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Traffic-related air pollution:

Exposure assessment and respiratory health effects

Doctoral dissertation

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Doctoral dissertation

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Abstract

Air pollution is a major public health concern causing annually 380 000 deaths in the European Union alone. It is now generally accepted that traffic-related air pollution is associated with adverse health effects. However there are still several issues that are not resolved and this thesis aims to fill some of the gaps regarding traffic-related air pollution exposure assessment and its association with respiratory health effects.

In epidemiology, a majority of studies use central measurements of air pollution concentrations and assume that all the subjects are exposed to those concentrations. It is necessary to validate that assumption in order to obtain accurate estimates of air pollution exposures when assessing adverse health effects of air pollution.

The relationship between outdoor and personal fine particulate matter (aerodynamic diameter $\leq$ 2.5 μm; $PM_{2.5}$), carbon (measured indirectly as absorbance) and sulphur content among post-myocardial infarction patients was assessed for the first time in a Southern European country. Outdoor and personal concentrations of sulphur, but not $PM_{2.5}$, were correlated; carbon levels were correlated only after excluding days with exposure to passive smoking. These findings support the use of central monitoring station concentrations to assess air pollution from exposure to combustion sources in epidemiological studies.

An alternative assessment of air pollution exposure was evaluated based on self-reported annoyance due to air pollution in a European study involving around 7000 subjects from 21 centres. High levels of annoyance were reported by 14% of the subjects. Moderate and heterogeneous associations between annoyance and background measures of pollution were found. Annoyance did not explain the home outdoor nitrogen dioxide (NO_2) variability even after adjusting for individual variables. However, we recommend its use as a marker of perceived ambient air pollution.

Association between traffic-related air pollution and asthma has been studied mainly in children and its role in the worsening of asthma symptoms and especially in new asthma onset in adults is still unclear.

In the same study mentioned above, self-reported traffic levels and outdoor NO_2 measured at subject's home were associated with asthma symptoms. Furthermore an association between incidence of asthma and home outdoor modelled NO_2 was

consistently positive, though not significant. The use of an asthma score based on symptoms, instead of a dichotomous definition, offered a new alternative to overcome misclassification and power problems in asthma incidence studies.
On the other hand, in a third study carried out in three European cities and with patients with cardiovascular disease, we showed that $PM_{2.5}$ from combustion might lead to an increase in the lung's epithelial barrier permeability.

Overall, present results reinforce that traffic-related air pollution is harmful, and policies should focus on new approaches for decreasing air pollution concentrations and therefore subjects' exposure.

Key words: Air pollution, traffic, $PM_{2.5}$, NO_2, exposure assessment, respiratory health, asthma

Resumen

La contaminación atmosférica es un problema de salud pública que causa más de 380 000 muertes, sólo en la Unión Europea. Actualmente, se sabe que la contaminación procedente del tráfico está asociada con efectos adversos en la salud, sin embargo aún hay cuestiones sin resolver. Esta tesis tiene como objetivo aportar nuevos conocimientos en dos de esas áreas en relación a la contaminación del tráfico: evaluación de la exposición y efectos sobre el tracto respiratorio.

En epidemiología, la mayoría de los estudios asumen que todos los sujetos están expuestos a las concentraciones de contaminación medidas por monitores centrales. Para evaluar los efectos de la contaminación en la salud, es necesario validar esa asunción para obtener estimadores adecuados de la exposición.

Se evaluó por primera vez en el sur de Europa, en pacientes sobrevivientes a infarto de miocardio, la asociación entre concentraciones exteriores y personales de material particulado fino (diámetro aerodinámico ≤ 2.5 μm; $PM_{2.5}$), así como de su contenido en carbón (medido indirectamente con absorbancia) y sulfuro. Las concentraciones de exteriores y personales de sulfuro, aunque no de $PM_{2.5}$, estaban correlacionadas y las de carbón solamente después de excluir los días con exposición pasiva a humo de tabaco. Estos hallazgos apoyan el uso de concentraciones ambientales centrales para evaluar la exposición a contaminación por fuentes de combustión en estudios epidemiológicos.

En un estudio europeo, que incluía aproximadamente 7000 sujetos de 21 ciudades, se propuso como una alternativa para evaluar exposición personal a contaminación el uso de molestia auto-reportada producida por la contaminación. Alrededor de 14% de los sujetos reportaron altos niveles de molestia. La asociación entre la molestia y los niveles de contaminación fue moderada y heterogénea entre los diferentes centros. La molestia tampoco explicó la variabilidad de niveles de dióxido de nitrógeno (NO_2) obtenidos para cada sujeto, aún después de ajustar por variables individuales. Sin embargo, recomendamos su uso como marcador de percepción de la calidad del aire.

En estudios anteriores, se ha sugerido una asociación entre la contaminación procedente del tráfico y el asma, sin embargo estos estudios se han hecho principalmente en niños y se han enfocado en la agudización de síntomas. El papel de la contaminación como causa del asma sigue sin respuesta.

En el mismo estudio mencionado anteriormente, el tráfico auto-reportado y los niveles de NO_2 medidos en el exterior de las casas se asociaron con síntomas de asma. También se observó una asociación, que aunque positiva no fue significativa, entre incidencia de asma y niveles exteriores de NO_2 modelizados para cada domicilio de cada sujeto. La utilización de una puntuación para medir asma basada en síntomas, en lugar de la definición dicotómica, ofrece la posibilidad de evitar sesgos y de aumentar el tamaño muestral facilitando el estudio de la incidencia de asma.

Por otra parte, en un tercer estudio europeo, llevado a cabo en tres ciudades y en sujetos con enfermedad cardiovascular, encontramos que la contaminación procedente de la combustión podría conllevar a la disminución de la permeabilidad de la barrera epitelial pulmonar.

Concluimos que la contaminación procedente del tráfico es dañina y se requieren políticas que tengan como objetivo disminuir los niveles de contaminación y, en consecuencia, la exposición de los sujetos.

Palabras clave: Contaminación atmosférica, tráfico, $PM_{2.5}$, NO_2, evaluación de la exposición, salud respiratoria, asma

Resum

La contaminació atmosfèrica és un problema de salut pública que causa més de 380 000 morts només a la Unió Europea. Actualment, se sap que la contaminació que prové del trànsit està associada amb efectes adversos sobre la salut, tanmateix encara queden preguntes sense resoldre. La present tesis té per objectiu aportar nous coneixements en dos d'aquests àmbits relacionats amb la contaminació per trànsit: avaluació de l'exposició i efectes sobre el tracte respiratori.

En epidemiologia, la majoria dels estudis assumeixen que tots els subjectes estan exposats a les concentracions de contaminació mesurades per monitors centrals. Per avaluar els efectes de la contaminació sobre la salut, és necessari validar aquesta assumpció per obtenir estimadors adequats de l'exposició.
Per primera vegada es va avaluar al sud d'Europa, en pacients que havien sobreviscut a infart de miocardi, l'associació entre concentracions exteriors i personals de material particulat fi (diàmetre aerodinàmic ≤ 2.5 μm; $PM_{2.5}$), així com el seu contingut en carbó (mesurat indirectament mitjançant l'absorbància) i sulfur. Les concentracions exteriors i personals de sulfur, però no de $PM_{2.5}$, estaven correlacionades i les de carbó tan sols després d'haver exclòs els dies corresponents amb exposició passiva a fum de tabac.
Aquests resultats van a favor de l'ús de concentracions ambientals centrals per avaluar l'exposició a contaminació procedent de la combustió en estudis epidemiològics.
En un estudi europeu, que incloïa aproximadament 7000 subjectes de 21 ciutats, es va proposar com una alternativa per tal d'avaluar l'exposició personal a la contaminació l'ús de la molèstia auto-percebuda generada per la contaminació. Al voltant del 14% dels subjectes van reportar alts nivells de molèstia. L'associació entre la molèstia i els nivells de contaminació va ser moderada i heterogènia entre els diferents centres. La molèstia tampoc explicava la variabilitat dels nivells de diòxid de nitrogen (NO_2) obtinguts per cada subjecte, tot i haver ajustat posteriorment per les variables individuals. Tanmateix, recomanem el seu ús com a marcador de percepció de la qualitat del aire.

En anteriors estudis, s'ha suggerit una associació entre la contaminació que prové del trànsit i l'asma, tanmateix aquests estudis s'han realitzat principalment en nens i s'han

focalitzat en la agudització de símptomes. El paper de la contaminació com a causa de l'asma segueix encara sense resposta.

En el mateix estudi citat anteriorment, el trànsit auto-percebut i els nivells de NO_2 mesurats a l'exterior de les cases es van associar amb símptomes de asma. També es va observar una associació, que tot i que positiva no va ser significativa, entre la incidència d'asma i nivells exteriors de NO_2 modelats per a cada un dels domicilis dels diferents subjectes. La utilització d'una puntuació per tal de mesurar l'asma basat en els símptomes, enlloc de la dicotòmica, ofereix la possibilitat d'evitar biaixos i d'augmentar el tamany mostral facilitant així l'estudi de la incidència d'asma.
D'altra banda, en un tercer estudi europeu, dut a terme en tres ciutats i en subjectes amb malalties cardiovasculars, vam trobar que la contaminació procedent de la combustió podria dur a la disminució de la permeabilitat de la barrera epitelial pulmonar..

Concloent, la contaminació procedent del trànsit és perjudicial, i es requereixen polítiques que tinguin per objectiu disminuir els nivells de contaminació i per tant l'exposició dels subjectes.

Paraules clau: Contaminació atmosfèrica, tràfic, $PM_{2.5}$, NO_2, avaluació de l'exposició, salut respiratòria, asma.

