at bedrooms, and hypertension (HT) and systolic (SBP) and diastolic (DBP) BP, considering outdoor annual average levels of nitrogen dioxide (NO_2).

Methods: We evaluated 1926 cohort participants at baseline (years 2003-2006). Outdoor annual average levels of night-time traffic noise (L_{night}) and NO_2 were estimated at postal addresses with a city-specific and land-use regression models, respectively. Individual indoor traffic L_{night} levels were derived from outdoor L_{night} applying the attenuations provided by reported noise protections, according to literature. We assessed associations for hypertension and BP with multi-exposure logistic and linear regression models, respectively.

Results: Median levels were 27.1 dB(A) (indoor L_{night}), 56.7 dB(A) (outdoor L_{night}), and 26.8 $\mu g/m^3$ (NO_2). Spearman correlations between outdoor and indoor L_{night} with NO_2 were 0.75 and 0.23, respectively. The indoor noise model provided more consistent findings both for L_{night} (per 5 dB(A)): Hypertension: OR=1.06, 95%CI: 0.99, 1.13; SBP: β=0.72, 95%CI: 0.29, 1.15); and NO_2 (per 10 $\mu g/m^3$): Hypertension: OR=1.16, 95%CI: 0.99,1.36; SBP: β=1.23, 95%CI: 0.21, 2.25; DBP: β=0.56, 95%CI: -0.03, 1.14). The indoor noise-SBP association was stronger and statistically significant with a threshold at 30 dB(A).

Conclusion: Obtaining indoor noise exposure estimates from traffic was essential to investigate the independent effects of traffic-related pollution and noise.

1. Introduction

Long-term exposure to outdoor road traffic noise has been associated with cardiovascular disease (CVD) (Babisch, 2006). The suggested underlying mechanistic pathway involves noise-stress reactions, leading to the hormonal and cardiovascular responses observed in experimental studies (Ising and Kruppa, 2004). Given that the exaggerated cardiovascular responses remain sustained over time, also while sleeping, it is suggested that chronic exposure to even low noise levels – particularly during the restorative periods of sleep at nighttime – may contribute to hypertension and, in turn, to CVD (Babisch, 2011).

Hypertension is a leading cause of morbidity and mortality according to the recent update of the Global Burden of Disease (Lim et al., 2012). A recent comprehensive meta-analysis reported an association between a 5 dB(A) increase in day-time road traffic noise levels (LAeq,16h) (range 45-75 dB(A)) and prevalent hypertension (Odds ratio (OR) of 1.03 (95%CI: 1.01, 1.06)) (van Kempen and Babisch, 2012). However, studies on the association between long-term exposure to noise and the continuous trait of blood pressure (BP) are heterogeneous (Babisch, 2006).

Furthermore, traffic is also the primary source of local air pollution, and recent cross-sectional studies indicate associations between long-term exposure to markers of traffic-related pollution and high BP (Chuang et al., 2011; Dong et al., 2013; Fuks et al., 2011; Schwartz et al., 2012). However, the evidence is still limited, particularly for hypertension (Coogan et al., 2012; Fuks et al., 2011; Sørensen et al., 2012).

A major unresolved concern is whether long-term effects of traffic-related air pollution and noise may be mutually confounded (Allen et al., 2009; Foraster et al., 2011). As emphasized in the literature (Babisch, 2011), current noise studies rely on outdoor traffic noise

estimates at the most exposed façade, whereas the true exposure may well differ depending on room orientation, shielding and coping behavior (Babisch et al., 2012). Knowing the indoor traffic noise exposure during sleep could be an essential step to ascertain its cardiovascular effects and to disentangle them from those of traffic-related air pollution.

We aimed at evaluating the association between long-term exposure to individually assigned estimates of traffic noise exposure at home indoors during night-time (L_{night}) and BP, and hypertension. To derive exposure to indoor traffic noise, we combine estimates of outdoor traffic noise levels with questionnaire information about bedroom orientation and the individual coping behaviors and noise protections at home. We also evaluate the confounding effect of traffic-related air pollution. The study was conducted within the well-defined population-based cohorts of the REGICOR (Girona Heart Registry) study in Girona city, a dense Mediterranean city of nearly 100,000 inhabitants in the North-East of Spain.

2. Methods

2.1 Study population

The initial study population consisted of 2067 participants, aged 36-82, evaluated at baseline (2003-2006) within a population-based REGICOR cohort (Grau et al., 2007), and who had answered a detailed questionnaire on household measures against noise at the follow-up visit (2009-2011). Briefly, the baseline population was a random selection of non-institutionalized inhabitants of Girona city, Spain, and who were called in a randomized order for the follow-up visit. All participants were non-movers (residing in the same dwelling at baseline and follow-up).

The study was approved by Parc de Salut Mar ethics committee and participants signed written informed consent.

2.2. Outcomes and health assessment

Participants were examined from 8 to 11am after fasting for 10h. Trained nurses measured BP following the Joint National Committee (JNC) VII recommendations (Chobanian et al., 2003), in sitting position, and with a calibrated automatic device (OMRON 711), which also registered heart rate. Two measurements were done after at least 10 and 3 minutes of rest, respectively. If measurements differed by ≥ 5 mmHg, a third one was taken. To minimize the 'white coat' effect, we used the last available measurement. The nurses also measured weight and height and withdraw blood to obtain cholesterol, triglyceride and fasting glucose levels.

We defined hypertension as having systolic (SBP) or diastolic (DBP) BP levels ≥ 140/90 mmHg, respectively (Chobanian et al., 2003), or as a positive response to the question "Do you take or have you taken any doctor prescribed medication to reduce blood pressure in the last two weeks?". For BP analyses, we defined a variable accounting for any "BP-lowering medication", described as a positive response to the previous question or use of "antihypertensive" medication (i.e. diuretics, ACE inhibitors, alpha or beta-blockers, angiotensin receptor II blockers, and calcium channel blockers). This variable was coded by a physician from the medication list provided by participants.

2.3. Exposure assessment

We assigned individual outdoor estimates of long-term average road traffic noise levels at night (L_{night}, 11pm-7am, in dB(A), from now

on outdoor traffic L_{night}) at the geocoded residential addresses, 2m away from the façades and at the floor's height of each dwelling. The estimates were derived with a detailed city-specific traffic noise model (year 2005) that took into account traffic density in small streets, and that complied with the European Noise Directive 2002/49/EC (END), as described elsewhere (Foraster et al., 2011) (See supplemental material, **p.128**). Since railway noise has also been associated with BP (Dratva et al., 2012) and a single railway crosses dense traffic areas from North to South, we also derived individual residential railway noise estimates (L_{night}) from a propagation model complying with the END (See supplemental material, **p.128**). Our study population was not exposed to aircraft noise from the small airport in Girona province.

In a face-to-face interview we collected information on room orientation and measures to abate noise, and on noise sensitivity (Weinstein, 1978) – 10-item score based on a non-verbal 6-point scale – and traffic noise annoyance (Fields et al., 2001) – non-verbal 11-point scales – at the bedroom during sleeping hours as done previously (Babisch et al., 2012). For this study, we evaluated 1) type of glazing and type of window (single, double, laminated or triple glazing, or double window), 2) bedroom orientation (facing the postal address street/side street/backyard), and 3) frequency of closing windows during sleeping hours (always / often / seldom / never). Availability of shutters and use of ear plugs was rarely reported and not used in this study.

We combined outdoor traffic L_{night} with the questionnaire data to calculate two estimates of "personal" noise exposure:

a) *Outdoor traffic L_{night} at bedroom façade*: Noise models generally provide estimates at the postal address façade, however, people may sleep at the backyard where noise levels are lower. Based on engineering literature on quiet façades (Salomons et al., 2009), we subtracted 20 dB(A) to outdoor

noise estimates to obtain backyard noise levels. We left outdoor estimates unchanged for bedrooms facing the postal address street or a side street. Noise levels at the side street façade were difficult to quantify and we assumed they were more similar to those at the postal address street around the corner.

b) *Indoor traffic L_{night} levels in the bedroom:* We corrected the *outdoor traffic L_{night} levels at the bedroom façade* (see point "a)" above) by subtracting standard attenuation factors for the reported window types and the frequency of keeping windows closed at night, as described in the Spanish Building Code and complementary technical information (Spanish Government, 2010; Tremco, 2004) and in the Good Practice Guideline on noise exposure (European Environment Agency, 2010), respectively. The insulation correction factors for closing windows were: if "Always closed" (100% time) -30 dB(A) (for single and double glazing) and -40 dB(A) (with sound-proved windows, namely: triple or laminated glazing or double windows); "Often" (75% time): -21 dB(A); "Seldom" (25% time): -16 dB(A); "Never" (0% time): -15 dB(A).

We followed step b) to obtain indoor railway noise levels from outdoor railway noise estimates.

We also derived individual outdoor estimates of annual average NO_2 concentrations ($\mu g/m^3$) (from now on NO_2) at each geocoded address with a city-specific land-use regression model (LUR) derived in 2010, as described elsewhere (Rivera et al., 2013). Briefly, the LUR was based on a dense network of residential outdoor NO_2 measurements (years 2007-2009). The main predictor variables were the height above street and traffic-related variables within different buffers (from 25 to 1000m radius) around the sampling locations. The coefficient of determination (R^2) of the model was 0.63.

2.4. Other data collection

We also assessed smoking (smoker/ex-smoker of more than one year/never smoker), weekly leisure time physical activity (in metabolic equivalents), daily alcohol intake (g/d), adherence score to Mediterranean diet (lowest to highest from 10 to 30), reported level of education (university/secondary/primary/illiterate), occupational status (employed/housemaker-inactive/retired/ unemployed), and socio-economical status (SES) at the census track with the deprivation index. We defined diabetes as fasting blood glucose levels ≥126 mg/dl or reported treatment with antidiabetic drugs, and body mass index (BMI) as weight/height^2 (kg/m^2). Intake of anxiolytics was assessed with the question "Did you take tranquilizers, sedatives, anxiety pills, sleeping pills, or muscle relaxants in the last two weeks?" (yes/no), (for further details and complementary variables: see Supplemental Material, **p.129**).

2.5. Statistical analysis

We performed descriptive analyses of all variables, assessed their linearity against the outcomes with generalized additive models, and transformed them accordingly. Analyses were performed with complete cases, i.e. excluding missing observations on the outcomes, exposure and covariates of the main models (n=141, 6.8%), resulting in 1926 cases with similar characteristics to the original sample. The inclusion of confounders in the multivariate logistic regression (for hypertension) and linear regression models (for BP) was based on the hypothesized causal pathway of traffic noise and air pollution on hypertension (Fuks et al., 2011) and on the previous literature. We controlled for individual SES with educational level and for short-term effects of daily temperature (lag 0) on measured BP. Occupational status, temperature at lags 1 to 3, instead of lag 0, and daily NO_2 (lags 0 to 3) did not contribute further to models. We adjusted for the same variables in all single

and multi-exposure models and checked regression diagnostics. Effect estimates changed < 10% by further inclusion of factors previously evaluated in literature (traffic annoyance, family history of cardiovascular death, heart rate, and CVD), thus they were not considered (data not shown).

Finally, we also assessed linear threshold models assuming noise effects to start at 30 dB(A) indoors, the recommended indoor noise levels at night (World Health Organization, 2009).

In interaction analysis, we tested population characteristics that could modify the association between noise (indoors) and hypertension (Babisch et al., 2013; van Kempen and Babisch, 2012), namely: age, gender, traffic annoyance, and noise sensitivity with a cut-off at the median. Age and traffic annoyance were tested both as continuous and categorical variables. We additionally evaluated the effect modification of anxiolytic intake, since the use of sleeping pills has been linked to noise levels (Floud et al., 2011), and its mechanism of action may directly impact the suggested biological stress pathway by which noise affects CVD.

Air pollution and noise may lead to high BP, and this to medication, which would be a mediator, not a confounder, of the observed (measured) BP levels. Thus, adjusting for medication may introduce bias. In sensitivity analyses, and as previously addressed (Foraster et al., unpublished data), we compared our results to those obtained in non-medicated (i.e. participants not taking BP-lowering medication) and "medicated" participants and tested alternative methodologies applied to the entire population (Tobin et al., 2005) (See supplemental Material, **Table S4**).

We reported estimated changes in the outcomes per 5 dB(A) for all noise indicators and per 10 $\mu g/m^3$ for NO_2, unless otherwise specified.

Analyses were performed with Stata 12.0 (StataCorp, College Station, TX) and R 2.12.

3. Results

The main characteristics of the study population are summarized in **Table 1** and the Supplemental Material, **Table S1**. The prevalence of hypertension was 36.6%, and 24.1% of the population took BP-lowering medication. The median age of the population was 56 years and a 45.5% were male. The median levels and interquartile range (Median (IQR)) of outdoor NO_2 were 26.8 (11.5 $\mu g/m^3$), of outdoor traffic L_{night} were 56.7 (6.8 dB(A)), of traffic L_{night} at bedroom façade were 53.5 (17.2 dB(A)), whereas those of indoor traffic L_{night} were 27.1 (16.2 dB(A)). A 66% of the population reported either coping behaviors (i.e. always closing windows) or 'protections' against noise (i.e. with bedroom facing the backyard or sound-proved windows at the bedroom), or both.

Outdoor NO_2 concentrations were highly correlated with outdoor levels of traffic L_{night} (Spearman's correlation coefficient, r=0.75), but not with outdoor traffic L_{night} at the bedroom façade and indoor traffic L_{night} (0.39 and 0.23, respectively), (See Supplemental Material, **Table S2**).