Abbreviations

ABS	absorbance, i.e. absorption coefficient
CI	confidence interval
CV	coefficient of variation
ED-XRF	energy-dispersive X-ray fluorescence
EU	European Union
GAM	generalized additive models
GLS	generalized least square
ME	multilinear engine
MI	myocardial infarction
NO	nitric oxide
NO_2	nitrogen dioxide
PCA	principal component análisis
OR	odds ratio
PM	particulate matter
$PM_{2.5}$	fine particulate matter, aerodynamic diameter $\leq$ 2.5 μm
PM_{10}	thoracic particulate matter, aerodynamic diameter $\leq$ 10 μm
RMS	Ratio of the mean scores
RR	risk ratio
SD	standard deviation
SE	standard error
SES	socio-economical status
TSP	total suspended particulate matter
WHO	World Health Organization

List of original publications:

This thesis is based on the following original articles:

1. Jacquemin B, Lanki T, Sunyer J, Cabrera L, Querol X, Moreno N, Pey J, Pekkanen J. Levels of outdoor $PM_{2.5}$, absorbance and sulphur as surrogates for personal exposures among post-myocardial infarction patients in Barcelona, Spain. Atmos Environ 2007; 41(7):1539-1549
2. Jacquemin B, Sunyer J, Forsberg B, Götschi T, Bayer-Oglesby L, Ackermann-Liebrich U, de Marco R, Heinrich J, Jarvis D, Torén K, Künzli N. Annoyance due to air pollution in Europe. Int J Epidemiol 2007; doi: 10.1093/ije/dym042
3. Jacquemin B, Sunyer J, Forsberg B, Götschi T, Vienneau D, Briggs d, Heinrich J, Torén K, Künzli N. Association between annoyance and individual's values of NO_2 in a European setting. "Submitted to Journal of Epidemiology and Community Health"
4. Forsberg B, Jacquemin B, Garcia-Esteban R, Götschi T, Järvholm B, Heinrich J, Sunyer J, Künzli N. Air pollution and asthma in ECRHS. "Submitted to European Respiratory Journal"
5. Jacquemin B, Sunyer J, Forsberg B, Götschi T, Vienneau D, Briggs D, García-Estbán R, Heinrich J, Jarvholm B, Künzli N. Home outdoor NO_2 and new onset of asthma in adults. "Submitted to Epidemiology"
6. Jacquemin B, Lanki T, Yli-Tuomi T, Vallius M, Hoek G, Peters A, Timonen K, Pekkanen J. Source-specific $PM_{2.5}$ and urinary levels of Clara cell protein CC16. The ULTRA study. "Submitted to Occupational and Environmental Medicine"

I Introduction

Air pollution is a major public health concern because it is a non-avoidable environmental risk for many people due to a world-wide traffic increase, expansion of cities and industrialization. WHO has calculated that outdoor air pollution is responsible for more than 800 000 premature total deaths per year, out of those 348 000 occur in the 25 member states of the European Union. WHO has estimated that the burden of outdoor air pollution on total mortality is 1.4% and 3% on cardio-respiratory mortality. The annual rate of attributable emergency respiratory hospital admissions is 7.03 (95%CI 3.83-10.30) per 10 $\mu g.m^{-3}$ PM_{10}[1].

The history of air pollution epidemiology probably started with the London fog episode[2;3]. Thereafter, it was assumed that only exposure to high concentration of air pollutants was associated with mortality[4-6]. Since then a long journey has been accomplished and currently it is accepted that air pollution is not only associated with mortality at high concentrations, but it is also associated with acute and chronic effects on disease, mainly respiratory and cardiovascular, at low concentrations[7-17]. No safe threshold of air pollutant levels has been identified[1].

1. Air pollution sources and composition

Air pollution has many sources; they can be anthropogenic or natural. In Europe transport contributes to around 25% of PM and about 40% of emissions of NO_2[1;18].

1.1 PM2.5

PM denotes to the solid and liquid particles found in the air. PM, also called particles, is actually a complex mixture of diverse components that can vary spatially and temporally. It can be classified in several ways. First as primary or secondary depending on whether the particles are directly emitted into the atmosphere or whether they are formed from precursor gases. Then, particles are classified by their size. They can go from few nanometres (ηm) to tens of micrometers (μm) in diameter. In epidemiology, particles have been traditionally classified using the aerodynamic diameter because this determines their transport in the atmosphere as well as their likelihood and site of deposition into the respiratory tract. Particles are divided in PM_{10} (aerodynamic diameter $\leq$ 10μm), $PM_{2.5}$ (aerodynamic diameter $\leq$ 2.5 μm) and $PM_{0.1}$ (aerodynamic

diameter smaller than 0.1μm), and they are referred as thoracic particles, fine particles and ultrafine particles, respectively. In addition, coarse particles go from 2.5 to 10 μm and Total Suspended Particles (TSP) denotes the total. Fine and thoracic particles contribute more to the total mass and ultrafines contribute more to the total count[19].

There are numerous sources of particles. They can be natural or anthropogenic. It has been suggested that in urban sites in developed countries more than two thirds of the particles are anthropogenic. The most common sources of $PM_{2.5}$ in urban sites are traffic, long-range transport and crustal[20-23]. Other common sources are oil combustion, biomass combustion, sea salt and industry. The proportion of each source into the total $PM_{2.5}$ depends on the characteristics of the location, which can include natural ones such as the inherent geographical location (coast, desert, winds, etc) and human ones as population density, industry, level of urbanization, type of vehicular fleet, etc.

Tracing of the sources of $PM_{2.5}$ is complex. First, elemental composition has to be determined but there are almost no sources with a unique "key" element. For traffic, lead used to be a very useful marker but since it has been banished from gasoline no unique element for traffic exists. Nowadays the elements used to identify traffic sources usually include copper (Cu), zinc (Zn), lead (Pb), bromine (Br), iron (Fe), calcium (Ca) and barium (Ba)[21-23]. Black carbon and absorbance measured on $PM_{2.5}$ filters are also good markers of combustion, and can help to identify traffic sources[24-27]. Traffic not only contributes to PM by the combustion of fuel or oil, but also by the wear of the car parts such as brakes, tyres, bearings, car body, etc. and also with the wear of the road and resuspension of road and soil dust[22;23].

1.2 NO_2

NO_2 is a reddish-brown gas with a pungent odour. It can be emitted directly to the atmosphere as NO_2 or transformed to NO_2 from nitric oxide (NO) when exposed to air. Actually, in most ambient situation NO_2 is emitted as NO and almost immediately transformed to NO_2. NO_2 is a strong oxidant that promotes several chemical reactions that play an important role in the atmosphere. NO_2 can contribute to impaired atmospheric visibility by absorbing solar radiation, thus contributing to global warming. It also regulates the oxidizing capacity of the troposphere and therefore it determines the ozone concentration in the troposphere. NO_2 forms secondary nitrate aerosols[28;29].

NO_2 also has natural and anthropogenic sources. Natural sources by far exceed the human ones on a global scale. The most common natural sources are intrusion of

stratospheric nitrogen oxides, bacterial and volcanic action, and lightning. The most important anthropogenic sources are those from combustion processes. They can be stationary (heating, power plants) or mobile (combustion from vehicles). Indoor sources are also important and they include, among others, smoking or cooking[29].

In epidemiological studies, NO_2 has widely been used as a marker of traffic because traffic is probably its main outdoor source in urban settings and because of the low cost and logistic advantages of NO_2 measurements, compared to the measurements of other pollutants[29-33].

2. Air pollution exposure

"Exposure to an environmental (…) substance is generally defined as any contact between a substance in an environmental medium (e.g. water, air, soil) and the surface of the human body (e.g. skin, respiratory tract); after uptake into the body it is referred to as dose"[34].

In epidemiological studies, it is very important to count on a reliable exposure in order to correctly evaluate the risks due to air pollution. However, even if exposure to air pollution is closely related to the concentration of air pollutants, it also depends on other factors, such as the distribution of pollutants in the atmosphere or where people spend their time. The assessment of the population's exposure to traffic-related air pollution is complicated and still presents some gaps.

2.1 Estimation of air pollution exposure

Air pollution concentrations are regulated and/or reported in annual, daily or hourly averages. The guidelines usually suggest annual mean and maximum 24-hour mean concentrations. The availability of such measurements depends on the characteristics of the pollutant and on the device with which it is measured.

2.1.1 Central fixed monitors

The fixed site monitoring stations are categorized in traffic, industrial or background. They can be located in urban, suburban or rural zones. The category depends on their proximity to the sources, those being mainly high-traffic roads in most cities[35]. Usually, several stations of the different categories are located in each urban setting althoug regulations tend to be based on background stations. The location of the

monitoring stations, in relation to both the sources and the population, also has to be taken into account in epidemiological studies, as they may affect the accuracy of the estimates and the comparability of the results between different cities[36]. Monitoring stations give concentrations, not exposure levels. In epidemiology, central levels are often used as a marker of exposure to air pollution, using the concentrations at regional, city or neighbourhood level. However, this approach has several limitations as it assumes that all the subjects in the same area are exposed to the same levels. Furthermore, it does not take into account spatial variability of air pollution nor the different characteristics among the individuals.

2.1.2 Individual measurements

As opposed to central measurements that are mainly used for regulatory purposes, individual measurements are usually used for research. Two different individual measurements may be undertaken: monitoring at subject's home (and rarely at his/her work place); or personal monitoring.

The measurement at the subject's home gives an opportunity to have an individual value for each subject. The personal measurements are probably the most accurate way to assess individual air pollution exposure, but they require devices with special characteristics such as light weight devices, quiet and long-lasting batteries. Furthermore, personal monitoring is very expensive and is rarely done in large populations[37].

2.1.3 Questionnaires and modelling

Questionnaires are an alternative way to assess self-reported exposure to air pollution. They may include information ranging from reported traffic in front of or close to home, to a specific description of activity patterns. The combination of the information collected could give estimates of exposure. However, as all information is collected through a questionnaire, it is susceptible to suffer from several biases[38;39].

Modelling is a relatively new and promising tool to assess air pollution exposure due to the expansion of the Geographic Information Systems (GIS) into the field of exposure analysis. Several levels of complexity and data demand exist in the modelling of air pollution exposure. Interpolation methods (like inverse distance weighting or kriging) typically model an air pollution surface based only on monitoring data from several locations. Source-based models generate measurements of information from the sources

and vary from a simple approach (source-proximity measures) to a more complex one (dispersion models). Land use regression models use traffic, geographic and air pollution data to build models which may be used to predict air pollution at unmeasured sites (i.e. subjects' home addresses). A more recent approach is the use of time-space models, which take into account the time spent by the subject in different environments and the spatial and temporal variations of air pollution levels. However, adequate information is not always available on source emissions, environmental measurements, geographic variables or time-activity patterns[40;41].