Participants with both coping behavior and protections against noise (14.5% of the population) were exposed to slightly higher median outdoor L_{night} levels (57.2 dB(A)) compared to those neither coping nor having protections (56.1 dB(A), 34%), or those only coping (56.9 dB(A), 31.4%) or only having protections (56.9 dB(A), 20%) (Kruskal-Wallis test p-value=0.044). Median outdoor traffic L_{night} levels were also higher in those reporting higher traffic annoyance (not annoyed: 56.1 dB(A), moderately: 57.3 dB(A), highly annoyed: 58.1 dB(A); Kruskal-Wallis test p-value < 0.001), but not with higher noise sensitivity.

3.1. Traffic L_{night}, NO_2 and high BP

In single-pollutant models for hypertension (**Table 2**), a 5 dB(A) increase of outdoor traffic L_{night} was associated with an OR of 1.18 (95%CI: 1.05, 1.32) and a 10 µg/m^3 of NO_2 was associated with an OR of 1.16 (95%CI: 0.99, 1.36). In two-exposure models (i.e. noise *and* NO_2), results for outdoor traffic L_{night} were similar (OR=1.19, 95%CI: 1.02, 1.40), whereas results for NO_2 became null (OR=0.98, 95%CI: 0.79, 1.22). In contrast, when modeling NO_2 with traffic L_{night} at the bedroom façade or indoor traffic L_{night}, changes in both noise and NO_2 were associated with higher hypertension, and no mutual confounding effect was observed. However, relationships with indoor traffic L_{night} and NO_2 did not reach statistical significance (OR=1.06, 95%CI: 0.99, 1.13, p-value=0.073) and (OR=1.16, 95%CI: 0.99, 1.36, p-value=0.058), respectively.

Regarding SBP, we observed a non-significant increment of 0.51 mmHg (95%CI:-0.24, 1.25) per 5 dB(A) increase of outdoor traffic L_{night}, and a significant increment of 1.19 mmHg (95%CI: 0.17, 2.21) per 10 µg/m^3 of NO_2 in single-exposure models (**Table 2**). In two-exposure models including outdoor traffic L_{night}, the point estimate for noise was negative (beta coefficient (ß)=-0.20, 95%CI:-1.25, 0.84), whereas the relationship with NO_2 became stronger, although less precise (ß= 1.39, 95%CI:-0.05, 2.82). Noise at the bedroom façade was suggestively associated with SBP after adjustment for NO_2. Finally, there was an increase of 0.72 mmHg (95%CI: 0.29, 1.15) per 5 dB(A) increase of indoor traffic noise, and the same model yielded a statistically significant but somehow smaller association between NO_2 and SBP (ß=1.23, 95%CI: 0.21, 2.25), compared to adjusting for outdoor traffic L_{night}. No mutual confounding effect was observed between indoor traffic L_{night} and NO_2. Finally, we observed an association between NO_2 and DBP, but not with traffic L_{night}.

3.2. Threshold effect for indoor traffic noise

Applying a threshold at 30 dB(A) to indoor traffic L_{night} in two-exposure models resulted in a stronger noise OR for hypertension: OR=1.14 (95%CI: 0.99, 1.31); and a stronger and significant association of noise with SBP: β=1.27 (95%CI: 0.34, 2.20). The associations between NO_2 and the outcomes in these models remained similar (See Supplemental Material, **Table S3**).

3.3. Effect modifiers

Most interestingly, associations between indoor traffic noise and hypertension were seen in subjects not taking anxiolytic medication (OR=1.10, 95%CI: 1.02, 1.18), (p-value of interaction=0.054) and not in those taking this treatment. Besides, there was a suggestive trend towards stronger associations between indoor traffic L_{night} and hypertension with increasing reported traffic annoyance – p-value of interaction (categorical variable)=0.141, p-value for trend=0.052; p-value of interaction (continuous variable)=0.033) – (**Figure 1**). Else, we found no indication for interactions by age, sex, or noise sensitivity (all p-values of interaction > 0.31).

3.4. Sensitivity analysis for BP-lowering medication

Associations between the different noise indicators and NO_2 with BP were robust across the different alternative methodologies to control for BP-lowering medication in the entire population. Although associations differed between "non-medicated" and "medicated" participants, no statistically significant interaction by medication was found (p-values of interaction > 0.12) (See Supplemental Material, **Table S4**, data only shown for the indoor traffic L_{night} multi-exposure model).

4. Discussion

This study combined long-term estimates of outdoor road traffic noise levels at night (L_{night}) with information on bedroom orientation and measures to abate noise to derive a measurement of indoor traffic noise levels at home. Besides attempting to get a more accurate estimate of the true relevant exposure, accounting for noise protections reduces the correlation observed between outdoor traffic noise and nitrogen dioxide (NO_2) levels (a marker of traffic-related air pollution), thus helping to disentangle the effects of these traffic-related stressors. Few studies evaluating high blood pressure (BP) to date have considered these confounding effects (Coogan et al., 2012; de Kluizenaar et al., 2007; Fuks et al., 2011; Sørensen et al., 2012, 2011). We observed associations between indoor traffic noise and both hypertension and systolic BP (SBP), and between NO_2 and hypertension, SBP and diastolic BP (DBP), which were independent of the other environmental factor. Results based on outdoor traffic L_{night} were less consistent, and associations between outdoor traffic L_{night} and NO_2 with the outcomes showed opposite tendencies when mutually adjusting for the other environmental factor.

Our findings for outdoor traffic L_{night} agree with literature, which indicates associations with hypertension, but limited evidence with BP (Babisch, 2006; Dratva et al., 2012; Sørensen et al., 2011; van Kempen and Babisch, 2012). Regarding the effect size, a recent meta-analysis reported a smaller OR (OR=1.03, 95%CI: 1.01, 1.06) per 5 dB(A) change of day-time noise (van Kempen and Babisch, 2012), than our findings for outdoor L_{night} (OR=1.19; 95%CI: 1.02, 1.40), though confidence intervals largely overlapped.

Indoor traffic L_{night} was suggestively associated with hypertension (OR=1.06, 95%CI: 0.99, 1.13, p-value=0.073), and with SBP. Increasing traffic noise was though not related to higher DBP, as also observed by Sorensen et al. (2011) with outdoor traffic noise.

Further research is needed to confirm and clarify whether the chronic noise-stress biological pathway may promote vascular changes resulting in isolated increased SBP (Black and Elliott, 2013).

To our knowledge, only one study in 1999 derived indoor traffic estimates (as a categorical variable) according to two terms: room orientation and always closing windows. Unlike outdoor estimates, the indoor yielded an increase in the risk of ischemic heart disease, though it was not statistically significant (Babisch et al., 1999). Our assessment further accounted for the frequency of opening windows, and used more precise, continuous noise estimates with a wider exposure contrast. The other few attempts to account for noise reducing factors consisted of stratification or interaction analysis by these factors on the noise-hypertension relationship, and only one study addressed this issue comprehensively (Babisch et al., 2012). Results have been heterogeneous. For comparison, we assessed similar interaction analyses with coping behaviors, protections, and a combination of the two, and did not identify differences among groups (data not shown). Stratified analyses have lower statistical power and might result in bias and spurious findings due to multiple comparisons. Furthermore, people may combine remedies against noise, and findings for specific noise reduction measures might be difficult to interpret if they co-vary with other protections, annoyance, or outdoor traffic noise and air pollution levels.

Our findings for NO_2 also agreed with the emerging literature. Long-term exposure to near-road pollution was more clearly associated with BP, as observed in some (Chuang et al., 2011; Dong et al., 2013; Fuks et al., 2011; Schwartz et al., 2012) although not all (Sørensen et al., 2012) studies. Furthermore, we also observed a borderline statistically significant association for hypertension, which was independent of indoor traffic noise. However, the association tended to the null when adjusting for outdoor traffic

L_{night}. To our knowledge, the association between NO_2 and prevalence of hypertension was only observed in two studies (Dong et al., 2013; Johnson and Parker, 2009), whereas the rest found null or inverse effects (Fuks et al., 2011; Sørensen et al., 2012). The evidence is more consistent for incidence of hypertension, but only based on two studies (Coogan et al., 2012; Sørensen et al., 2012).

The tendency of outdoor traffic L_{night} and NO_2 to show opposite effects in multi-exposure models was not explained by the variance inflation factors (VIFs), a common diagnostic for collinearity, which were low to be considered problematic (VIFs for outdoor noise and $NO_2 < 2.8$) (common rule of thumb for collinearity is VIF > 5 or even > 10). However, the correlation between the regression coefficients of the two variables was -0.70. We implemented a simulation to illustrate how the observed level of collinearity would affect the results for SBP if the study were to be replicated many times (See Supplemental Material, **p.130**). The simulation showed unbiased average regression coefficients after 10,000 replications. However, when looking at individual replicates of the study, those finding a high coefficient for NO_2 found a low coefficient for outdoor traffic L_{night}, and vice versa. In our setting, this tendency could be strong enough to reverse the sign of one of the two coefficients in some instances. Similar results are expected in other studies of similar size where the correlation between NO_2 and noise is of the same magnitude (around 0.7) or higher, making it difficult to disentangle both effects. This might have been the case in two of the few studies combining both stressors, which observed some slightly negative confounding in their estimates (de Kluizenaar et al., 2007; Sørensen et al., 2012). Nevertheless, these tendencies disappeared in our results when assessing markers of personal exposure at the bedroom, which were less correlated with NO_2. This was also confirmed in the simulation study. This underscores the need for appropriate exposure measurements for both, noise and air pollution, to adequately disentangle their effects, i.e. to avoid

spurious correlations and thus spurious adjustment patterns when one factor (i.e. noise in our case) is a poor proxy of exposure.

4.1. Threshold effects for indoor noise

Interestingly, we found stronger effects for hypertension and SBP when assuming indoor traffic noise effects to start at 30 dB(A), although some departures from linearity were only observed for SBP (See Supplemental Material, **Figure S2**). However, we cannot exclude the possibility of a threshold given that indoor noise sources at night-time could well reach levels of 30 dB(A), thus masking partly or totally the contribution of traffic noise levels below 30 dB(A) indoors. This low threshold indicates that even low road traffic noise levels may affect BP and agrees with the WHO recommendations for night-time noise at bedrooms (30 dB(A)) (World Health Organization, 2009).

4.2. Effect modification

Interestingly, we observed no association between indoor traffic L_{night} and hypertension among participants taking anxiolytics in interaction analysis. This observation agrees with the proposed biological pathway of noise, since anxiolytics antagonize stress reactions, thus possibly blocking the noise-induced stress response by which noise affects BP. This agrees with a laboratory study reporting less noise-induced sleep responses with intake of anxiolytics (Cluydts et al., 1995).

Associations in our study were slightly confounded by annoyance (data not shown), suggesting traffic noise levels to affect BP directly (direct mechanistic pathway) independently of noise perception (indirect pathway), which is plausible while sleeping (Babisch, 2002; Ising and Kruppa, 2004). Nevertheless, as observed

in interaction analysis, increasing noise annoyance may lead to stronger associations between indoor traffic noise and hypertension (**Figure 1**). Few studies to date have analyzed this pattern (Babisch et al., 2013).

Finally, we could not confirm previous reports of stronger associations in some age groups or men (van Kempen and Babisch, 2012).

4.3. Strengths and limitations

In this study, we derived markers of traffic noise exposure at the bedroom façade and indoors from questionnaire data on noise reducing factors and the best-available literature on insulation (European Environment Agency, 2010; Salomons et al., 2009; Spanish Government, 2010; Tremco, 2004). We acknowledge that these corrections may have introduced some error, resulting in less precise or biased estimates, which are difficult to predict. For instance, while we deducted standard values to adjust for window type, the true insulation provided by the different windows may vary, as it also depends on proper window seals. Nevertheless, a small proportion of the population had sound-proved windows (4.5%) and still a 50% of the population opened windows to some degree (a factor we also accounted for), thus, heavily reducing the effect of window insulation. Besides, housing height and type of construction is quite homogenous in Girona, thus possibly yielding similar insulations in backyards. However, models that estimate noise at all building façades are required to improve precision, as already commented (Babisch, 2011). In summary, in this study both markers of noise exposure at the bedroom provided more plausible results than outdoor noise at the postal address. This was particularly true for the indoor marker, which reinforces the suitability of this questionnaire-based approach. Future studies

should confirm our results and could improve noise questionnaires and models to obtain even more precise information.

We emphasize that the exposure misclassifications now addressed for noise do not apply to the same extent to air pollution. Many exposure studies confirmed that indoor concentrations of pollutants from outdoor origin are highly correlated with the outdoor concentrations although the absolute levels may differ (Chen and Zhao, 2011).

We relied on a detailed noise and land-use regression model for the city of Girona and a comprehensive set of adjustment variables, including information on noise reducing factors at home, which improved noise exposure assessment. However, our findings could be affected by other sources of exposure misclassification. Both air pollution and noise are considered to have effects as a consequence of long-term exposure. Our exposure models were derived for a specific year only. However, the city had no major changes in traffic during the 5 years up to follow-up and subjects were non-movers, therefore, we expect spatial distributions of both exposures to be rather stable over years.

The proper use of medication in the analyses can be debated and, as previously argued (Foraster et al., unpublished data), no perfect method exists to treat medication use in the entire population (Foraster et al., unpublished data). Nevertheless, results for BP were robust across all alternative methods, which is reassuring (Tobin et al., 2005). Thus, for simplicity, and to increase statistical power in this rather small study, we retained all study participants and presented the results with the common approach of adjustment for medication.