2.2 PM2.5 exposure assessment

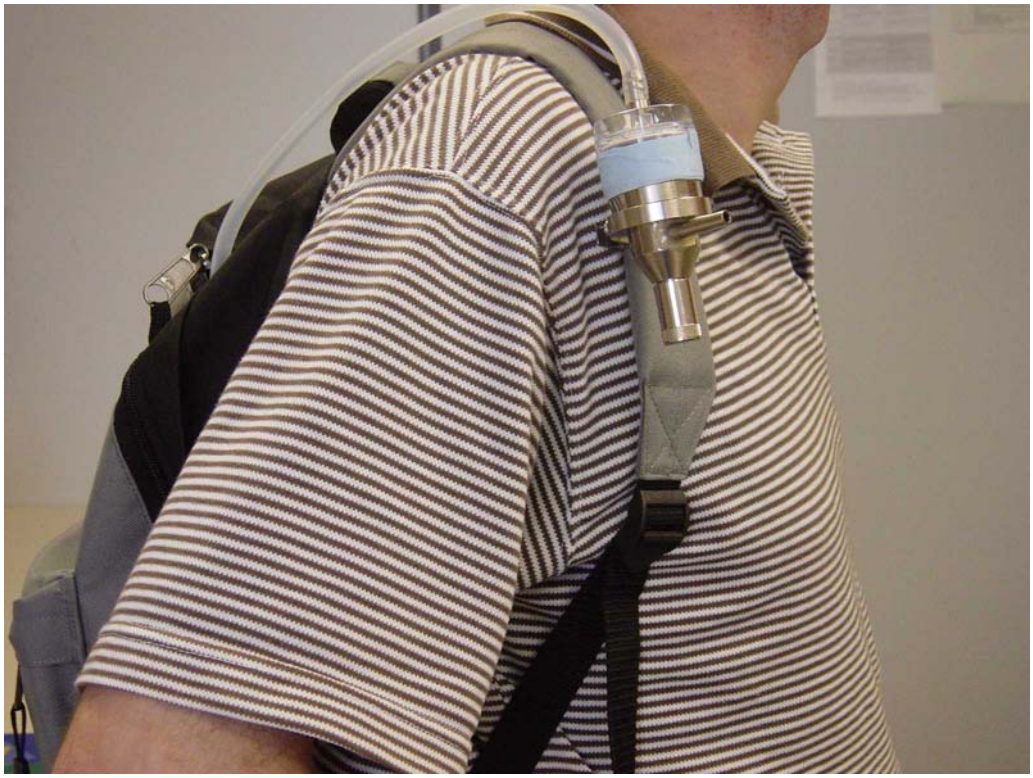
The routine measurement of PM started with TSP, then with PM_{10} and only a few years ago with $PM_{2.5}$. The measurement of $PM_{2.5}$ has not been regulated in the EU and suggested maximum levels appeared for the first time in the 2005 European guidelines[1].

Measurement of $PM_{2.5}$ may usually be done with two different methods: continuous or gravimetric. The first one refers to the continuous measurement of the particles and it may be performed weighing the particles on near real time with a tapered element oscillating microbalance or measuring the volume concentration with indirect optical methods that are then transformed into mass. The gravimetric method is the gold standard. It consists in pumping the air through a selective size inlet and then collecting the mass on a filter. Then, the mass accumulated on the filter is weight and transformed into concentration, based on the pump flow and the duration of the collection phase.

Both technologies are available for central fixed site monitoring, as well as for individual measurements (Figure 1). Several studies have shown a high correlation between central and individual measurements even if the individual concentrations are 2 to 3 times higher than the central outdoor concentrations. The correlation was better when assessing only the combustion components or the sulphates of the $PM_{2.5}$ that do not have typical indoor sources. It is usually believed that personal or indoor sources (with the exception of smoking or specific combustion processes) are harmless.

The individual exposure assessment of total $PM_{2.5}$ trough questionnaire and/or GIS is complicated due to the high variability of sources, temporal, spatial and geographical patterns of the particles and the lack of studies validating those.

Figure 1: Personal $PM_{2.5}$ sampling device



2.3 NO2 exposure assessment

NO_2 has been routinely measured in developed countries for several years, it is regulated by the EU since the 90's. It is also widely used as a marker of traffic in urban sites. NO_2, as other gaseous pollutants, may be measured continuously or with passive samplers. For the continuous measurements several methods are available, but the most widely used and accepted is ozone chemiluminescence[42]. The passive samplers operate by diffusing the gas from the atmosphere across the sampler volume, usually an inverted tube, to a sink or chemical absorbent. Rate of gas absorption is controlled by the diffusion path length and the internal cross-sectional area of the sampler. The concentration of the gas is based on the time the sampler has been exposed in the ambient[43].

Usually continuous measurements are used for central monitoring and passive samplers for individual measurements. Passive samplers are small, light and do not require batteries or special handling, thus they allow the measurement of NO_2 at individual level much easier than for $PM_{2.5}$.

The modelling of NO2 concentrations is more and more frequently used, particularly at the intra-urban level. The fact that the passive samplers are easy to use and not too expensive has permitted validating the technique in different settings[44].

3. Effects of air pollution on respiratory system

It is now widely accepted that outdoor air pollution is one of the environmental issues of major concern in both developed and developing countries due to its ubiquity and to the severity of its effects (Figure 2). Adverse health effects have been reported for short and long term exposure, even at relatively low levels of air pollution. Air pollution has been associated mainly, but not exclusively, with respiratory and cardiovascular adverse effects[10;14].

The respiratory tract is the main way of entrance of air pollution into the organism. The pathophysiological pathways of air pollution damage in the lung are not completely clear yet. Furthermore, it is difficult to separate the effects of the different pollutants, as they are usually correlated and probably interact among themselves[29].

3.1 Effects related to PM2.5

Particles have been categorized according to their size in relation to their site of deposition in the respiratory tract[19]. $PM_{2.5}$ is small enough to deposit on the alveoli[45] where the clearing mechanisms are less developed and less efficient than in the upper airways[46].

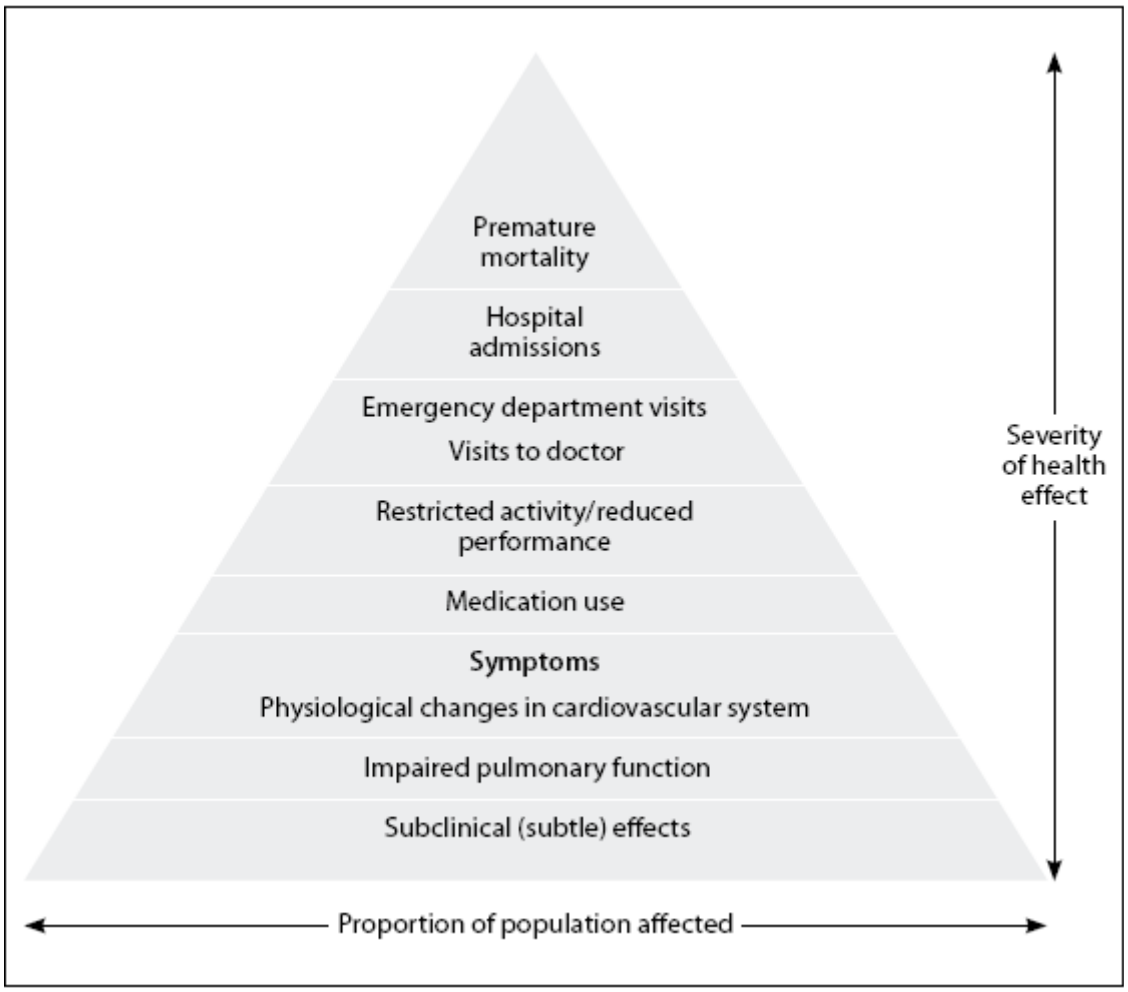
3.1.2 Mechanisms

The most accepted mechanisms of lung damage caused by PM are inflammation, exacerbation of pre-existing airway disease and reduction of the defence capacity increasing the susceptibility to infections[47]. However, of the three, probably the most relevant is inflammation that is closely linked to the other two. Inflammation is mainly due to oxidative and nitrosative stress that could lead to antioxidant depletion, mitochondrial damage and even apoptosis[48-54]. It has also been suggested than PM could cause direct and indirect genotoxicity[55-61]. The reactive oxidative specied formation has demonstrated to increase the macrophages activity and the production of IL6, resulting in an increase of fibrinogen protein, coagulability and decrease of the heart frequency variability[62;63]. Genes involved in the metabolism of antioxidants have been demonstrated to play an effect modification role with air pollution[62].

The mechanisms of how air pollution could cause asthma exacerbations follow the same pathways listed above, involving in addition allergic sensitization[64;65]. Toxicity of the different elements of PM still needs further investigation as there are still issues to be

clarified, especially regarding source-specific $PM_{2.5}$, gene-environment and environment-environment interactions and also when assessing long term exposure.

Figure 2: Pyramid of health effects associated with air pollution

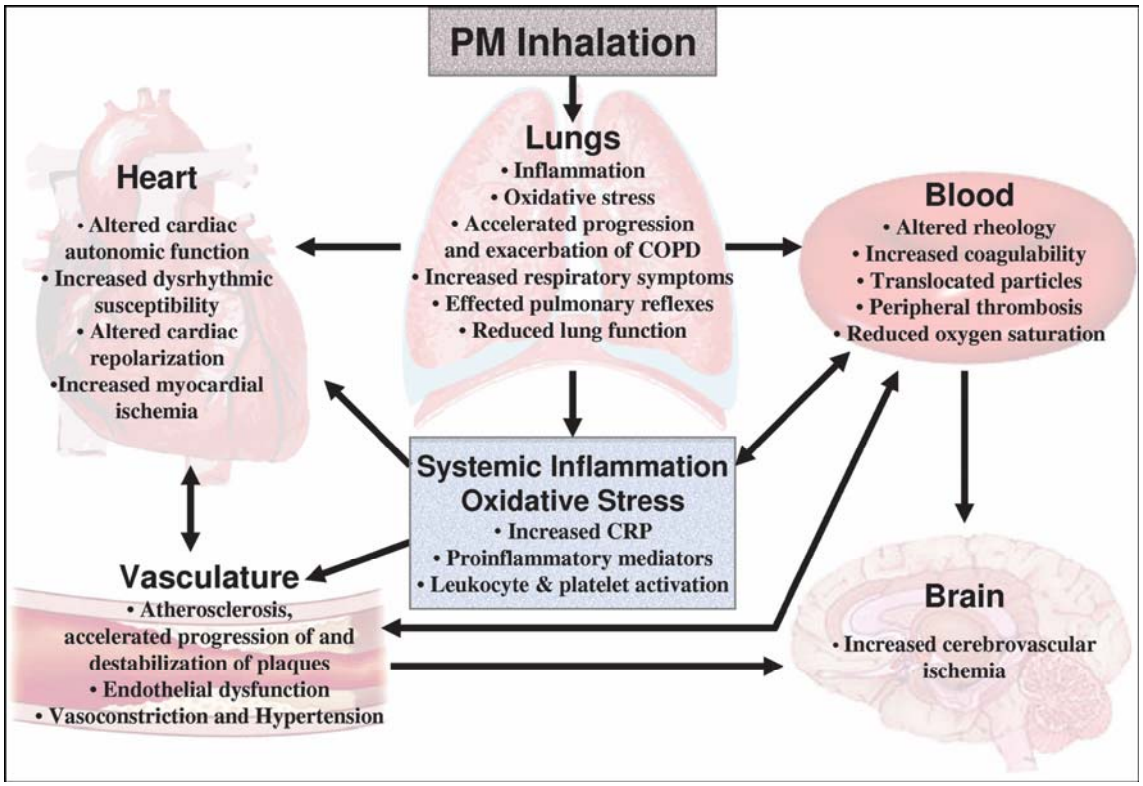


Source: American thoracic society[66]

3.1.2 Health effects

PM exposure in human experimental studies are inconsistent and present several limitations[67]. One of them is that PM is a fluctuating mixture of so many components that is difficult to reproduce and even concentrating the outdoor air could alter the characteristic of the PM. However, several studies have found health effects associated with concentrated ambient particles, including pulmonary inflammation, decreased arterial oxygenetation and light changes in respiratory function tests[68].

Figure 3: Potential general pathophysiological pathways linking PM exposure with cardiopulmonary morbidity and mortality



Source: Pope and Dockery JAWMA 2006[14]

In epidemiological studies, daily PM concentrations has been consistently associated with acute increase of cardiopulmonary mortality, and increase of emergency admissions for myocardial infarction, asthma and COPD exacerbation[14;69-73]. In cohort studies, fine particles have been associated with a reduced survival mainly due to increase on lung cancer, and cardiopulmonary diseases[7;12;74-78].

Whereas it is accepted that fine particles are related with an increase of exacerbations among asthmatics, the role in asthma onset is more contradictory. Several panel and cohorts studies in children have recently shown an increase of asthma diagnosis in relation to proximity to traffic, but there are scarce data among adults.

3.2 Effects related to NO2

When inhaling, 70-90% of NO_2 may be absorbed from the respiratory tract but from 40 to 50% could be removed in the nasopharynx. Thus, when breathing with the mouth (e.g. because of exercise) the amount of NO_2 reaching the lower respiratory tract increases[29].

3.2.2 Mechanisms

The toxic effect of NO_2 on the human respiratory tract at levels in the urban atmospheres are less important than for other gases such as ozone or particles. At experimental level, as a free radical, NO_2 has the capacity of depleting the antioxidants of the lung tissue, causing subsequent injury and inflammation. Using animal or in vitro models, NO_2 produces eosinophilic inflammation, enhances epithelial damage, reduces mucin expression and increases baseline smooth muscle tone[79-82]. Repeated exposure to high doses of NO_2 is associated to increased breath frequency and decreased lung distensibility and gas exchange[83-85]. It has also been described that NO_2 decreases bactericidal activity and alveolar macrophage activity[79;86;87].

However, it is important to note that the extrapolation of those findings to human exposures at real life levels should be made with precaution.

3.1.2 Health effects

Clinical studies have shown that in subjects with pre-existing lung disease, acute exposure to high NO_2 concentrations is associated with changes in the pulmonary function, the asthmatics being the most responsive[88-92]. Studies looking at changes in respiratory function tests at low concentrations or in healthy adults are inconsistent. It has also been described that NO_2 exposure could enhance bronchial responsiveness and provoke inflammation in the airways, especially in subjects with asthma, the latter observed as increased inflammatory cell counts in bronchoalveolar lavage fluid[93-102].

In epidemiological studies, it has been suggested that NO_2 is associated with mortality and morbidity; however it is difficult to disentangle NO_2 from PM effects as both pollutants are highly correlated. Short NO_2 exposure has also been associated with asthma exacerbations in children[103], but few studies have looked at such association in adults[104;105]. The role of NO_2 in new asthma has been suggested[104;106-109].

The use of NO_2 in epidemiological studies is mostly as a surrogate of the traffic pollution mixture, rather than to assess its own toxic effect.

II. Studies involved in the thesis

This thesis involves three different European projects that are briefly summarized below describing mainly the study population and the methodology of the measurements of air pollution.

1. European Community Respiratory Health Survey (ECRHS)

The ECRHS is a European project whose objective was to estimate the variation in the prevalence, exposure, risk factors and treatment of respiratory diseases, and especially asthma, in young to middle age adults living in Europe; air pollution being one of the risk factors with major interest. The ECRHS was carried out in twenty-eight urban centres, in eleven European countries. It was first conducted in 1991-3 and repeated in 1999-2001. Centres were chosen by convenience. Subjects were randomly selected from the populations aged 20-44 in 1991-3. A questionnaire on respiratory health and potential risk factors was applied to all the participants as well as allergies, lung function and bronchial responsiveness tests[110;111].

Air pollution was assessed only at the follow-up in three different ways:

Central monitoring:

These measurements are available for 21 centres from a 12 month measurement campaign. Between June 2000 and December 2001, at a central monitoring site, 7 days were sampled over a two-week period during each month, using identical equipment and procedures in each centre. Elemental content on $PM_{2.5}$ filters was analysed using energy dispersive X-ray fluorescence spectrometry (ED-XRF)[25;112;113].

Home outdoor NO_2 measurements:

Measurements of NO_2 as a marker for local tail pipe emissions were made at the homes of a subset of participants. At this individual level, outdoor (at the kitchen, or bedroom when kitchen was not available, window) and kitchen indoor NO_2 concentrations were collected during a 14 day period in 16 centres during 2001, involving around 2050 households of subjects who did not move house during the follow up. After about six months this procedure was repeated in 40% of the households. Values below limits of detection were set at half the detection limit (0.34 $\mu g.m^{-3}$) and values above 150 (maximum 180) $\mu g.m^{-3}$ were set to 150 $\mu g.m^{-3}$. The passive samplers (Passam AG, Switzerland) were analysed in a central laboratory. For subjects with two measurements the mean of the two was calculated[114].

Individual modelled concentrations:

Modelled NO_2 derived from the EU-funded APMoSPHERE (Air Pollution Modelling for Support to Policy on Health and Environmental Risks in Europe). As part of APMoSPHERE 1-km-resolution emission maps of several pollutants, including NO_2, were developed for the then member states (EU15). Estimates were obtained by disaggregating national emissions estimates, categorised by sources of air pollution (SNAP categories), to the 1 km level on the basis of relevant proxies (e.g. population density, road distribution, land cover). Modelling of NO_2 concentrations was then done using focal sum techniques, in a GIS, to relate emissions within concentric zones around each monitoring site to the monitored concentrations. Models were developed using monitoring data from 714 background sites for 2001, drawn from the EU Airbase database. Validation was conducted by comparing predictions with observations for a separate set of 228 sites ($r^2 = 0.60$)[115].

2. MOCHILA within AIRGENE (Air pollution and inflammatory response in myocardial infarction survivors: gene-environment interactions in a high-risk group)

The main objectives of AIRGENE were to assess inflammatory responses in association with ambient air pollution concentrations in myocardial infarction survivors in six European cities and to define susceptible subgroups of myocardial infarction survivors based on genotyping. For the AIRGENE, 200 patients were recruited in each location. The patients were myocardial infarction survivors, with no chronic inflammatory diseases, aged between 35 and 80 years. The baseline visit included a questionnaire, some clinical tests and a blood sample extraction. The six follow-up visits included a short questionnaire and a blood sample extraction. Among the 187 Barcelona subjects, 37 were randomly recruited in the baseline visit for personal $PM_{2.5}$ samplings[116].

Central monitoring:

The outdoor $PM_{2.5}$ measurements were conducted using two devices: the first one was the personal measurement system and the second one was a high volume pump. The high volume sampler is used routinely to measure $PM_{2.5}$. The samplers were located on a 2nd floor terrace of a research institute in the centre of a university campus, 8 meters above street level and 125 meters from one of the avenues with the highest road traffic

density of Barcelona (Diagonal Av.). Thus, the central site is an urban background monitoring station, with a high influence of traffic[116].

Personal measurements:

Personal $PM_{2.5}$ exposure was measured 24 hours before each visit, with a low flow pump. The pump and the batteries were placed in a backpack; the cyclone was attached to the strip of the pack. The participants were instructed to carry the backpack with them as closely as possible. Participants were asked to record the type and duration of the activities conducted when not carrying the measurement system, and the place where it was kept during the activity.

3. Exposure and risk assessment for fine and ultrafine particles in ambient air (ULTRA)

ULTRA was carried out in three cities during the winter period: in Amsterdam (Netherlands) from November 1998 to June 1999, in Erfurt (Germany) from October 1998 to April 1999 and in Helsinki (Finland) from November 1998 to April 1999. The main objective of ULTRA was to study the effects of air pollution in a high risk subgroup of patients with cardiovascular disease. In each city, elderly subjects with stable coronary heart disease were followed biweekly for six months, and during each visit a clinical examination was performed, and daily symptoms and medication were recovered through diaries. The clinical examination included the collection of a urinary sample, a spirometric exam and an ECG. In Amsterdam 37 subjects were recruited, and 47 in both Erfurt and Helsinki[117].