A main limitation of this study was its cross-sectional design, thus distinguishing causes from effects is not possible. However, results for indoor traffic noise and NO_2 seem plausible and in line with the

biological mechanisms (Brook et al., 2009; Ising and Kruppa, 2004). Nonetheless, longitudinal assessments are needed to confirm findings.

As other limitations, we assessed BP with standard protocols of repeated measurements during one single exam, which do not allow a clinical diagnose of hypertension. We know that at least 50% of those with high BP in our survey confirm their hypertension in the next years (Foguet et al., 2008). Furthermore, most hypertensive subjects were classified according to antihypertensive treatment and we selected the last BP measurement available to minimize the "white-coat" effect. However, we cannot exclude a remaining non-differential misclassification, which would bias results towards the null.

Our study had a rather small sample size, thus, probably a lack of statistical power, particularly for the binary variable of hypertension and the stratified analyses. Finally, we selected participants attending the follow-up, therefore, some self-selection of healthier participants might have occurred, potentially biasing results towards the null too.

4.4. Public health implications

Even low levels of both traffic-related factors (noise and air pollution) may contribute to hypertension, and thus CVD – a primary cause of morbidity and mortality. Although effect sizes were small, these stressors are ubiquitous, thus decreasing their levels could benefit millions of people. Our results further suggest that measures against noise at the individual level in Girona were insufficient to protect from traffic noise-related BP effects. Actually, whether current noise reducing measures reduce BP is unclear (Babisch et al., 2012).

5. Conclusions

In this cross-sectional study we identified an association between long-term exposure to indoor road traffic noise at night and both hypertension and SBP, as well as an association between long-term exposure to NO_2 – a marker of traffic-related air pollution– and both hypertension and BP. These results underscore the relevance of using detailed exposure assessment to identify the independent effects of both road traffic noise and traffic-related air pollution (Künzli, 2013). Questionnaires on measures against noise could be a useful tool to derive indoor noise markers in future studies.

Table 1. Description of the main characteristics of the study population (N=1926).

	Total	
Variable	Median	(IQR)
Systolic blood pressure (mmHg)	123.0	(24.0)
Diastolic blood pressure (mmHg)	78.0	(13.0)
Age (years)	56.0	(18.0)
Mediterranean diet adherence score[a]	20.0	(4.00)
Deprivation index[b]	-1.9	(0.90)
Outdoor annual average NO_2 ($\mu g/m^3$)	26.8	(11.5)
Outdoor traffic L_{night} (dB(A))	56.7	(6.80)
Outdoor traffic L_{night} at bedroom façade (dB(A))	53.5	(17.2)
Indoor traffic L_{night} (dB(A))	27.1	(16.2)
Indoor railway L_{night} (dB(A))	10.5	(21.6)
Noise sensitivity score (10-60)[c]	33.0	(17.0)
Variable	N	(%)
Hypertension, Yes	704	(36.6)
Gender, Male	876	(45.5)
Body mass index, < 20	68	(3.50)
20-25	605	(31.4)
25.1-30	851	(44.2)
> 30	402	(20.9)
Educational level, University or similar	596	(30.9)
Secondary	618	(32.1)
Primary	681	(35.4)
Illiterate	31	(1.60)
Smoking, Never smokers	981	(50.9)
Smokers	406	(21.1)
Former smokers	539	(28.0)
Diabetes, Yes	261	(13.6)
BP-lowering medication	464	(24.1)
Bedroom orientation, Backwards[d]	582	(30.2)
Coping[e], Yes	885	(46.0)
Protections[f], Yes	666	(34.6)
Traffic annoyance[g], No (0 points)	1198	(62.6)
Moderate (1-5 points)	549	(28.7)
High (6-10 points)	168	(8.80)
Anxiolytics, Yes	425	(22.2)

NO_2: nitrogen dioxide; L_{night}: Long-term average nighttime noise levels.
[a] 10 (lowest) and 30 (highest) adherence to diet.
[b] High deprivation corresponds to high values.
[c] Higher noise sensitivity to higher values, 10.8% of missing observations.
[d] vs. bedroom facing postal address street or side-street.
[e] Coping, Yes: always close windows vs. No: never, seldom, often close windows.
[f] Sound-proved windows or bedroom facing the backyard.; [g] N < 1926 (< 1% missing observations).

Table 2: Estimated change in prevalence of hypertension, systolic and diastolic blood pressure[a] per increasing[b] residential levels of traffic noise (L_{night}) and annual average outdoor nitrogen dioxide (NO_2).

	Hypertesion (N=1926)		SBP (N=1926)		DBP (N=1926)	
	Odds ratio (95%CI)	Odds ratio (95%CI)	beta coefficient (95%CI)	beta coefficient (95%CI)	beta coefficient (95%CI)	beta coefficient (95%CI)
Models[c]	L_{night}	NO_2	L_{night}	NO_2	L_{night}	NO_2
Outdoor model[d] - Single-exposure	1.18 (1.05, 1.32)**	1.16 (0.99, 1.36)*	0.51 (-0.24, 1.25)	1.19 (0.17, 2.21)**	0.20 (-0.23, 0.63)	0.55 (-0.04, 1.14)*
Outdoor model[d] - Multi-exposure	1.19 (1.02, 1.40)**	0.98 (0.79, 1.22)	-0.20 (-1.25, 0.84)	1.39 (-0.05, 2.82)*	-0.17 (-0.77, 0.44)	0.71 (-0.12, 1.54)*
Façade model[e] - Single-exposure	1.08 (1.01, 1.15)**	1.16 (0.99, 1.36)*	0.42 (0.00, 0.83)**	1.19 (0.17, 2.21)**	0.08 (-0.16, 0.32)	0.55 (-0.04, 1.14)*
Façade model[e] - Multi-exposure	1.07 (1.01, 1.14)**	1.14 (0.97, 1.33)	0.36 (-0.06, 0.77)*	1.07 (0.04, 2.10)**	0.06 (-0.18, 0.29)	0.53 (-0.06, 1.13)*
Indoor model[f] - Single-exposure	1.06 (0.99, 1.13)*	1.16 (0.99, 1.36)*	0.71 (0.28, 1.14)**	1.19 (0.17, 2.21)**	0.09 (-0.16, 0.34)	0.55 (-0.04, 1.14)*
Indoor modelf - Multi-exposure	1.06 (0.99, 1.13)*	1.16 (0.99, 1.36)*	0.72 (0.29, 1.15)**	1.23 (0.21, 2.25)**	0.10 (-0.15, 0.34)	0.56 (-0.03, 1.14)*

SBP (systolic) and DBP (diastolic) blood pressure.
[a] Units in mmHg.
[b] per 5 dB(A) of traffic L_{night} and 10 µg/m^3 of NO_2.
[c] All models adjusted for age, age squared, sex, education, Mediterranean diet, exercise, alcohol consumption, smoking, BMI, diabetes, deprivation, daily temperature, BP-lowering treatment, and indoor railway noise.
[d] Uses outdoor traffic L_{night} as noise indicator.
[e] Uses outdoor traffic L_{night} at the bedroom façade as noise indicator.
[f] Uses indoor traffic L_{night} at the bedroom as noise indicator.
Single exposure models for NO_2 or the corresponding traffic noise indicator (See [d-f]).
Multi-exposure models adjusted for NO_2 and the corresponding traffic noise indicator (See [d-f]).
**p<0.05, *p<0.1

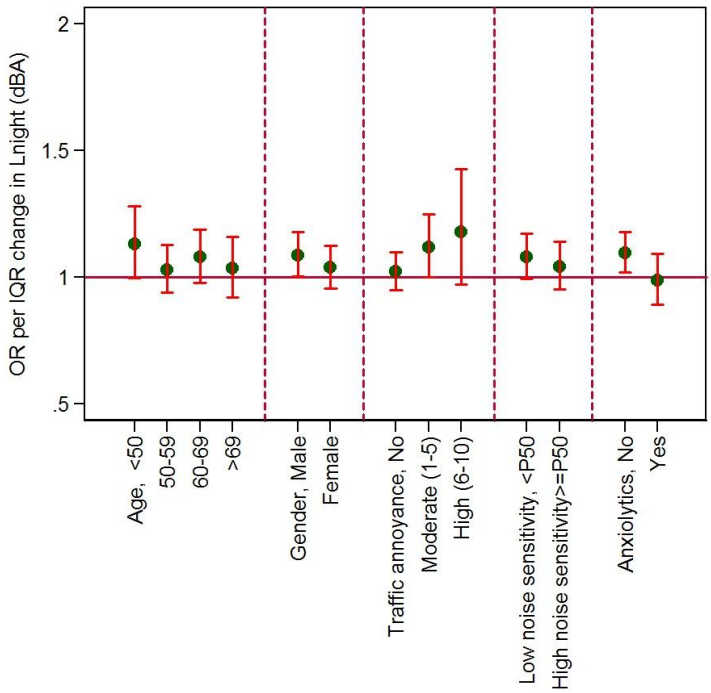


Figure 1. Effect of a 5 dB(A) increase of annual average home indoor traffic noise at night (L_{night}) and 95% confidence intervals on prevalent hypertension by subgroups of the population. Each multivariate logistic regression model is adjusted for the corresponding interaction-term, one at a time, and annual average NO_2 levels, age, age squared, sex, education, Mediterranean diet, exercise, alcohol consumption, smoking, BMI, diabetes, deprivation, daily temperature, and indoor railway L_{night}. N=1926.
All p-values of interaction with an α level > 0.05.

Supplemental material

Title: Blood Pressure and Long-Term Exposure to Indoor Noise and Air Pollution from Road Traffic

Authors: Maria Foraster[1,2,3], Nino Künzli[4,5], Inmaculada Aguilera[1,2], Marcela Rivera[6], David Agis[1,2], Joan Vila[2,7], Laura Bouso[1,2], Alexandre Deltell[8,9], Jaume Marrugat[7], Rafel Ramos[10,11], Jordi Sunyer[1,2], , Roberto Elosua[7], Xavier Basagaña[1,2]

Noise exposure assessment

The road traffic noise model was based on the interim noise model NMPB-routes 96 model (CERTU/CSTB/LCPC/SETRA, 1997) and estimates were derived at each receptor point (in the x, y and z axis) using Cadna-A, inc. The main input variables were: speed limit, street slopes, type of asphalt, urban topography and traffic density, the latter also considering small streets based on the Good Practice Guidelines for noise mapping (WG-AEN, 2003). The model was validated with 119 noise measurements carried out at a 1.5m height above ground and distributed across the city. The validation reached a coefficient of determination (R^2) of 0.93.

Railway noise estimates were derived from a propagation model, based on ISO 96/13 and accepted by the European Noise Directive 2002/49/EC. The propagation model was built upon source identification of railway noise. This consisted of day-time and nighttime measurements of the spectra (i.e. noise frequency in 1/3 octave bands) and noise equivalent levels (in dB (A)) of freight and normal trains (a total of 72 measurements). Measurements were taken with a SC-30 sound level meter and CB-5 calibrator (CESVA, inc.).

Additional information on covariates

We defined weekly leisure time physical activity based on Minnesota's questionnaire (in metabolic equivalents) (Elosua et al., 2000). Mediterranean diet was described with the REGICOR adherence score (Schröder et al., 2004), being 10 the lowest and 30 the highest adherence, and was based on a comprehensive food frequency questionnaire. We calculated the deprivation index at the census track for each baseline residential address (Domínguez-Berjón and Borrell, 2005). Further information from questionnaire data included family history of cardiovascular deaths (coded as: yes/no), cardiovascular disease as having ever had a cardiovascular event (myocardial infarction or stroke) or cardiovascular-related surgery intervention (coded as: yes/no).

We derived daily means of temperature (ºC) and NO_2 (µg/m^3) 0 to 3 days before the day of examination (lags 0 to 3). We obtained temperature for Girona town from the Catalan Meteorology Service, and daily means of NO_2 concentrations at an urban background station from the regional air quality monitoring network.

Simulation for collinearity

In this study, the point estimates (beta coefficients, β) of outdoor road traffic noise at night-time (L_{night}) and of outdoor nitrogen dioxide (NO_2) tended to go in opposite directions when modelled together in multi-exposure models. We observed a Spearman correlation coefficient of 0.75 between outdoor traffic L_{night} and NO_2. According to VIF and the commonly used thresholds, our data did not have strong collinearity problems, which suggests that collinearity does not explain these results.

In order to further understand this issue, we repeatedly simulated datasets with a similar structure than the observed one, fitted the multivariate model in each of them, and assessed the properties of the resulting estimates for the effect of traffic L_{night} and NO_2.
Each simulated dataset was created as follows:

1. Data on all predictors of the model (including L_{night} and NO_2) were simulated from a multivariate normal distribution, with means and covariance matrix equal to the means and covariance matrix observed in the original dataset.
2. The response variable (SBP) was simulated using the regression equation of SBP vs. all predictors obtained in the original dataset, plus normally-distributed random error with mean zero and variance equal to the estimated residual variance in the original dataset.

Using these processes, we created 10,000 datasets and in each dataset we fitted the regression model to obtain 10,000 pairs of beta coefficients of NO_2 and outdoor road traffic noise.