Central monitoring and source apportionment

During the study period PM and gaseous components were monitored according to a SOP. Locations of the monitors were chosen such that they would be representative of urban background air pollution in each city. $PM_{2.5}$ filters were collected daily from noon to noon with a single stage Harvard Impactor and particle concentrations were measured gravimetrically. After the filters had been weighed their blackness was assessed using reflectometry, used as surrogate for elemental carbon. All $PM_{2.5}$ filters were analysed for elemental composition with energy dispersive X-ray-fluorescence spectrometry[117]. The sources of $PM_{2.5}$ were resolved using two methods principal component analysis (PCA)[118] and Multilinear Engine (ME)[119].

III Rationale

There are still many questions to be answered. First of all, measurement of the exposure to air pollution is complicated and still not resolved. On the other hand, air pollution is a complex mixture of gases and aerosol particles that may have health effects per se, but that may also interact among themselves and furthermore interact with other environmental and genetic factors. Even if it is now widely assumed that air pollution is associated with adverse health effects, its role in more specific diseases and in specific populations still needs further investigation. In addition, the mechanisms of air pollution damage on the organism are still not completely understood.

The thesis presented here aims to answer some of those questions. It focuses on traffic-related air pollution and especially on $PM_{2.5}$ and NO_2 in Europe.
Epidemiological studies on traffic air pollution effects have generally used fixed site central measurements and have assumed that the population is exposed to the same concentration or to the same variations. There is need to validate that assumption and to implement individual exposure surrogates.
On the other hand, there is little epidemiological information on the role of traffic-related air pollution on asthma in adults.

IV Objectives

1. General

1. To assess the validity of central outdoor measurements or self-reported annoyance to estimate personal exposure to air pollution
2. To assess the association between air pollution and respiratory effects in adults

2. Specific

1. to assess the temporal relationship between outdoor and personal levels of $PM_{2.5}$, absorbance, and sulphur among survivors of a myocardial infarction in Barcelona, Spain
2. to describe the personal and socio-demographic determinants of annoyance due to air pollution and to assess its association with central measurements of air pollution
3. to assess the association between reported annoyance due to air pollution and individual outdoor levels of NO_2
4. to investigate whether asthma incidence and asthma-related symptoms are associated with $PM_{2.5}$ mass concentration or sulphur content of $PM_{2.5}$ and with traffic-related pollution at home outdoors
5. to assess the association between modelled NO_2, used as a marker of traffic air pollution, and new onset of asthma in adults
6. to test whether source-specific $PM_{2.5}$ or absorbance was associated with Clara Cell protein CC16

Levels of outdoor $PM_{2.5}$, absorbance and sulphur as surrogates for personal exposures among post-myocardial infarction patients in Barcelona, Spain.

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Levels of outdoor $PM_{2.5}$, absorbance and sulphur as surrogates for personal exposures among post-myocardial infarction patients in Barcelona, Spain

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Abstract

Outdoor levels of fine particles ($PM_{2.5}$; particles <2.5 μm) have been associated with cardiovascular health. Persons with existing cardiovascular disease have been suggested to be especially vulnerable. It is unclear, how well outdoor concentrations of $PM_{2.5}$ and its constituents measured at a central site reflect personal exposures in Southern European countries. The objective of the study was to assess the relationship between outdoor and personal concentrations of $PM_{2.5,}$ absorbance and sulphur among post-myocardial infarction patients in Barcelona, Spain.

Thirty-eight subjects carried personal $PM_{2.5}$ monitors for 24-hrs once a month (2-6 repeated measurments) between November 2003 and June 2004. $PM_{2.5}$ was measured also at a central outdoor monitoring site. Light absorbance (a proxy for elemental carbon) and sulphur content of filter samples were determined as markers of combustion originating and long-range transported $PM_{2.5}$, respectively.

There were 110, 162 and 88 measurements of $PM_{2.5}$, absorbance and sulphur, respectively. Levels of outdoor $PM_{2.5}$ (median 17 $\mu g/m^3$) were lower than personal $PM_{2.5}$ even after excluding days with exposure to environmental tobacco smoke (ETS) (median after exclusion 27 $\mu g/m^3$). However, outdoor concentrations of absorbance and sulphur were similar to personal concentrations after exclusion of ETS. When repeated measurements were taken into account, there was a statistically significant association between personal and outdoor absorbance when adjusting for ETS (slope 0.66, p <0.001), but for $PM_{2.5}$ the association was weaker (slope 0.51, p=0.066). Adjustment for ETS had little effect on the respective association of S (slope 0.69, p <0.001).

Our results suggest that outdoor measurements of absorbance and sulphur can be used to estimate both the daily variation and levels of personal exposures also in Southern

European countries, especially when exposure to ETS has been taken into account. For $PM_{2.5}$, indoor sources need to be carefully considered.

Key words: exposure, fine particles, air pollution, elemental carbon, cardiovascular disease

I Introduction

Epidemiological studies have established an association between ambient particulate matter and cardiorespiratory health[1;2]. In most of the studies, outdoor measurements at central site(s) have been used to estimate particle exposure, in some cases taking into account the distance between subjects' homes and main roads[3] or individual patterns of daily activity (4). More reliably exposure to particles can be assessed using indoor or personal measurements. However, these kinds of measurements are not feasible in large epidemiological studies. Nevertheless, it is important to assess the associations between outdoor measurements and personal exposures, in order to ensure that if a relationship is found between health and outdoor concentrations of a pollutant, the association is also true for actual exposure.

Elderly persons with compromised health are more vulnerable to the effects of air pollution than general population[5-7]. The use of outdoor levels of particulate air pollution to estimate exposures among these population subgroups has been questioned, partly because they tend to spend more time at home and elsewhere indoors than general population[8]. Exposure studies have found quite varying correlations between outdoor and personal fine particles ($PM_{2.5}$; particles <2.5 μm) concentrations among elderly and diseased subjects, but in general the longitudinal correlations have been considerable[9-13]. In epidemiological time series studies the focus is on this temporal, within-subject variation in exposure and its association with the daily variation in health.

It has been suggested that combustion particles are especially harmful for cardiovascular health[14;15]. Elemental carbon indicates combustion particles, especially diesel particles in urban settings[16], but common methods to measure it are expensive and require destruction of the filter. The light absorption (absorbance (ABS)) of particulate matter on the filter has been used as its surrogate[17]. The few studies that

have measured ABS have shown a good longitudinal correlation between personal and outdoor measurements[18].

The aim of the study was to assess with repeated measurements the relationship between outdoor and personal levels of $PM_{2.5}$ mass, ABS, and sulphur (S) among survivors of a myocardial infarction, in Barcelona, Spain. This kind of information is absent for Southern European countries where cities have relatively high levels of air pollution. Typically, people in those countries spend a large fraction of the day outdoors and are frequently exposed to environmental tobacco smoke (ETS).

II Material and Methods

Study design and population

The study took place in Barcelona, Spain, within the AIRGENE project, a longitudinal epidemiological study on myocardial infarction survivors conducted in 6 European cities. AIRGENE subjects were followed with monthly clinic visits. During the first visit all the non- and occasional smokers who were physically able to carry a personal $PM_{2.5}$ device were asked to participate in the personal monitoring project. Questionnaires were used to collect information on patient and housing characteristics, and on time-varying health and exposure conditions.

In the current study, conducted between January and June 2004, each subject's personal exposure was measured during the 24 hours preceding clinic visit. The samplers were distributed to participants from Monday to Thursday between 7 am and 4 pm, the median hour being 11 am. They were collected back from Tuesday to Friday between 7 am and 5 pm. The aim was to keep the day of the week and the time of the day the same for each visit of a participant.

Outdoor concentrations of $PM_{2.5}$, ABS and gaseous pollutants were measured at fixed sites. The measurements were conducted from Monday to Thursday from 9 am to 9 am.

Sampling Methods

Personal measurements were conducted using BGI GK2.05 cyclones and battery operated BGI AFC400S pumps (BGI Inc., Waltham, MA, U.S.)[19]. Andersen 37mm-2μm pore size-Teflon filters (SA240PR100, Andersen Instruments, Smyrna, GA, U.S.) and Millipore filter holders (M00037AO, Millipore, Bedford, MA, U.S.) were used in the study. The pump and the batteries were placed in a backpack; the cyclone was attached to the strip of the pack, just below the shoulder line, with the inlet forward. The participants were instructed to carry the backpack with them as closely as possible, but they were allowed to place the sampler nearby (but not on the floor) during sedentary activities such as resting, watching TV, sleeping, etc. If the noise of the pump prevented patients from sleeping, they were asked to put the device in a room with similar characteristics as the bedroom (i.e. facing the same street, leaving the window in the same state as the one in the bedroom). Participants were asked to record the type and duration of the activities conducted when not carrying the measurement system, and the place where it was kept during the activity.

Flows were adjusted at the beginning of each measurement to 4 l (± 0.2) with a bubble flow meter (M-30, Buck Inc., Orlando, FL, USA), and checked at the end of each measurement. Measurements where ending flows were below 3.6 l or above 4.4 l were excluded, as well as samples for which the measurement period was below 16 or above 30 hrs.

Field blanks were taken weekly: filters were loaded in a filter holder, the holder attached shortly to the cyclone and then the holders were left in the backpack for the duration of the measurement. The average field blank value was subtracted from all

results. Personal duplicate samples were collected by healthy volunteers. The samples were spread evenly over the study period. The detection limits were calculated by dividing three times the standard deviation of field blanks by average sample volume.

The outdoor $PM_{2.5}$ measurements were conducted with two devices: the first one was the personal measurement system and the second one was a high volume pump (MCV-CAV with a flow rate of 30 m^3*h^{-1}, equipped with a DIGITEL $PM_{2.5}$ inlet). The high volume sampler is used routinely to measure $PM_{2.5}$. The samplers were located on a 2nd floor terrace of a research institute in the centre of a university campus, 8 meters above street level and 125 meters from one of the avenues with the highest road traffic density of Barcelona (Diagonal Av.). Thus, the central site is an urban background monitoring station, with a high influence of traffic. It is located at 41º23' 05'' N 2º 07' 09'' E (69 m above the sea level), i.e. North West of the city, on the southern flank of a hill. The study participants lived within 1 to 12 km from the site.

Laboratory methods

Filters were weighted following the standard operating procedure of the ULTRA study (20) before and after the measurement using a microbalance with 1 μg reading (Mettler Toledo MX5, Greifensee, Switzerland). Two consecutive measurements of a filter had to agree within 1 μg for the result to be accepted. The filters were kept at least for 24 hours in a desiccator prior to the weighing. Used filters were stored in -20ºC prior to weighing. The static electricity was controlled using an electric deionizer (Power unit type A2C7S with antistatic bar type MED, Simco, USA). During the study it turned out that 45 seconds of deionising on both sides of a filter was needed. Filters for which too short deionising time was used in the beginning of the study were excluded. Exclusion was based on the results of the control filters. The temperature, relative humidity and atmospheric pressure in the weighing room were recorded at the beginning and at the

end of each session. The maximum difference between the start and the end reading was 3°C for temperature, 6% for relative humidity, and 1 hPa for atmospheric pressure. Although the weighing conditions were relatively stable, we corrected the results for buoyancy (Hanninen et al. 2002) to fully take into account the possible minor effects of varying weighing conditions.

The blackness of the filters was measured according to the standard operating procedure of the ULTRA study[20], using a reflectometer (EEL, Model 43, Diffusion Systems Ltd., UK). To compensate minor inhomogeneities of collected material on filters, each filter was measured in five different locations and the average was used in analyses. The formula for the calculation of ABS can be found elsewhere (ISO9835; Janssen et al. 2000). The unit of ABS is $m^{-1}*10^{-5}$.

The reflectometer was calibrated with the blank filter after every 25 filters, and 10% of the filters were measured again at the end of each measurement session. If the (average) reflectance of the duplicates deviated more than ± 3 % from the original results, all the filters of the session were measured again.

The $PM_{2.5}$ filters were leached at 60ºC using distilled water to determine the concentrations of S by Inductively Coupled Plasma Atomic Emission Spectroscopy (Thermo Jarrell-Ash, model: Iris Advantage Radial ER/S).

Data analysis

Two subjects with only one valid observation were removed from the analysis. Missing daily values in outdoor measurements were imputed using data from other outdoor air pollution measurements. The $PM_{2.5}$ measured with the high volume pump was used to impute $PM_{2.5}$ measurements conducted with personal measurement system; in total 5 missing values were imputed using the regression equation $PM_{2.5\ outdoor} = 0.72*PM_{25\ high}$

$_{vol\ pump}$ − 0.37. Measurements of gaseous pollutants were used to impute missing values in ABS data. The correlation between the ABS and different gases was calculated, the highest correlations were $r^2 = 0.61$ for CO and $r^2 = 0.66$ for NO, using both in the same model the r^2 was 0.76; in total 9 missing values were imputed using the regression $ABS_{outdoor} = 0.05*NO+2.93*CO+0.67$.

The associations between outdoor and personal measurements of $PM_{2.5}$, ABS and S were assessed by linear regression. The outdoor concentrations used to perform the regressions were the ones from the personal measurement device at the fixed central site. All analyses were conducted both using all valid measurements, and using only the measurements with no exposure to ETS. In the first analyses all measurements were pooled together, even when there was more than one measurement per person. Genuine cross-correlations were calculated for reference by including only one randomly picked sample from every person at a time in a regression model, and taking the mean of 10 repetitions. Individual correlation coefficients were not calculated because the number of data points per person was considered too low for obtaining reliable estimates. However, the repeated nature of the data was taken into account by applying random mixed models (GLS random-effect model in Stata 8.0 software). Random intercepts were used for subject-effects. We expected no covariance structure other than simple compound symmetry, as the consecutive samples were taken in minimum 3 weeks apart.

III Results

There were 110 valid measurements of $PM_{2.5}$, 162 of ABS and 88 of S from 37, 38 and 36 subjects (with at least two valid measurements), respectively.

Table 1 describes the general characteristics of the study population. 83% were males; almost 50% were still working (82% of which full time). The median time spent indoors (home and elsewhere) was 18 hrs. The median time spent in traffic (in any vehicle or walking) was two hours. Almost half of the measurements had ETS.

For quality control purposes 15 blanks and 6 duplicate measurements were obtained. The median mass of $PM_{2.5}$ blanks was 2 μg and mean 1.3 μg (SD 8.19). The limit of detection was thus 4.4 $\mu g/m^3$. For absorption the median was 0.05, the mean 0.03 (SD 0.06), and the limit of detection 0.04 $m^{-1}*10^{-5}$. The median of the coefficients of variation was 7.2% for $PM_{2.5}$ duplicates and 2.6% for ABS duplicates.

In outdoor air, there was a good correlation between the sampler used for personal measurements and the high volume sampler (r = 0.92), but the levels of the former were lower. The high volume sampler meets the requirements of the $PM_{2.5}$ cut-off inlet described for one of the reference instruments proposed in the EU standard for $PM_{2.5}$ measurements (prEN-14907). To make the concentrations measured with the personal monitoring system more comparable with reference methods the concentrations should be divided by a factor of 0.72. The mean $PM_{2.5}$ concentration measured with the personal monitoring system at the central outdoor station (24$\mu g/m^3$ after dividing the obtained mean by 0.72) was very similar to the annual mean values reported for 2003-2005 (25$\mu g/m^3$), supporting the representativity of the measurements. The correlation between S measured from the filters of the personal monitoring system sampler and of the high volume sampler was very good (r = 0.99).

The correlation between outdoor $PM_{2.5}$ and ABS was 0.71, and between outdoor $PM_{2.5}$ and S 0.81.

Table 1: General characteristics of the study population

a) Personal characteristics of the study population (n = 38)

	n	%
Gender		
Males	32	84
Age		
Over or equal to 65	15	34
Marital status		
Married	32	84
Divorced, single or widowed	6	16
Smoking		
Never	3	8
Ex	31	82
Current	4	10
Employment		
No workers	20	53
Full time	15	39
Part time	3	8
Education		
End of studies before the age of 12	30	79

b) Exposure characteristics of the study population (n = 164)

	Min	p 25%	Median	p75%	Max	Mean
Time spent at home (hrs)	4.5	14	18	22	25	18
Time spent indoor elsewhere (hrs)	0	0	0.5	2.5	13	2
Time spent in traffic[a] (hrs)	0	1	2	3.7	14	2.9
Time spent outside, no traffic (hrs)	0	0	0	1	8	0.5
Time with ETS at home (min)	0	0	0	0	960	25
Time with ETS elsewhere indoors (min)	0	0	0	30	480	41

Personal $PM_{2.5}$ concentrations were higher than the central outdoor concentrations, even after excluding ETS (Table 2). The median of personal ABS was higher than outdoor ABS, but the two were very similar after excluding ETS. Personal S levels were very similar to the central ones.

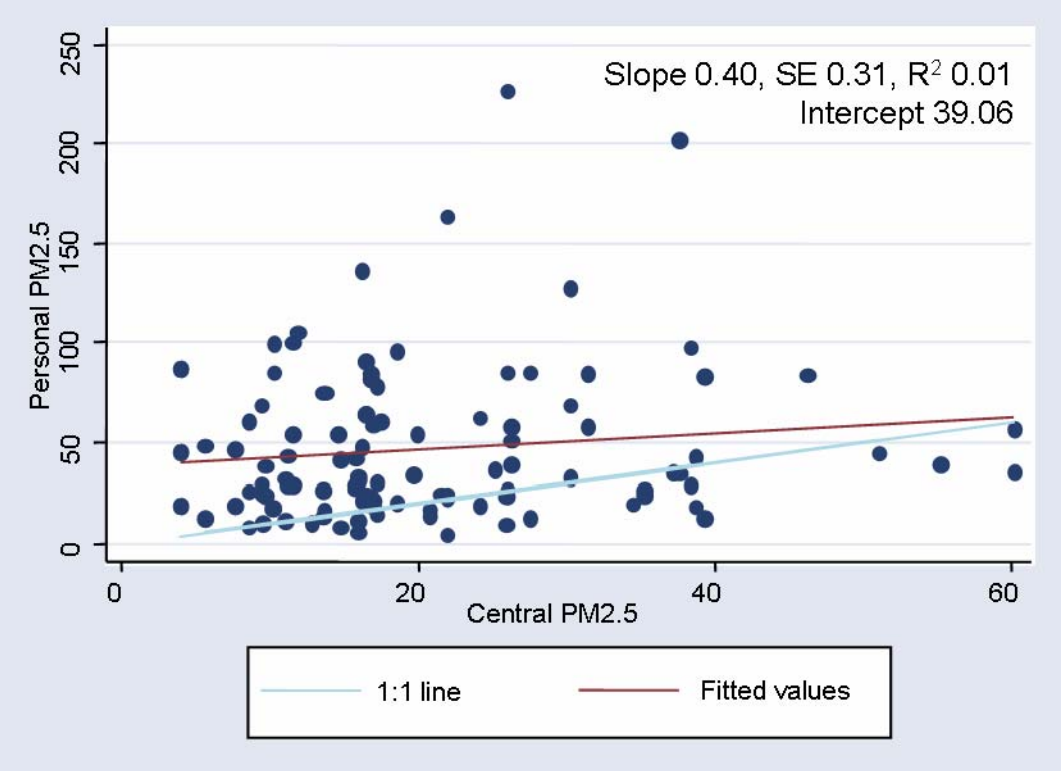
Table 2: Individual, cross-sectional (including a varying number of repeats per person) and central outdoor levels of $PM_{2.5}$ mass (in $\mu g/m^{-3}$), ABS ($m^{-1}*10^{-5}$) and S (in $\mu g/m^{-3}$)

	Individual means of $PM_{2.5}$	Cross-sectional $PM_{2.5}$	Without ETS	Outdoor $PM_{2.5}$	Individual means of ABS	Cross-sectional ABS	Without ETS	Outdoor ABS	Individual means of S	Cross-sectional S	Without ETS	Outdoor S
Sample size	37	110	58	54	38	162	80	79	36	101	52	46
Min	13.6	4.9	4.9	3.8	2.0	0.8	0.8	1.1	0.7	0.4	0.4	0.2
p 25%	27.1	22.0	17.4	12.6	3.3	2.9	2.4	2.2	0.9	0.8	0.7	0.7
Median	44.5	34.6	26.6	17.2	4.0	3.9	3.0	3.1	1.3	1.1	1.0	0.9
p 75%	60.3	63.0	46.8	27.4	5.2	5.8	4.2	4.3	1.4	1.4	1.4	1.4
Max	153.8	226.5	136.6	59.8	10.5	13.4	8.3	7.2	3.0	3.7	3.7	3.5
Mean	47.8	47.3	36.5	21.9	4.6	4.5	3.4	3.9	1.3	1.2	1.2	1.2

Personal $PM_{2.5}$ concentrations were not correlated (semi)cross-sectionally with outdoor measurements, not even after excluding days with ETS (Figures 1a and 1b). The correlation between personal and outdoor ABS was modest (Figure 2a). After excluding days with ETS exposure (Figure 2b), the correlation improved notably. The correlation between personal and outdoor S (figure 3) was high.