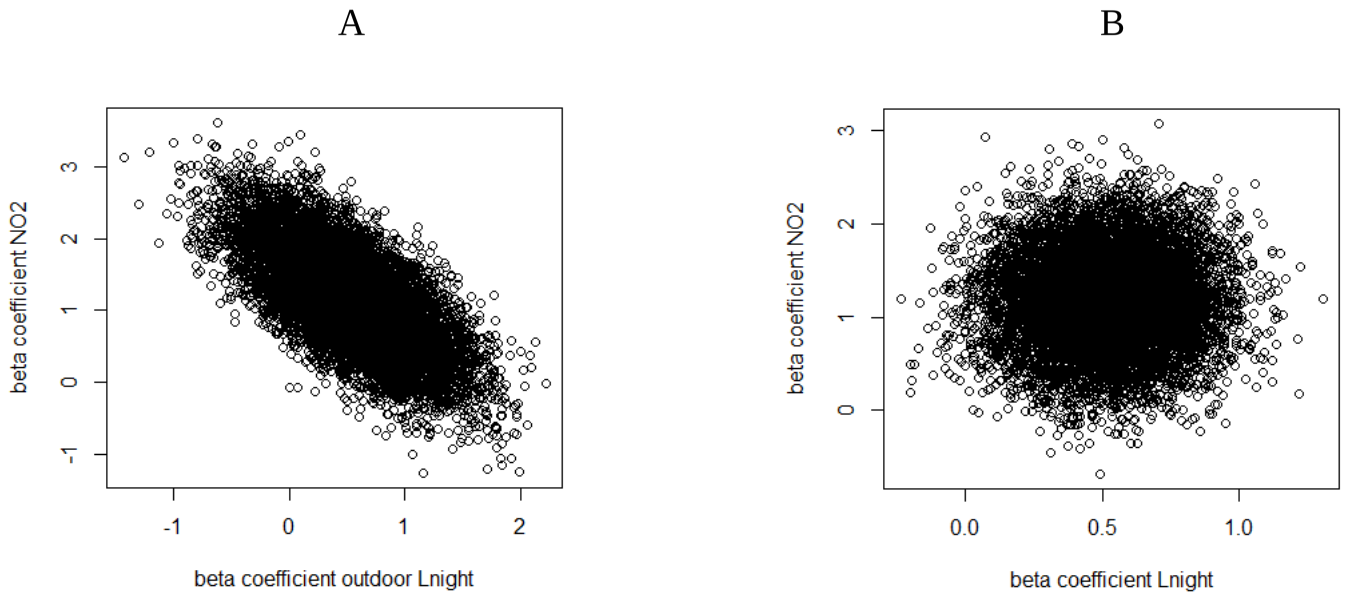
The average beta coefficients of the 10,000 simulations were β (NO_2) = 1.19 and β (outdoor traffic L_{night}) = 0.51, and their Pearson

correlation was -0.70. The figure below shows the plotted coefficients of NO_2 and outdoor traffic L_{night} (**Figure S1, A**).

Finally, we carried out the same simulations for the multivariate linear regression model for the association between SBP and indoor traffic L_{night} and NO_2. In this case, the resulting correlation between the simulated beta coefficients of NO_2 and indoor traffic L_{night} was of 0.03 (**Figure S1, B**).

These results indicate, first, that results from multiple studies using linear regression and even with a NO_2 – outdoor L_{night} correlation of 0.75 would provide unbiased estimates on average. In other words, a meta-analysis of many studies using both NO_2 and noise and with a high correlation would get to the correct effects for both NO_2 and noise.

However, in single studies like the one presented here, the tendency will be that those studies finding a high effect of NO_2 will find a low effect of noise and vice versa, as illustrated in **Figure S1**. In particular, around a 15.1% of coefficients would have a reversed sign for noise. Therefore, there is a risk that literature finding an effect on NO_2 does not find an effect of noise and vice-versa, as a result of collinearity. The issue was much less of a problem when we used indoor noise.



Supplemental Material, Figure S1. A: Correlation between beta coefficients of NO_2 and *outdoor* traffic L_{night} from 10,000 simulated databases. B: Correlation between beta coefficients of NO_2 and *indoor* traffic L_{night} from 10,000 simulated databases. Multi-exposure regression models for systolic blood pressure and L_{night} and NO_2 adjusted for for: age, age squared, sex, education, Mediterranean diet, exercise, alcohol consumption, smoking, BMI, diabetes, deprivation, daily temperature (lag 0), BP-lowering medication, indoor railway L_{night}.

Supplemental Material, Table S1. Extension of Table 1 on the main characteristics of the study population (N=1926).

Variable	Total (N=1926) Median	(IQR)
Outdoor railway noise levels, L_{night} (dB(A))	33.0	(17.0)
Daily mean temperature at lag 0 (ºC)	13.8	(12.9)
	N	(%)
Daily alcohol intake (g/l), No alcohol	441	(22.9)
Little	1227	(63.7)
Moderate	198	(10.3)
Excessive	60	(3.10)
Weekly physical activity (MET), Tertile 1	630	(32.7)
Tertile 2	641	(33.3)
Tertile 3	655	(34.0)

L_{night}: Long-term average nighttime noise levels
MET: Metabolic equivalents

Supplemental Material, Table S2. Spearman correlations[a] between annual average home outdoor NO_2 levels, outdoor and indoor road traffic noise levels (L_{night}) and traffic in the city of Girona (N=1926).

Variable	Outdoor annual NO_2	Outdoor L_{night}	Outdoor L_{night} at façade	Indoor L_{night}
Outdoor annual average NO_2 ($\mu g/m^3$)	1			
Outdoor L_{night} (dB(A))	0.75	1		
Outdoor L_{night} at bedroom façade, (dB(A))	0.39	0.55	1	
Indoor L_{night} (dB(A))	0.23	0.35	0.78	1

NO_2: Nitrogen dioxide
L_{night}: Long-term average nighttime noise levels
[a]All correlations are statistically significant at a level of $\alpha < 0.001$

Supplemental Material, Table S3. Estimated change in prevalent hypertension and in blood pressure (mmHg) per 5 dB(A) increase of indoor traffic noise at night (L_{night}) and per 10 μg/m^3 increase of annual average levels of outdoor nitrogen dioxide (NO_2) applying a linear threshold model for indoor noise at 30 dB(A), N=1926.

	Hypertension	SBP	DBP
Multi-exposure model	Odds ratio (95%CI)	beta coefficient (95%CI)	beta coefficient (95%CI)
Indoor traffic L_{night}	1.14 (0.99, 1.31)*	1.27 (0.34, 2.20)**	0.17 (-0.36, 0.71)
NO_2	1.17 (1.00, 1.37)*	1.25 (0.23, 2.27)**	0.56 (-0.03, 1.15)*

Model adjusted for indoor traffic L_{night}, annual average NO_2, age, age squared, sex, education, Mediterranean diet, exercise, alcohol consumption, smoking, BMI, diabetes, deprivation, daily temperature, BP-lowering medication, and indoor railway L_{night}.
**p < 0.05, *p < 0.1

Supplemental Material, Table S4. Estimated change in systolic blood pressure (SBP, mmHg) and diastolic blood pressure (DBP, mmHg) per increments[a] of annual average levels of nitrogen dioxide (NO_2) and traffic noise indicators at night (L_{night}) using different methods to control for BP-lowering medication.

		Systolic blood pressure (mmHg)				Diastolic blood pressure (mmHg)			
	N	beta coefficient (95%CI)		beta coefficient (95%CI)		beta coefficient (95%CI)		beta coefficient (95%CI)	
Multi-exposure models [b]		L_{night}		NO_2		L_{night}		NO_2	
Non-medicated [c]	1462	0.4	(-0.08, 0.83)	1.1	(0.03, 2.18)**	-0.1	(-0.33, 0.22)	0.6	(-0.06, 1.24)*
Medicated [c]	464	1.6	(0.57, 2.70)**	1.6	(-1.02, 4.20)	0.6	(0.04, 1.15)**	-0.01	(-1.37, 1.35)
Not adjusting for medication [d]	1926	0.8	(0.32, 1.18)**	1.3	(0.23, 2.30)**	0.1	(-0.14, 0.37)	0.6	(-0.02, 1.18)*
Adjusting for medication [e]	1926	0.7	(0.29, 1.15)**	1.2	(0.21, 2.25)**	0.1	(-0.15, 0.34)	0.6	(-0.03, 1.14)*
SBP + 10 mmHg [f]	1926	0.8	(0.33, 1.25)**	1.3	(0.22, 2.42)**	-	-	-	-
DBP + 5 mmHg [f]	1926	-	-	-	-	0.1	(-0.13, 0.40)	0.6	(-0.03, 1.24)*
Censored regression [g]	1926	0.8	(0.26, 1.26)**	1.2	(0.05, 2.44)**	0.1	(-0.17, 0.42)	0.7	(-0.05, 1.35)*

[a] per 5 dB(A) of traffic L_{night} and 10 µg/m^3 of NO_2

[b] All models adjusted for age, age squared, sex, education, Mediterranean diet, exercise, alcohol consumption, smoking, BMI, diabetes, deprivation, daily temperature, indoor railway L_{night}, NO_2, and indoor traffic L_{night}.

[c] Medicated means use of BP-lowering medication.

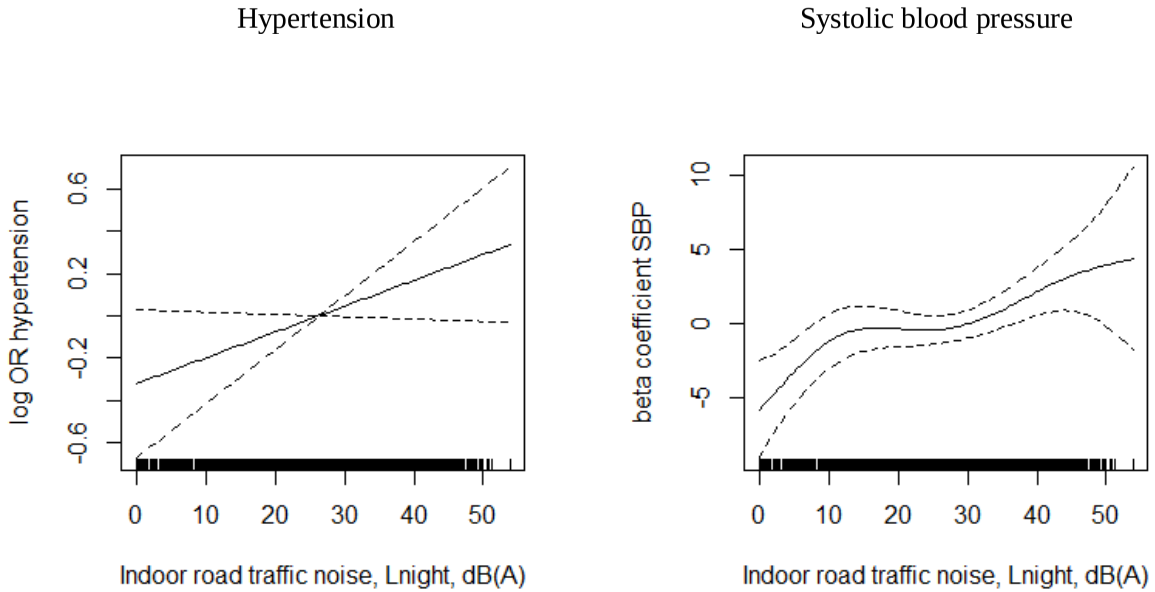
[d] Model for the entire study sample, adjusted for variables in [a], but not for BP-lowering medication.

[e] Model for the entire study sample, adjusted for variables in [a] and for BP-lowering medication.

[f] Addition of 10 mmHg to SBP or 5 mmHg to DBP levels if participant uses BP-lowering medication.

[g] Model for the entire study sample. It assumes that had participants under BP-lowering medication not been treated, they would have BP levels at least as high as the current measured levels.

**p < 0.05, *p < 0.1



Supplemental Material, Figure S2. Smooth spline for the effect of 1 dB(A) increase in indoor road traffic L_{night} and 95% confidence intervals in a generalized additive model for hypertension (left) and systolic blood pressure (mmHg) (right). Model adjusted for: age, age squared, sex, education, Mediterranean diet, exercise, alcohol consumption, smoking, BMI, diabetes, deprivation, daily temperature (lag 0), BP-lowering medication, indoor railway L_{night}, and annual average NO_2. N=1926.

7 DISCUSSION

This section is complimentary to the discussion addressed in each of the Papers (Results section). It aims at providing an overall and integrated interpretation of the entire thesis.

7.1 Contribution to the current knowledge

The association between long-term exposure to traffic-related air pollution and both hypertension and blood pressure (BP) has been little studied, and results have been particularly heterogeneous for hypertension. In contrast, although the thin literature on noise provides some evidence for a relationship between long-term exposure to traffic noise and hypertension, BP has been less studied and results have been inconsistent. The evaluation of each of these outcomes has its own inherent methodological difficulties. Thus, assessing both is a good complement to confirm associations (which one would expect to go in the same direction with both outcomes). Furthermore, all the available evidence relies on outdoor residential noise estimates. Although shielding and protections against noise at home may well modify the true (but unknown) indoor traffic noise exposure, this has not received much attention and no methods have been developed yet to improve exposure assessment.

Traffic has been identified as a potential major hazard for cardiovascular diseases (Brook et al., 2010). Identifying whether air pollution and/or noise are the responsible traffic emission for this association is relevant to apply adequate abatement policies for each of the two factors. However, this remains unclear and very few studies accounted for this mutual confounding effect. Disentangling their independent effects may be difficult due to their common source and high correlation, and the unequal validity of the usually used markers of exposure to noise and pollution, respectively.

This is the first comprehensive and integrative research addressing at the same time the effects of traffic-related air pollution and traffic noise on high BP and also aiming at disentangling their effects in a typical mid-sized Mediterranean area where a substantial spatial correlation between the two factors exists. This region is of further interest as it has low cardiovascular mortality rates despite the high prevalence of common cardiovascular risk factors (Masiá et al., 1998).