Figure 1: Relationship between personal and outdoor $PM_{2.5}$. Regressions are cross-sectional and do not take into account that each subject has several repeated measurements

a) Personal and outdoor $PM_{2.5,}$ all measurements



b) Personal and outdoor $PM_{2.5}$, only measurements without ETS exposure.

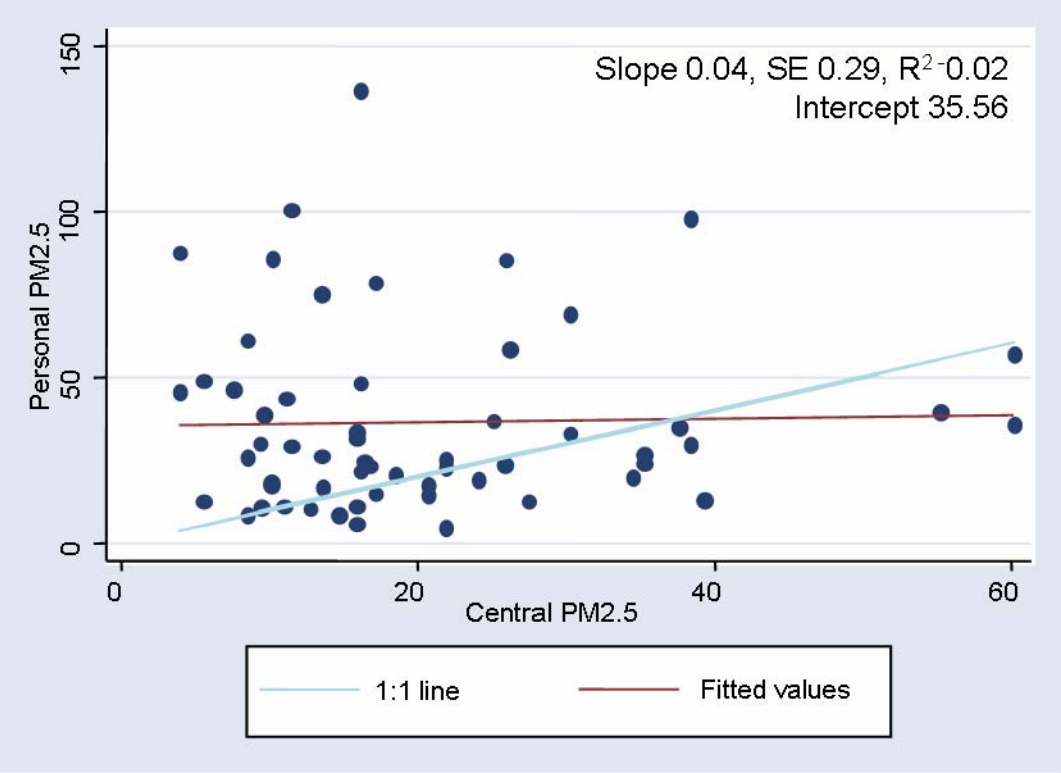
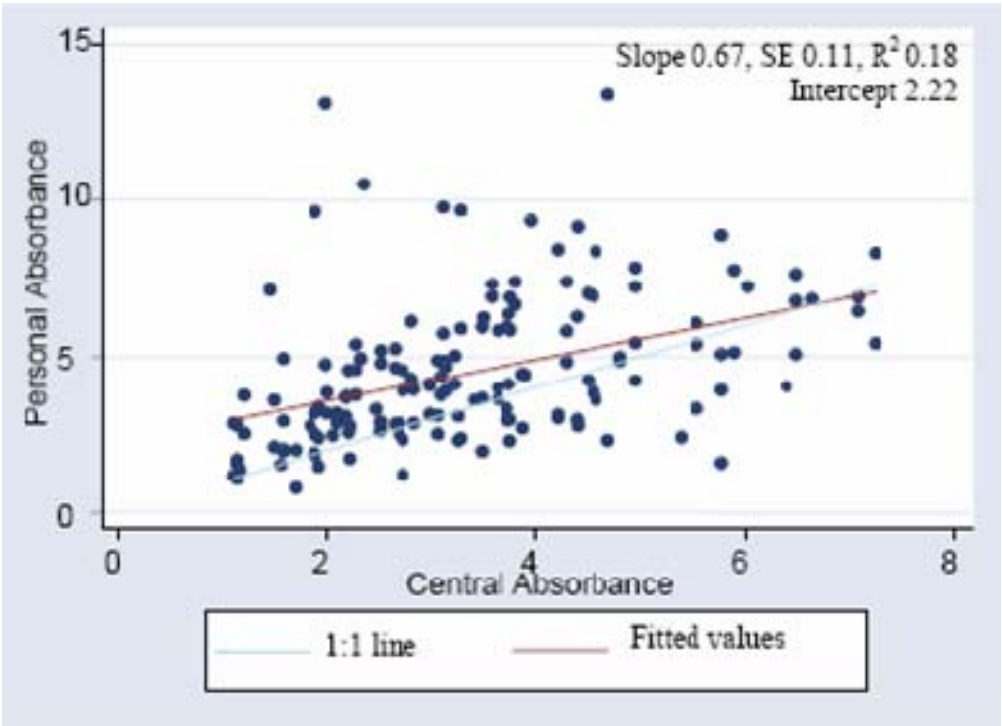


Figure 2: Relationship between personal and outdoor ABS. Regressions are cross-sectional and do not take into account that each subject has several repeated measurements

a) Personal and outdoor ABS, all measurements



b) Personal and outdoor ABS, only measurements without ETS exposure

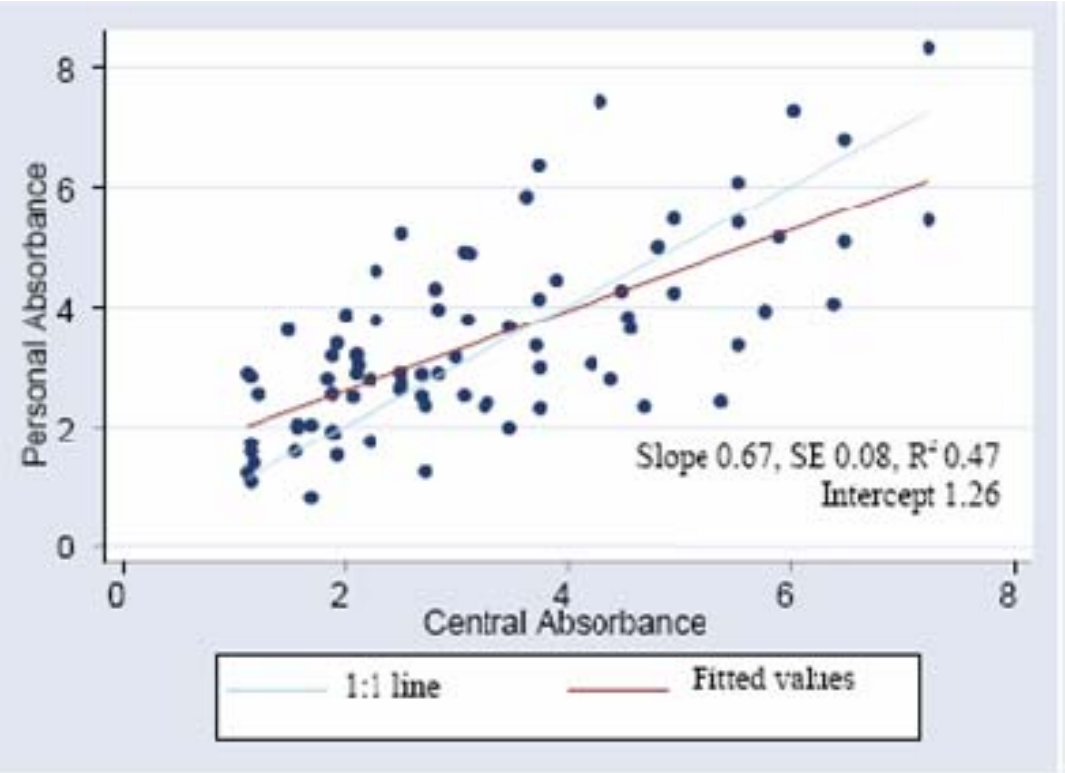
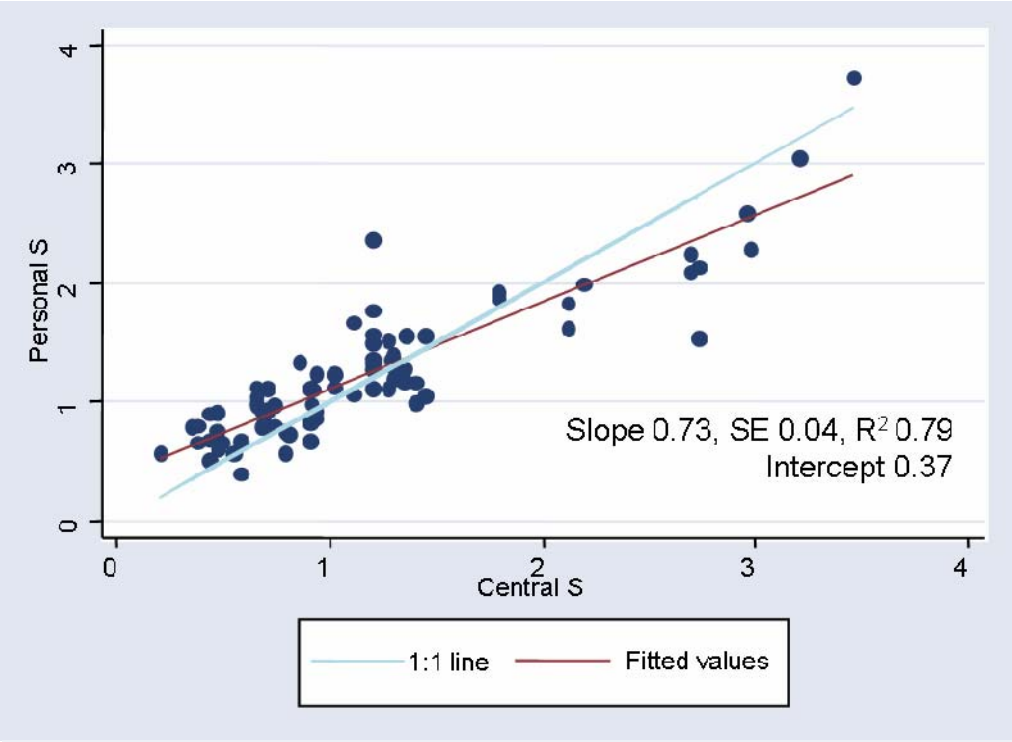


Figure 3: Relationship between personal and outdoor S, all measurements. Regression is cross-sectional and does not take into account that each subject has several repeated measurements



The means of the slope, standard error and R^2, of the regressions between the personal and outdoor levels were 0.72, 0.76 and 0.23 for $PM_{2.5;}$ 0.60, 0.25 and 0.35 for ABS; and 0.69, 0.08 and 0.76 for S, when one sample per person was picked randomly ten times. ETS was included in the models for PM2.5 and ABS.