In this thesis we observed independent associations of long-term exposure to NO_2 and indoor traffic noise with both hypertension and BP, although some results were not statistically significant. Indeed, only by using indoor traffic noise estimates at the bedroom instead of outdoor noise estimates, we could observe more consistent results for the ambient stressors with both outcomes. The use of indoor traffic noise improved the noise exposure assessment and it had the added benefit of reducing the correlation with outdoor NO_2. This thesis also observed that the association between air pollution and noise with BP may be biased by BP-lowering medication.

Therefore, this thesis adds to the limited evidence on a positive relationship of each of these traffic-related environmental stressors with both the prevalence of hypertension and BP, and suggests the presence of potential susceptibility groups. It also expands on the study of the adverse health effects of noise, an area that has received far less attention compared to the investigation of air pollution effects, and proposes a method to improve noise exposure assessment. The observed results strongly suggest the use of better estimates of exposure to traffic noise based on approaches that characterize indoor traffic noise in the bedroom, instead of the traditionally used estimates of outdoor traffic noise. Finally, our findings suggest that the investigation of BP should be followed by sensitivity analysis to control for the potential biases of BP-lowering medication which we could show to be substantially dependent on the choice of adjustments.

7.1.1 Correlation between traffic-related air pollution and traffic noise

Paper I was the first study to analyze the spatial correlation between traffic-related air pollution and traffic noise in a Mediterranean area. This area is characterized by a densely populated and urbanized center where traffic is expected to be the main contributor to the local contrasts of air pollution and noise. Characterizing the spatial correlation of both environmental factors contributed to understanding the determinants of the spatial variability of both factors and was crucial to know the degree of potential confounding between these factors in Girona city.

Our results suggest a substantial correlation between long-term exposure to annual mean concentrations of measured NO_2 and long-term averages of modeled traffic noise (L_{24h}) levels in Girona city (*Spearman r*=0.62), which could result in a mutual confounding effect of NO_2 and traffic noise on common cardiovascular outcomes. We also observed that this spatial correlation varied across the city according to different urban structures and traffic patterns. Thus, the observation of different correlations in different studies (Allen et al., 2009; Davies et al., 2009; Tang and Wang, 2007; Tobias et al., 2001; Weber and Litschke, 2008) is now complemented with the evidence that one cannot assume stable correlations between these two stressors even within one city.

The distribution of the annual mean concentrations of NO_2 and of traffic noise (L_{24h} and L_{night}) in Girona was mostly explained by common determinants, namely traffic density, degree of urbanization, and distance to the street in front of the location. These determinants were expected because the typical Mediterranean construction brings residences close to the local traffic source, thus NO_2 and acoustic waves reach the residences with similar spatial patterns. This differential distribution is also prevented by the high building density. However, the same

determinants an a similar correlation were observed in Vancouver (Davies et al., 2009), a city with very different characteristics.

We observed that the correlation may differ in street canyon conditions (Tang and Wang, 2007) with NO_2 increasing in a larger extent than noise. Besides, it should be noted that NO_2 levels increase linearly with traffic, while traffic noise increases logarithmically. Therefore, the NO_2-noise correlation may be stronger at low rather than at high traffic densities at the nearest street from home. In fact, the correlation was suggestively smaller at sites with traffic levels of more than 1000 vehicles per day. This may explain why the street width was a determinant of higher NO_2 levels (i.e. a proxy of the number of street lanes and traffic) but not of noise levels. The higher correlations observed around the historical center and the quieter area of Montjuïc might also relate to lower traffic densities at the nearest street from home. Further studies would be needed to clarify this finding.

Finally, we analyzed the outdoor correlation because of its direct application to epidemiological studies, which rely on outdoor estimates. However, we also highlighted that future research should evaluate the impact of personal exposure on the correlation, given that traffic noise levels may well differ indoors with noise abatement measures.

The strengths and limitations of this study are addressed in **Section 7.2 (p. 157)**.

7.1.2 Association between traffic-related air pollution and high blood pressure

Since each of the environmental stressors required special attention, we first focused on air pollution (with adjustment for noise outdoors and a detailed assessment of different techniques to control for BP-lowering medications) (Paper II). Paper III focused on traffic noise and on disentangling associations from those of air pollution. The air pollution analyses (Paper II) could be based on a much larger sample size, whereas Paper III was reduced to the study population with available data on the more refined (indoor) traffic noise levels.

In Paper II we observed an association between long-term exposure to NO_2 and BP (particularly SBP), which was consistent with Paper III. In the latter, we additionally identified a borderline statistically significant association with prevalence of hypertension and a suggestive association with DBP. Our findings add to the limited evidence of the effects of air pollution, and traffic-related air pollution, on BP and the prevalence of hypertension (Chuang et al., 2011; Dong et al., 2013; Fuks et al., 2011; Johnson and Parker, 2009; Schwartz et al., 2012; Sørensen et al., 2012).

The robustness of findings between outcomes in Paper III is important, as one may expect air pollution to affect both. However, according to the limited literature and our overall findings, air pollution might be more associated with BP than with hypertension. We only observed trends or borderline significant associations with hypertension in participants not taking BP-lowering medication in Paper II, and in the population of Paper III. Both populations were characterized by being "healthier" (i.e. having less comorbidities) and being slightly younger compared to the entire population. However, we could not identify any characteristics that suggested a stronger risk in the selected groups compared to the entire population, and they did not live closer to traffic and were not exposed to higher NO_2 levels. Potentially, the effects of NO_2 may

be easier to detect among less severe cases or in earlier stages of high BP (e.g. prehypertension), which are identified in younger yet undiagnosed or recently diagnosed individuals. Alternatively, NO_2 estimates might not correctly capture the more toxic local components of traffic-related air pollution, such as UFP, which may be more related to stronger effects and thus to hypertension.

Interestingly, there was no association between NO_2 and DBP in the population-based sample (Paper II) whereas a suggestive association was found in the younger sample of Paper III. These observations were independent of age within each of the studies (we adjusted for age and for age squared to control for its non-linear association with DBP).

The null NO_2-DBP association may indicate that the biological pathway of NO_2 is more closely related to endothelial dysfunction and to subsequent stiffening of arteries in our population-based sample. This limited elasticity translates into higher SBP but lower DBP (i.e. to increased pulse pressure) (Kaplan and Opie, 2006). Stiffening of the central aorta, is a long-term process that starts affecting pulse pressure after age 55, and it is a determinant of CVD (Franklin, 2006). Besides, endothelial dysfunction is associated with atherosclerosis. In ancillary analyses not shown in Paper II, we indeed observed an association between increased NO_2 and an elevation in pulse pressure. One previous study reported similar results between 2-month averages of $PM_{2.5}$ and SBP and pulse pressure (Auchincloss et al., 2008). Indirect evidence suggests that this phenomenon is only present under urbanization and a modern stressful lifestyle, as it is not observed in isolated populations such as cloistered nuns or some African tribes (Kaplan and Opie, 2006; Timio et al., 1988).

Potentially, traffic-related air pollution may play a role in this process. Furthermore, endothelial dysfunction and high SBP may be

a pathway through which air pollution impacts atherosclerosis and CVDs **(See section 1.4.4, p. 21)**.

In contrast, at younger ages, (e.g. Paper III) isolated high DBP or combined high BP due to autonomic drive is more likely (Black and Elliott, 2013), and NO_2 seems to also be associated with it. In any case, associations were still stronger for SBP, thus associations in the age range represented in this sample may also relate to endothelial dysfunction.

In this study, we also identified two potential susceptible groups. Firstly, the association between long-term exposure to outdoor NO_2 at home and both SBP and DBP was stronger in individuals with CVD. This was only identified once before (Sørensen et al., 2011). Individuals with CVD may have a more unstable vascular function which might be more affected by air pollution and lead to increased BP. Alternatively, it may be related to temporality and previous air pollution effects. However, these findings require confirmation given the small numbers of participants with CVD in our sample.

Secondly, our results indicated a stronger NO_2-SBP association in participants living alone compared to those not living alone. We analyzed this group because it constitutes a socio-economical (SES) determinant and it has been identified as a predictor of uncontrolled BP (Morgado et al. 2010), a main contributor to cardiovascular risk **(See section 1.3.1, p. 12)**. Living alone was closely related to aging, but this finding might not simply constitute a proxy for age, as no interaction by age was observed in the study. It may further relate to uncontrolled BP due less social support and to a higher exposure to environmental factors in the elderly as a consequence of spending more time at home. This is though a speculative argument which should be confirmed with further analyses on individuals living alone and those with uncontrolled BP. Finally, we also adjusted for this variable in Paper II, as it was associated with the outcome and exposure, and to have a better control of SES and aging factors.

However, it was a weak confounder in the multivariate regression analysis, particularly in Paper III. Thus, for simplicity and in adherence to the causal diagram (DAG) **(See appendix VI)** we finally did not consider the variable "living alone" in Paper III.

Finally, we observed a stronger association between NO_2 and SBP for individuals exposed to traffic noise levels ≥ 55 dB(A) or to high traffic, particularly for high traffic loads in a 500 m around home. Although we hypothesized a synergistic effect between NO_2 and traffic noise, these interactions may also indicate that NO_2 was more representative of near-road traffic-related air pollutants at higher traffic densities or loads **(See Paper II, p. 84)**. The later reason might be likely as we observed the same trends with higher outdoor traffic L_{night} in Paper III (data not shown) but not with indoor traffic L_{night}, a variable that is less correlated with traffic.

A negative confounding by adjustment for transportation noise was observed and disclosed in Paper II (i.e traffic and railway noise). After performing the analysis in Paper III, one may argue that the effect size for BP was somehow inflated in Paper II due to collinearity. With collinearity standard errors are expected to increase. In our study, the increase in standard errors was not as extreme as to conclude that collinearity was a problem, based on the common diagnostic for collinearity of the Variance Inflation Factor (VIF). In addition, in terms of association, NO_2 and SBP were related in both Papers, which supports an association between NO_2 and SBP independently of traffic noise, although slightly biased in Paper II. In contrast, adjustment for noise did not seem to explain the null association between NO_2 and hypertension in Paper II, as not adjusting for it also yielded a null result for NO_2 and hypertension.

The control for BP-lowering medication was comprehensively addressed in Paper II and it is fully discussed in **Section 7.1.5, p. 153.**

7.1.3 Association between traffic noise and high blood pressure

In Paper III, long-term exposure to outdoor nighttime traffic noise (L_{night}) at the postal address was only associated with prevalence of hypertension, and point estimates for SBP were negative, after adjustment for NO_2. The same pattern was observed in Paper II, with only a suggestive association of noise with prevalence of hypertension (data not shown). In contrast, outdoor traffic L_{night} at the bedroom façade and indoor traffic L_{night} at the bedroom were related to both the prevalence of hypertension and SBP, independently of traffic-related air pollution. The association between indoor traffic L_{night} and hypertension was borderline significant and the point estimate for SBP was stronger with indoor traffic noise levels than with outdoor L_{night} at the bedroom façade.

These results add to the current evidence on the association between long-term exposure to traffic noise and prevalence of hypertension (van Kempen and Babisch, 2012) and particularly to the inconsistent evidence for BP (Babisch, 2006; Dratva et al., 2012; Sørensen et al., 2011). More interestingly, results were most consistent across the outcomes with indoor traffic noise estimates, an approach that was only used once and that was based on a cruder exposure assessment (Babisch et al., 1999). Although the use of remedies against noise may differ across locations, thus results cannot be generalized, these findings strongly suggest further attention to markers of personal exposure to noise in other studies.

In contrast, we did not observe a relationship between traffic L_{night} and DBP. Potentially and as also hypothesized for NO_2, L_{night} may more closely relate to endothelial dysfunction in this population, leading particularly to higher SBP **(See section 7.1.2, p. 143)**.

As addressed in the discussion of Paper III **(See page 117)**, the few previous studies that accounted for remedies against noise generally

performed stratified or interaction analyses on the association between outdoor traffic noise levels and hypertension, and sometimes observed counterintuitive findings (van Kempen and Babisch, 2012). While useful, findings may be difficult to interpret, since they still rely on a misclassified exposure, and especially if each factor is examined separately while participants may combine many remedies. Another difficulty is that the interactions rely on outdoor noise estimates which correlate with annoyance or air pollution (Babisch et al., 2012), two factors related to hypertension that may also explain the interactions. In our study we did not observe a modification of the studied associations by a combination of different remedies against noise.

In this thesis we built a method to estimate outdoor traffic noise at the bedroom façade and indoor traffic noise levels in the bedroom based on outdoor noise estimates and questionnaire data. This method was based on an extensive research of engineering literature and official documents to identify the elements that would greatly contribute to insulation and to group them in a practical way according to their noise attenuation rates. However, the use of these indoor traffic noise estimates may also introduce bias. For example, the use of standard attenuation factors does not consider the different quality of window sealings which also contribute to the final insulation in dB(A). Among other considerations addressed in Paper III **(p. 120)**, a potential limitation is that attenuation factors do not take into account that low noise frequencies penetrate surfaces more easily than higher frequencies (Buratti and Moretti, 2010). This means that in locations where the low frequency component of the traffic pattern (i.e. heavy duty vehicles) is higher, one would underestimate the real indoor traffic noise levels. However, heavy duty traffic within the city at night is smaller and the dB(A) already give less weight to low frequencies **(See Section 1.1.1, p. 3)**. Therefore, the impact might be less pronounced in our nighttime A-weighted noise estimates. In summary, to date no indoor models exist, and performing indoor measurements for

traffic-related noise exposure for the entire population is not feasible and might not be well accepted. In turn, the proposed approach may provide a better proxy of the true noise exposure at the supposedly most relevant room (the bedroom) compared to outdoor noise estimates. Future studies could rely on the same questionnaire approach followed in this thesis, use refined versions of it, and perform validation studies of the indoor estimates on a subsample of the population. Models that estimate noise at all the building façades or even indoors would also help this purpose.

Our results further indicated that individuals taking anxiolytics did not show increases in the prevalence of hypertension with increasing indoor traffic L_{night} levels compared to those that did not report this treatment. An increased use of anxiolytics in relation to aircraft noise had been already identified (Floud et al., 2011; Franssen et al., 2004). No previous study, however, had analyzed whether anxiolytics, which antagonize stress-reactions and thus may block the noise-induced stress reaction, may modify the effects of traffic noise on high BP. This hypothesis is supported by an experimental study that observed less noise-induced stress responses in humans after intake of anxiolytics (Cluydts et al., 1995). However, they evaluated high noise levels and strong arousal responses such as awakenings against hypnotics, which have stronger sedative properties. Unconscious responses such as the elevation in BP and at lower environmental levels might be also antagonized by anxiolytics prescribed at lower doses.
Interestingly, in this thesis we also observed a suggestive stronger association between indoor traffic L_{night} and prevalence of hypertension with increasing reported traffic noise annoyance during the sleeping period. This effect modification has been little studied (Babisch et al., 2013; Björk et al., 2006; Lercher et al., 2011) and suggests a synergistic effect between the direct (objective sound level) and the indirect (noise perception) noise stress pathways **(See section 1.4.2, p. 19)**.

The association between indoor traffic L_{night} and SBP was stronger when applying a threshold at 30 dB(A). In light of the uncertain shape of this association at the very low end of noise exposure, **(See Paper III, Supplemental Material, p. 137)** one needs to interpret the threshold finding with caution. However, the notion of a noise threshold is indeed intriguing and may be rather plausible, as indoor background noise levels could well mask indoor traffic noise at 30 dB(A). Further research is needed to confirm the existence of a threshold for noise effects. Some previous studies reported thresholds at outdoor traffic noise levels of ≥ 55 dB(A) (Barregard et al., 2009; Bodin et al., 2009; de Kluizenaar et al., 2007).

Finally, interaction results for the effect modification by age or sex on the association between indoor traffic L_{night} and hypertension were far from significant. Some previous studies reported effects on specific middle-age groups (Bodin et al., 2009; de Kluizenaar et al., 2007) or in men (Barregard et al., 2009; Jarup et al., 2008), or less frequently in women (Bluhm et al., 2007) although p-values for interaction were not always provided. If anything, and in case of limited statistical power, our results may indicate smaller effects at older ages and a stronger effect in men, which would agree with literature (van Kempen and Babisch, 2012).

7.1.4 Disentangling the associations of traffic-related air pollution and noise on high blood pressure

Whether the association between traffic noise and high BP is confounded by traffic-related air pollution and vice-versa has been little studied. As we already observed in Paper I, the few noise or air pollution epidemiological studies that adjusted for the other factor (Beelen et al., 2009; Coogan et al., 2012; de Kluizenaar et al., 2007; Dratva et al., 2012; Fuks et al., 2011; Klæboe et al., 2000; Schwartz et al., 2012; Selander et al., 2009; Sørensen et al., 2012, 2011) did not always use specific traffic-related air pollutants or

used low-resolution traffic noise data, which precludes the correct assessment of confounding, as previously commented (Künzli, 2013).

The results from this thesis indicate that both long-term exposure to traffic noise and traffic-related air pollution are independently associated with BP and prevalence of hypertension, but only after adjustment for indoor traffic noise levels. Indoor traffic noise levels reduced noise exposure misclassification and also reduced the correlation between outdoor NO_2 and noise levels. Although findings cannot be directly generalized to other locations this issue itself needs attention in other studies.

The correlation between modeled estimates of traffic-related air pollution and noise was higher (*Spearman r*=0.75) than that already observed with measured NO_2 concentrations and modeled traffic noise (*Spearman r*=0.62) **(See section 7.1.1, p. 141)**. This may be due to the fact that, even though traffic was a main local determinant of the measured NO_2 concentrations, NO_2 measurements may also account for non-traffic primary sources and secondary NO_2. In contrast, modeled NO_2, as well as modeled traffic noise, is more specific for traffic and does not account for the residual variability not explained by the model. Thus, using modeled instead of measured NO_2 potentially yields stronger correlations with traffic noise. In summary, the correlation between modeled estimates was coherent with Paper I and confirmed the substantial correlation in the study area **(See section 7.1.1, p. 141)**. The rather good agreement is reassuring, since noise and air pollution models may greatly overestimate or underestimate the true correlations depending on the input variables and quality.

Conceptually this correlation is low enough to allow the mutual adjustment of noise and air pollution in regression models, preventing strong biases derived from collinearity. Even if the estimators are unbiased (i.e. on average they will lead correctly

estimate true values), one of the potential consequences of collinearity is that in single studies one can get an inflated estimate for one of the coefficients and an attenuated one for the other. In Paper II the positive association between NO_2 and SBP was related to a negative confounding effect by outdoor traffic L_{night} and this negative confounding was also observed in Paper III between NO_2 and SBP when adjusting for outdoor traffic L_{night} estimates. In turn, the positive association between outdoor traffic L_{night} and hypertension was also related to a slight inverse association between NO_2 and hypertension. Nevertheless, these patterns disappeared when adjusting for indoor instead of outdoor traffic noise estimates **(See Paper III, Table 2, p. 125)**.

Although the high correlation between the outdoor environmental factors was not strong enough to be detected by collinearity tests such as the VIF, the inflation was observable and precluded the observation of the associations for the two factors. In consequence, in a simulation study in Paper III, we illustrated how the high correlation with outdoor estimates coupled with the relatively small sample size would lead to the observation of a positive effect for NO_2 with SBP while it would lead to a negative effect for L_{night} in a 15% of cases. This tendency may be similar in studies with a similar correlation and sample size. In contrast, while improving exposure assessment, the use of indoor traffic noise levels decreases the correlation between NO_2 and L_{night} which in turn allows disentangling the effects between both factors. Thus, our results suggest again the use of indoor traffic noise levels in future studies. Although findings cannot be directly generalized to other locations, this issue itself needs attention in other studies.

While our best approach to disentangle the effects was to account for indoor traffic noise estimates, we had previously proposed alternative approaches to separate these effects. Based on Paper I, we knew that the correlation was area-dependent. Thus one may expect to disentangle the effects in the areas where the correlation

between the two exposures is lower. We therefore carried out the same geographical weighted regression used in Paper I **(See appendix V)** and corroborated that the beta coefficients and coefficients of determination of the association between modeled estimates of NO_2 and L_{night} were too high in most city-areas. Thus, we could not identify an area with a low NO_2-L_{night} correlation to evaluate the potential separate effects of the two factors. Moreover, as residential areas are related to SES, and likely age, disease and also to air pollution and noise levels, findings from stratified analysis by city-area could be biased and difficult to interpret. This analysis also has the problem of reduced power.

7.1.5 Use of BP-lowering medication

As explained in the introduction **(Section 1.4.6, p. 24)** BP-lowering medication is not a confounder but a mediator of the association between the exposure (i.e. air pollution or noise) and the final observable BP levels. Epidemiological studies need to control for medication, but no perfect method exists (Tobin et al., 2005). Some previous studies acknowledged the potential for bias in the association between air pollution and BP levels both by adjustment or not adjustment for medication (Auchincloss et al., 2008; Fuks et al., 2011; Schwartz et al., 2012). However, no further assessment has been done.

In this thesis we addressed this open question as a main objective of Paper II, as it was the air pollution literature the one that had mainly investigated BP and encountered this problem. We developed for the first time a comprehensive comparison of the existing methodologies – as identified by us from a simulation study (Tobin et al., 2005) – to try to understand and to disclose the potential bias introduced by BP-lowering medication in the analyses..

In Paper II we observed that the association between NO_2 and BP was sensitive to the chosen techniques. Although no perfect method exists to control for medication, our analyses support that the effect of BP-lowering medication on BP levels was probably heterogeneous in our population. In this case, the medication would be a weaker mediator between the exposure and the observed BP levels. In consequence, the common approach of adjusting for medication might be less biased than expected. We also suggested that analyzing the group not taking BP-lowering medication (i.e. "non-medicated") could be used as a conservative approach.

The conclusion of a limited bias when adjusting is based on the fact that Tobin et al. (2005) suggested that, under bias, the "non-favored" techniques (i.e. adjusting or not adjusting for medication) would create shrinkage of results towards the null, i.e. against our hypothesis. In contrast, the "favored" techniques (i.e. adding a fix value to BP levels in those taking BP-lowering medication or censored regression) would provide higher point estimates, closer to the true ones. However, the opposite was observed in our analysis, in other words we observed smaller effects with the "favored" than with the "non-favored" techniques and this shrinkage increased with every additional 5 mmHg added to correct for the unknown effect of treatment. Another explanation for these results could be sampling variability. However, to which extent this is a likely explanation cannot be ascertained with a single study.

The smaller point estimates with the "favored" techniques, and assuming that an association between NO_2 and BP exists, suggested that the assumptions underlying these techniques were violated in our study population. For example, the fixed correction method assumes that the effect of medication on BP can be quantified. However, adding higher fixed corrections led to smaller point estimates for the studied association, which may indicate that the effect of medication was actually weak and not quantifiable (i.e. heterogeneous) in our population. Moreover, effect estimates had

wide confidence intervals in the group taking BP-lowering medication, which may be also an indication of the heterogeneous effect of medication on the outcome. I.e. the medication's effect was not systematically decreasing BP levels, which would have led to an inverse association between air pollution and the observed BP. A complementary reason for the wide confidence intervals may be the smaller sample size in this group. Besides, the censored regression, another suggested technique, assumes that the distribution of the underlying – unknown – BP in treated subjects is the same as the distribution of the observed BP in untreated subjects, which might be often wrong (Tobin et al. 2005), but cannot be checked.

The idea of heterogeneity in the effect of medication is likely because the effect of medication depends on adequate compliance, individual effectiveness, and the combination of anti-hypertensive treatments. Heterogeneity might be particularly the case when analyzing a wide age range of the population. The idea of heterogeneity agrees with the theoretical reasoning already provided by Fuks et al. (2011). Alternatively, as we expect small effects of air pollution on BP, its impact on medication may be weak and difficult to observe, thus the bias would be limited when adjusting for medication.

In Paper II, we further suggested the use of the group of non-medicated participants. All of the different methodologies above showed some potential limitations and findings within the group of non-medicated participants were of prime interest as this was the only group where the main outcome was measured without bias (i.e. measured BP was not modified by medication). Although this may be a highly self-selected group, we hypothesized this selection to bias results towards the null, as it would most probably be a self-selection of healthier individuals and with a potential exclusion of individuals affected by the exposure. The main determinants of being part of this group were being younger and having less

comorbidities. Thus, we argued that we probably did not select a particularly susceptible or disadvantaged group where stronger effects of air pollution could be expected. We have also no reason to believe that the selection phenomena inherent in this subgroup to be related to exposure, as the median NO_2 levels were the same in the medicated and non-medicated groups. Therefore, we considered the analyses among the untreated group to be the most conservative approach and the only group where the association was not masked by medication.

In Paper III, analyses were far less sensitive to the choices of the treatment correction methods. As results were robust across the several techniques **(See Paper III, Supplemental Material, Table S4, p. 136)**, we only reported the main results for BP adjusting for medication. This was reassuring, as said, because there is no perfect methodology, and it provided the opportunity to use the entire sample. Nonetheless, we could have reported results in non-medicated individuals, for which results were also positive. As hypothesized in Paper II, this indeed seemed to be the most conservative approach, given that point estimates in this group were smaller, particularly for the association between L_{night} and SBP. Moreover, although not statistically confirmed, an interaction by medication may exist on the association between L_{night} and SBP.

7.2 Strengths and limitations

The main strength and differential trait of this thesis was the estimation of indoor traffic noise levels from outdoor traffic noise estimates based on detailed questionnaire data on noise abatement measures at home and room orientation. This substantially improved the noise exposure assessment in comparison to previous studies and ultimately helped to disentangle the effects of traffic noise from those of traffic-related air pollution. Besides, we expect indoor residential exposure to traffic noise to differ in a greater extent from outdoor residential levels than NO_2. While coping behavior against noise and room orientation strongly shields noise, the reported NO_2 infiltration rates from outdoors are high (Chen and Zhao, 2011) even if the absolute concentrations may differ.

Exposure misclassification is inherent to any study. We had access to a validated traffic noise model that allowed the precise estimation of residential outdoor noise levels. This may have reduced the random error in comparison with previous studies that relied on less precise data. We also analyzed wide contrasts of both traffic noise and NO_2, which increases the ability to detect differences, thus to observe associations. Moreover, NO_2 was also estimated with a detailed land-use regression model that was based on extensive measurement campaigns and whose main predictors were traffic-related variables at different radius buffers, thus NO_2 could be considered as a marker of traffic-related air pollution. In order to capture the impact of the most locally distributed traffic-related pollutants, such as UFP, we further took into account traffic proximity in Paper II. Finally, although the NO_2 model was based on measurements performed after the health assessment, no major changes in traffic and NO_2 levels occurred during this period, thus, as already reported (Eeftens et al., 2011), we expect the spatial contrasts of NO_2 to be rather stable over time.

Exposure could be also misclassified due to past residential mobility. However, this population has a small proportion of movers and the studied associations were not affected by it **(See Paper II, Supplemental Material, Table S5, p. 97).** It is also relevant to assess the correct time window of exposure for the health effects. In our case, accounting for exposure during the last 10 years instead of the last year did not change results for NO_2. Thus, one-year estimates might be a good proxy of long-term exposure. This was not evaluated for traffic noise, as noise levels are particularly stable over time. A doubling in traffic is needed to increase noise in only 3 dB(A) (World Health Organization, 1999), **(See Section 1.1.1, p. 3)**. Furthermore, we evaluated the nighttime as the most relevant time window. However, since L_{night} and L_{24h} are highly correlated (*Spearman r*=0.99), we would expect similar results with the later indicator.

We assessed individual residential exposure instead of personal exposure during the 24h. This had no impact on the noise inferences, as the effects of noise are expected to happen during the sleeping period, thus at the bedroom at home. Regarding NO_2, the misclassification related to residential exposure cannot easily be ruled out. Nevertheless, it should be noted that people spend much of their time at home (Leech et al. 2002) and its surroundings, thus the additional value of personal exposure might be somehow limited.

In this thesis, we also characterized the spatial correlation between NO_2 and noise in a large number of locations that covered the traffic contrasts across Girona city and we used many objective data on local urban features. The selected locations were the residences of participants, thus, the findings might be a rather reliable estimate of residential outdoor conditions. Previous studies had only analyzed correlations at street level (Allen et al., 2009; Davies et al., 2009; Tang and Wang, 2007; Tobias et al., 2001; Weber and Litschke, 2008). In contrast with previous evaluations in epidemiological

studies, we used NO_2 measurements instead of models, as the latter could have unpredictable biases on the correlation. In turn, NO_2 measurements were a good surrogate of traffic-related exposure, and indeed traffic was a main determinant of their spatial distribution. Although we used modeled noise levels, those predictions had a high correlation with noise measurements (R^2=0.93).

It should be mentioned that one of the aims of Paper I was to identify the main determinants of the spatial distribution of both traffic noise and NO_2, not to build predictive models. Even if we measured NO_2 and modeled traffic noise, the different measurement error did not prevent the detection of the main determinants and their coefficients were not affected, although measurement error could change their p-values and R^2s. We also acknowledged that some common determinants explaining the NO_2-noise correlation could not be identified. This may include meteorological variables. However, obtaining information on factors such as wind at each location was not feasible. Finally, the substantial spatial correlation was confirmed by a high correlation between modeled NO_2 and traffic noise levels.

This project evaluated a population-based sample, thus, results can be generalized to the entire population. However, the potential for selection bias in the recruitment cannot be rejected. If the exposures progress to hypertension and CVDs and these individuals are less likely to participate, the resulting associations would underestimate the true relationship. This may particularly affect the study population of Paper III, a selection of participants at baseline that had attended the follow-up 5 years after, and that were somehow younger and healthier, thus likely biasing findings towards the null.

In this population, many factors were associated with the exposure and outcomes, thus it required a careful statistical assessment, which we reinforced with the application of directed acyclic graphs

(DAGs). These graphs illustrate the relationships across variables based on previous knowledge and the own observations, and help to detect potential biases and decide on the variables to be considered in the adjustment set **(See appendix VI)**. To limit bias we also assessed the potential shrinkage introduced by BP-lowering medication on the association between NO_2 and traffic noise on BP and reported results with all methodologies to disclose the uncertainties.

Reducing confounding is particularly important in studies such as ours that analyze small effects. We relied on a comprehensive set of confounders, we additionally adjusted for the short-term exposure to environmental factors, area-level deprivation, and mutually controlled for long-term exposure to NO_2 and noise. We also controlled for noise from the single railway in Girona. This variable had a negative confounding effect even after using indoor railway noise levels. We could not identify any reasons for this pattern and considered it as a relevant confounder based on our DAG and previous literature (Dratva et al., 2012). Even with the comprehensive control for different factors in this thesis, residual confounding cannot be avoided, given that some variables might not be good enough surrogates, thus they might not totally capture the variability of the true confounding factor.

Our assessment of BP was based on several measurements in a single visit but followed standard procedures to improve precision. The potential misclassification of hypertensive cases was evaluated in sensitivity analysis in Paper II and the association with NO_2 was consistent across the different definitions of hypertension. To try to avoid the "white-coat" syndrome, which means that individuals exhibit higher BP levels in a clinical setting than expected in other settings, we took the last BP measurement, which is less likely to be affected by this syndrome. As we do not expect the misclassification of hypertensive and non-hypertensive individuals to depend on air pollution and noise, the remaining misclassification

is likely to be non-differential, thus to underestimate the true associations.

The main limitation of our evaluation was its cross-sectional design. Thus, the causal link (i.e. whether the exposure precedes the disease) cannot be determined. Reverse causation may happen if participants with hypertension are more likely to move to areas with more traffic compared to non-diseased individuals. This option cannot be discarded in Mediterranean areas where the city centers are the most polluted but also the areas with more accessible services, which may provide an advantage to diseased individuals. Nevertheless, the observed associations between NO_2 and noise with high BP agree with findings in other countries in Europe (for noise), and in Asia and the United States (for air pollution) where this pattern might be less likely. Besides, the plausibility of the results is supported by experimental studies (Brook et al., 2009; Ising and Kruppa, 2004; Mills et al., 2008). Nonetheless, longitudinal evaluations with repeated BP measurements are needed to establish a causal association. To our knowledge, only two studies performed longitudinal analysis between air pollution and incidence of hypertension, one finding no increased risk (Sørensen et al., 2012) and the other confirming an increased risk of hypertension (Coogan et al., 2012). No such studies have been yet done for traffic noise.

Finally, we relied on a rather large sample size in Paper II which provided more statistical power to detect associations. However, this was not the case in Paper III. In Paper III, the statistical power may have been particularly limited to detect statistically significant associations in interaction analysis and with the binary outcome of hypertension.

7.3 Implications for public health

Our findings in an adult Mediterranean population indicate higher BP levels (particularly SBP) and possibly an increased prevalence of hypertension among those individuals exposed in the long-run to higher traffic noise at the bedroom at night, but also to higher outdoor traffic-related air pollution. High BP could be a mediator of the cardiovascular effects of both noise and air pollution.

Even if these environmental stressors would not be associated with a current diagnosis of hypertension, the cardiovascular risk associated with high BP increases in a linear fashion, with no defined threshold, thus, the findings of higher SBP or DBP are relevant. Furthermore, it should be elucidated whether less severe effects not reaching a diagnosis of hypertension could lead to prehypertension, a condition that is also associated to increased cardiovascular risk **(See Section 1.3.2, p. 14)**.

Although the effect sizes were small, and may have a small impact at the individual level, an important part of the population is exposed to traffic noise and traffic-related air pollution and may be affected by their adverse effects on high BP. In turn, high BP is the leading individual factor contributing to morbidity and mortality worldwide. If the association is causal, noise and air pollution abatement policies that target the entire population would therefore contribute to a shift in the distribution of BP towards lower average levels which could benefit millions of people (Rose, 1985). For example, it has been reported that a reduction of only 2 mmHg in the population mean SBP translated into a 25% reduction in stroke events (Girerd and Giral 2004). This type of policies may be particularly important, as individual measures to reduce high BP have been little effective and primary prevention measures at the population level have been requested **(See Section 1.3.1, p. 12)**.

Disentangling the effects of long-term exposure to traffic noise and traffic-related air pollution is of prime interest from a public health perspective. As discussed by Brook et al. (2010), abatement policies for each of these factors are different. Thus, one could tailor the specific challenges that a city or region might have with any or both of those stressors. Moreover, in the evaluation of policies that target the general reduction of traffic, one would need to take the complementary impact of both factors into account to properly value the policy impact. If both environmental stressors would be indeed associated with high BP, policies aiming at reducing total traffic levels, starting in densely populated areas with high traffic levels, could result in substantial health benefits.

Specific abatement policies for traffic-related air pollution may include the promotion of "zero-emission" vehicles. In addition, these vehicles are quieter. However, it is being discussed whether they should artificially be made noisier – which would not be supported from a noise and health perspective – for safety reasons and tire noise would not be avoided. Thus, to date "zero-emission zones" do indeed primarily abate air pollution.

Specific noise policies at the population level may seek for a reduction of the vehicles' noise emission levels, combined with other policies, such as the promotion of natural noise absorption elements (i.e. trees) together with noise barriers at major roads and highways. Traffic levels could be also reduced in highly populated areas during the nighttime, which seems to be the most susceptible time window for cardiovascular noise effects. Another action could be to provide a pleasant quiet side to dwellings. However, this should be implemented with new city planning and its real benefits have not been yet fully studied.

One may also think of improving overall noise insulation of buildings with new construction. Buildings already have to comply with a certain insulation code. However, we observed associations

between indoor traffic noise levels and high BP, which suggests that current buildings in Girona are insufficiently protected to prevent adverse effects. The insulation levels that should be achieved are unknown and actually, the potential benefits are not fully understood (Babisch et al., 2012). Most importantly, the World Health Organization alerts of the health benefits of ventilation to keep indoor air quality at night (World Health Organization, 2009). Insufficient insulation or not having the freedom to open windows at night may result in increased annoyance (Babisch et al., 2012) and, as observed by us, those annoyed by traffic noise may suffer a stronger elevation of hypertension with increasing indoor traffic noise levels.

Our results should be further confirmed and the risks related to noise and air pollution should be quantified in terms that can be used for prevention. This way one would know the fraction of morbidity and mortality that can be attributed to each of these environmental stressors and the health benefits from reducing a certain proportion the long-term exposure of the population to each of these stressors.

7.4 Implications for future research

Several uncertainties remain that suggest further investigation in the following areas:

- Validation with indoor traffic noise measurements of the indoor traffic noise estimates obtained by means of long-term outdoor noise estimates at the postal address and questionnaire data, and refinement.

- Production of traffic noise models that estimate noise at all the building façades and/or indoors at home.

- Further confirmation of the results for the association between long-term exposure to indoor traffic noise levels at night at the bedroom and also to traffic-related air pollution with both BP and hypertension. These studies should be conducted in different populations worldwide. Larger sample sizes are recommended.

- Further joint evaluations to verify the independent effects of long-term exposure to traffic noise and traffic-related air pollutants on BP and hypertension. This should be also evaluated with prehypertension and on other cardiovascular outcomes that have been associated with traffic, such as subclinical atherosclerosis. Specific traffic noise and traffic-related air pollution information is necessary for this assessment. Several traffic-related air pollutants should also be assessed, as their toxicological properties and correlation with traffic noise may differ.

- Investigation of the relationship between long-term exposure to traffic noise and traffic-related air pollution with hypertension and BP in longitudinal analyses to look at incidence of HT and change of BP over time. Longitudinal

analyses would also help to control for the effects of BP-lowering medications on BP levels.

- Investigation of the exposure-response curves and thresholds of effects of traffic noise and traffic-related air pollution on high BP.

- Investigation of the possibly synergistic effects of being co-exposed to high traffic noise and high traffic-related air pollution levels in the long-run.

- Identification of susceptible groups to the cardiovascular effects of long-term exposure to traffic noise and traffic-related air pollution levels.

- Further understanding of the synergistic effects of the indirect (annoyance) and direct (objective noise) noise stress pathways on high BP.

- Verifying the biological pathways that may result in an elevation of SBP but not of DBP with long-term exposure to higher traffic noise and traffic-related air pollution.

8 CONCLUSIONS

1. *The correlation between long-term average NO_2 levels and long-term average traffic noise levels in the city of Girona is substantial, and it is endorsed by common determinants of the spatial distribution of both factors. However, it is area-dependent.* This calls for a careful evaluation of both environmental factors and indicates that the cardiovascular effects associated with long-term exposure to traffic noise can be confounded by NO_2, and vice-versa.

2. *Long-term exposure to higher residential outdoor NO_2 levels (a marker of near-road traffic-related pollution) is associated with higher SBP levels in a population-based sample,* with a stronger association among participants living alone, and those exposed to higher traffic levels around home and higher road traffic noise levels. The association between NO_2 and both SBP and DBP is also stronger for individuals with CVD. The association between NO_2 and SBP in this population is sensitive to adjustment for transportation noise and to the use of different techniques to control for BP-lowering medication.

3. *In a slightly healthier adult population of Girona, long-term exposure to higher residential outdoor NO_2 levels is consistently associated with higher BP levels and with a suggestive increase of prevalence of hypertension while taking indoor traffic noise levels into account*. Taking instead outdoor traffic noise levels into account results in a dilution of the association of NO_2 with hypertension; and the associations of the two traffic-related exposures cannot be properly disentangled.

4. *Long-term exposure to higher indoor traffic L_{night} at the bedroom is consistently associated with higher SBP and with a suggestive increase of prevalence of hypertension, and not confounded by NO_2.* Outdoor traffic L_{night} is though only

associated with hypertension and its association with SBP tends to an inverse relationship when adjusting for NO_2; therefore associations of the two outdoor traffic-related exposures cannot be properly disentangled. The association between indoor traffic L_{night} and hypertension is stronger in individuals annoyed by traffic noise and diluted in individuals taking anxiolytic medication. A threshold of effect may exist for indoor traffic L_{night} at the low noise levels regularly encountered at night indoors.

5. *Individual epidemiological studies in areas with an outdoor noise-air pollution correlation around 0.7 and with a similar sample size to that in our study may not be able to disentangle the long-term effects of each of these environmental stressors with high BP by mutual adjustment for the outdoor levels of traffic noise and air pollution.*

6. *These results underscore the relevance of using detailed exposure assessment to identify the independent effects of both road traffic noise and traffic-related air pollution and to ascertain the effects of traffic noise per se. Questionnaires on measures against noise could be a useful tool to derive indoor noise markers in future studies.*

7. *No perfect technique to control for BP-lowering medication exists in cross-sectional studies and all techniques can shrink associations with BP. Although this issue cannot be resolved in cross-sectional studies, it can be assessed by comparing different techniques.* Investigating the association in the group not taking BP-lowering medication might be a conservative approach in our study. In turn, under a heterogeneous effect of BP-lowering medication, the common technique of adjusting for medication might be less biased.

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APPENDIX I: Environmental noise guidelines

Table I.1. World Health Organization recommendations[1]

General recommended Ambient noise levels	dB(A)
Outdoors	
Daytime outdoor ambient noise	< 50
Night-time outdoor ambient noise (desired)	< 40
Night-time outdoor ambient noise (interim value)	< 55
Indoors	
Dwelling – daytime and evening	< 35
Night-time – inside bedrooms	< 30

Table I.2. Catalan Government Legislation for Noise Protection (updated in 2009) [2]

Catalan Government Legislation (2009)[2]	dB(A)
High-sensitivity area [3]	
Daytime	< 55-60
Night-time	< 45-50

[1] (World Health Organization, 2009, 1999).
[2] (*Catalan Government Order 176/2009*, 2009)
[3] Area with the most restrictive legislation. It includes: parks, the coast (beaches), school, hospital and residential areas, residences for the elderly, and libraries, among others.

APPENDIX II: Noise levels from common sources

Source	dB(A)*
Air raid siren at 50 feet (15.2 m)	120
Maximum levels in audience at rock concert	110
On platform by passing subway train	100
On sidewalk by passing truck or bus	90
On sidewalk by passing car	70
Busy office / Conversation / Urban background (day)	60 - 50
Urban-suburban background (night)	50 - 40
Rural area at night / Library / Bedroom at night	30
Leaves rustling	20
Threshold of hearing (without hearing damage)	0

*Approximate dB(A) for each source (Cowan, 1994)

APPENDIX III: Air quality criteria for Europe

Pollutant	Concentration	Averaging period	Legal nature - Entry into force	Permitted exceedences each year
Fine particles ($PM_{2.5}$)	25 μg/m³	1 year	Target value - 1.1.2010	n/a
			Limit value - 1.1.2015	
	20 μg/m³ *	3 years	Legally binding in 2015	n/a
	18 μg/m³ * Reduction target	3 years	Where possible in 2020, determined on the basis of the value of exposure indicator in 2010**	n/a
PM_{10}	50 μg/ m³	24 hours	Limit value - 1.1.2005	35
	40 μg/ m³	1 year	Limit value - 1.1.2005	n/a
Nitrogen dioxide (NO_2)	200 μg/ m³	1 hour	Limit value - 1.1.2010	18
	40 μg/ m³	1 year	Limit value - 1.1.2010	n/a
Sulphur dioxide (SO_2)	350 μg/ m³	1 hour	Limit value - 1.1.2005	24
	125 μg/ m³	24 hours	Limit value - 1.1.2005	3
Lead (Pb)	0.5 μg/ m³	1 year	Limit value - 1.1.2005	n/a
Carbon monoxide (CO)	10 mg/ m³	8 hours	Limit value - 1.1.2005	n/a
Benzene	5 μg/ m³	1 year	Limit value - 1.1.2010	n/a
Ozone	120 μg/ m³	8 hours	Target value - 1.1.2010	25 days averaged over 3 years
Arsenic (As)	6 ng/ m³	1 year	Target value - 31.12.2012	n/a
Cadmium (Cd)	5 ng/ m³	1 year	Target value - 31.12.2012	n/a
Nickel (Ni)	20 ng/ m³	1 year	Target value - 31.12.2012	n/a
Benzo(a)pyrene	1 ng/ m³	1 year	Target value - 31.12.2012	n/a

*AEI: Average exposure indicator. A 3-year running annual mean $PM_{2.5}$ concentration averaged over the selected monitoring stations in agglomerations and larger urban areas, set in urban background locations to best assess the $PM_{2.5}$ exposure to the general population

**Depending on the value of AEI in 2010, a percentage reduction requirement (0, 10, 15, or 20%) is set in the Directive. If AEI in 2010 is assessed to be over 22 μg/m³, all appropriate measures need to be taken to achieve 18 μg/m³ by 2020.

Source: http://ec.europa.eu/environment/air/quality/standards.htm

APPENDIX IV: Noise questionnaire's pilot study.

Table IV.1: Summary of the participants' opinion about the preliminary noise questionnaire

Variable [a]	N	Percent (%)
Is the questionnaire clear? If not, indicate the question and why.		
No	11	36.7
Yes	19	63.3
Did you have room to answer the questions? If not, indicate the question.		
Yes	29	96.7
No	0	0
Missing	1	3.3
Was the questionnaire long?		
No	29	96.7
Yes	1	3.3
Finally, could you please indicate if you live in a:		
High-road traffic area	6	20.0
Moderate-road traffic area	16	53.3
Low-road traffic area	4	13.3
Area with no road traffic at all	3	10.0
Missing	1	3.3

Variable [a]	N	Mean (SE [b])	Median	Minimum	Maximum
How long it took you to answer the questionnaire? (Missing=1)	29	5.9 (0.44)	5	3	10

[a] The variables have been translated from Catalan to English
[b] Standard error of the mean

APPENDIX V: Geographically weighted regression between modeled NO_2 and modeled L_{24h} at the residences of the study participants of Girona city.

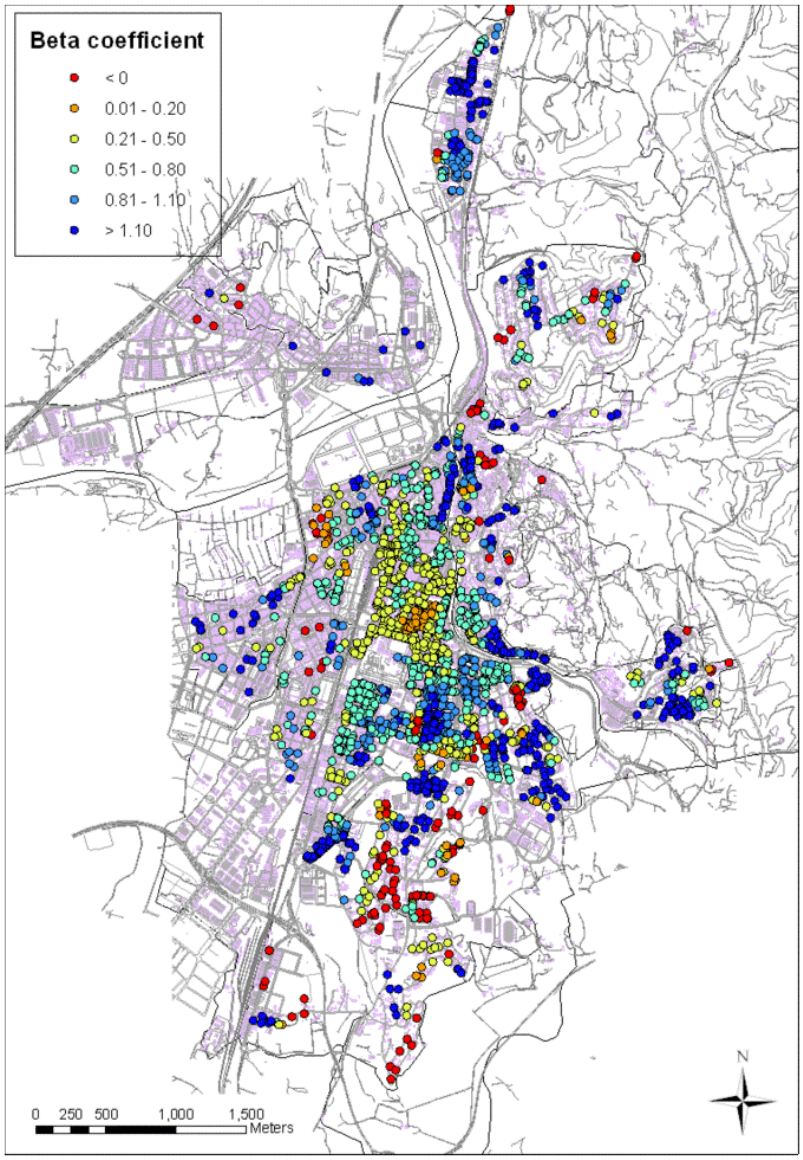

Figure V.1. Spatial variation of the beta coefficient based on a geographically weighted regression (Fotheringham, 2002) between modeled NO_2 and modeled L_{24h} at the residences of the study participants of Girona city.

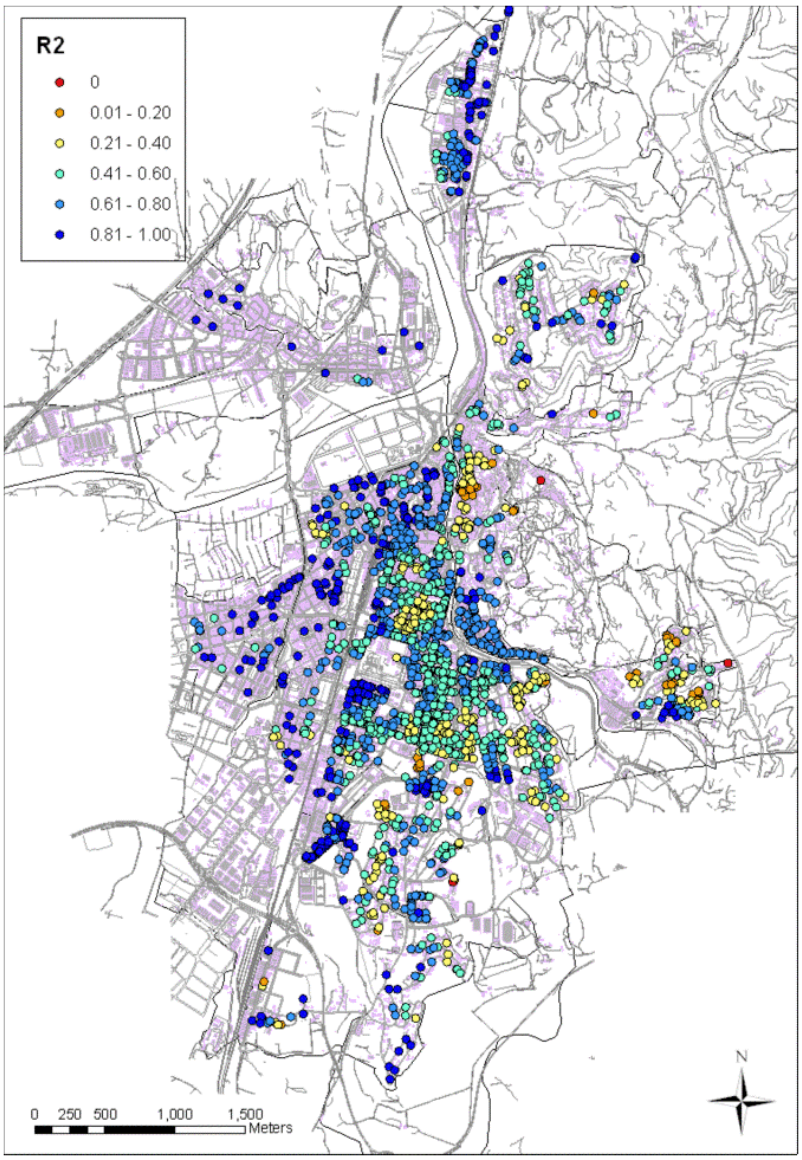

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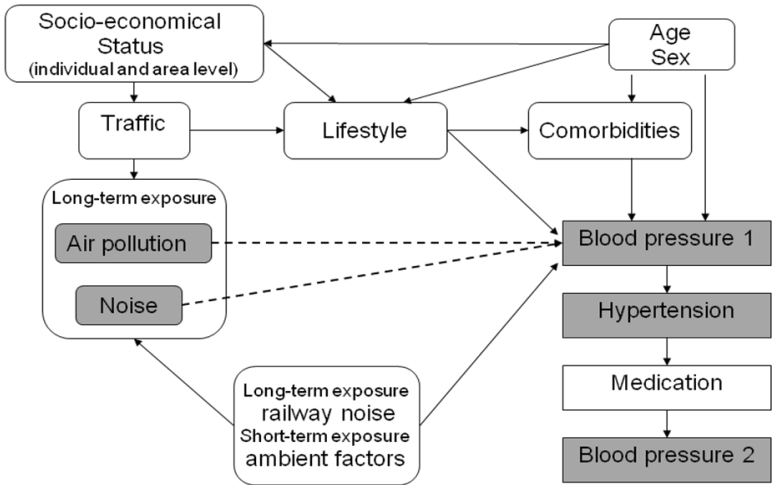
Figure V.2. Spatial variation of the coefficient of determination (R^2) based on a geographically weighted regression (Fotheringham, 2002) between modeled NO_2 and modeled L_{24h} at the residences of the study participants of Girona city.

APPENDIX VI: Directed Acyclic Graph (DAG) for the association of traffic noise and traffic-related air pollution with blood pressure



Adapted from Fuks et al. (2011)