Personal ABS concentrations were moderately correlated with central $PM_{2.5}$ concentrations (r = 0.33). The correlation improved when excluding days with ETS exposure (r = 0.51). The correlation improved further when adding ETS in the model instead of excluding the subjects with ETS (slope 0.7, standard error 0.1, r 0.64).

The association between personal and central $PM_{2.5}$ was significant when taking into account the repetitive nature of the measurements, but did not further improve after adjusting for ETS and/or traffic (Table 3). Due to the rather non-normal distribution of residuals, analyses for $PM_{2.5}$ were conducted also using $\log_{10}$ transformed data as a sensitivity analysis. However, the conclusions did not change. The patterns of the associations between personal and outdoor ABS and S, were similar to the ones found for $PM_{2.5}$. ETS was associated with personal levels of PM2.5 and ABS. Traffic was associated with personal levels ABS.

Table 3: Associations between personal and outdoor measurements in mixed models. Repeated measurements taken into account by including random persons effects.

	Random effect (p-value)	Random effect adjusting for ETS[a] (p-value)	Random effect adjusting for traffic[b] (p-value)	Random effect adjusting for ETS[a] and traffic[b] (p-value)
$PM_{2.5}$				
N	110	109	108	108
Intercept	35.46 (<0.001)	27.92 (0.001)	35.02 (<0.001)	27.02 (0.003)
Central PM2.5	0.58 (0.033)	0.51 (0.066)	0.56 (0.050)	0.50 (0.077)
ETS[a]		18.87 (0.019)		16.86 (0.021)
Traffic[b]			2.26 (0.759)	2.23 (0.758)
ABS				
N	162	161	160	160
Intercept	2.41 (<0.001)	1.79 (<0.001)	2.05 (<0.001)	1.43 (0.001)
Central ABS	0.66 (<0.001)	0.66 (<0.001)	0.68 (<0.001)	0.67 (<0.001)
ETS[a]		1.21 (<0.001)		1.22 (<0.001)
Traffic[b]			0.68 (0.022)	0.67 (0.021)
S				
N	88	88	87	87
Intercept	0.43 (<0.001)	0.42 (<0.001)	0.43 (<0.001)	0.45 (<0.001)
Central S	0.70 (<0.001)	0.69 (<0.001)	0.69 (<0.001)	0.69 (<0.001)
ETS[a]		0.02 (0.737)		0.02 (0.775)
Traffic[b]			0.03 (0.574)	0.02 (0.593)

a ETS defined yes/no
b Traffic defined as less or equal to two hours/ more than two hours

IV Discussion

This is the first study in a Southern European country to evaluate with repeated measurements the relationship between outdoor and personal $PM_{2.5}$, ABS, and S among post-myocardial infarction patients. Personal $PM_{2.5}$ concentrations were higher than central outdoor concentrations, even after excluding days with exposure to ETS. Personal ABS levels were also higher than outdoor levels, but the two were very similar after excluding ETS. Personal S levels were similar to the central ones. Outdoor and personal concentrations of S, but not $PM_{2.5}$, were correlated cross-sectionally, ABS concentrations only after excluding days with ETS. In longitudinal analyses, outdoor and personal levels of both ABS and S were significantly associated; for $PM_{2.5}$ the association was weaker.

It has been demonstrated that some population subgroups are especially susceptible to the adverse effects of air pollution, for example persons with chronic obstructive pulmonary disease[21], conduction disorders[22], congestive heart failure[23], diabetes[24] and myocardial infarction[7;25]. It is important to validate the use of outdoor concentrations for the estimation of exposure among these subpopulations, because the characteristics of their exposure may be different from general population. Elderly persons with compromised health typically spend more time at home or indoors elsewhere and less time outdoors or in traffic[26-29]. Williams et al. [30], found very similar levels of ambient and personal $PM_{2.5}$ in 30 patients with severe Chronic Obstructive Pulmonary Disease (COPD). In a study among 37 elderly subjects with coronary heart disease in Amsterdam and 47 in Helsinki, personal levels of $PM_{2.5}$ and ABS were very similar to the outdoor levels, and also longitudinally highly correlated with both outdoor and indoor concentrations[31]. In Vancouver, the personal levels of $PM_{2.5}$ in 16 COPD patients were higher than ambient levels. There was a moderate longitudinal correlation for $PM_{2.5}$ and a high correlation for SO_4. The study also demonstrated high influence of ETS on the personal concentrations[32]. In Boston among elderly subjects, Rojas-Bracho et al.[33] found that personal $PM_{2.5}$ levels were higher than ambient concentrations, but the two were longitudinally correlated for only 10 out of the 17 subjects. Williams et al.[13] also showed that personal $PM_{2.5}$ levels were higher than outdoors in North Carolina, and the longitudinal correlation between both was moderate.

In Barcelona, main outdoor sources of particles are traffic, regional re-circulation (typical of the Western Mediterranean), industrial sources (mainly inorganic secondary compounds and heavy metals such as Zn, Cd, Pb, with relatively low levels), and crustal source, which is mainly associated with anthropogenic activities

(construction works, street dust, re-suspension from parks), but sporadically African dust contributes to the source[34]. Indoor sources in Barcelona have not been described, but the main sources are probably the same as described in other European studies, i.e. ETS, cooking, heating, dusting[35], although potentially in different proportions. It is also important to note that exposure to ETS is ubiquitous in Barcelona, because almost 30% of subjects above 14 years of age are smokers[36]. Until now there are only limitedly regulations on smoking in public places, except in working places.

In our study the personal levels of ABS were similar to the central ones when excluding the measurements with ETS exposure, and even the cross-sectional correlation was quite good. The fact that personal and outdoor ABS levels are well correlated is consistent with the results of previous studies conducted in Northern and Central Europe[37;38]. Exposure to ABS seems to be better correlated with central outdoor levels than $PM_{2.5}$. Some authors have found also cross sectional indoor-outdoor correlations to be better for elemental carbon than for $PM_{2.5}$[39]. Personal ABS was positively associated to the time spent in traffic, which is consistent with some previous studies[15;35]. Probably most of the elemental carbon in outdoor air in Barcelona originates from traffic, whereas $PM_{2.5}$ could have many other outdoor sources such as resuspension of soil and sea spray[34]. Speciation studies carried out at the central site in Barcelona[40] showed that elemental carbon (close to ABS) in $PM_{2.5}$ may account for 12-16% of the total $PM_{2.5}$ mass, while 16-20% could be attributable to mineral matter and 28-36% to secondary inorganic. The reason for the better correlation of outdoor and personal ABS than $PM_{2.5}$ might simply be due to the fact that most of the elemental carbon comes from outdoors, whereas for $PM_{2.5}$ there are more considerable indoor sources. This hypothesis is supported by the fact we have a very good correlation between personal and outdoor S, which is expected to be even less influenced by indoor

sources than ABS. High correlations for ABS and S suggest that exposures to combustion related PM (of outdoor origin) and PM from long range transport, respectively, are well estimated by central outdoor measurements.

The results of the current study suggest that central measurements of $PM_{2.5}$ might work as a proxy for exposure to combustion originating particles, as indicated by ABS, better than for personal $PM_{2.5}$. It is interesting to note that in a recent study Sarnat et al[41] showed that ambient concentrations of gaseous pollutants may be better surrogates for $PM_{2.5}$ exposure (especially of ambient origin) than for gaseous pollutants themselves. There is some evidence that the health effects of air pollution are closely related to the combustion originating fraction of particles[15;42]. All this might explain the associations of outdoor $PM_{2.5}$ and gaseous pollutants with cardiovascular health.

One limitation of the study was caused by the problems with static electricity during weighing in the beginning of the study. Due to reduced number of valid $PM_{2.5}$ measurements the final number of repetitions per subjects was too low to do regressions separately for each subject, as has often been done before. However, the random mixed model used in the present study provides a viable alternative for such analysis. Another limitation is the restricted study period: the valid measurements were obtained from January to June. Therefore it was not possible to study seasonality, although parts of both cold and warm season were included.

V Conclusions

The central outdoor levels of $PM_{2.5}$ were poorly to moderately (cross-sectional versus longitudinal approach) associated with exposure. Longitudinal associations between outdoor and personal concentrations were stronger for ABS and S than for $PM_{2.5}$. However, ETS exposure was important to take into account both for $PM_{2.5}$ and ABS.

Our results show that personal exposure to combustion originating fraction of $PM_{2.5}$, both from local traffic and long-range transported air pollution, can be reliably estimated with outdoor measurements at a fixed site. The observation is especially important because of the suggested link between combustion particles and cardiovascular health.

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Annoyance due to air pollution in Europe.

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Annoyance due to Air Pollution in Europe

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Abstract:

Background: Annoyance due to air pollution is a subjective score of air quality, which has been incorporated into the National Environmental monitoring of some countries. The objectives of this study are to describe the variations in annoyance due to air pollution in Europe and its individual and environmental determinants.

Methods: This study took place in the context of the European Community Respiratory Health Survey II (ECRHS II) that was conducted during 1999-2001. It included 25 centres in 12 countries and 7867 randomly selected adults from the general population. Annoyance due to air pollution was self-reported on an 11 point scale. Annual mean mass concentration of fine particles ($PM_{2.5}$) and its sulphur (S) content were measured in 21 centres as a surrogate of urban air pollution.

Results: 43% of participants reported moderate annoyance (1 to 5 on the scale) and 14% high annoyance (5 or more) with large differences across centres (2 to 40% of high annoyance). Participants in the Northern European countries reported less annoyance. Female gender, nocturnal dyspnoea, phlegm and rhinitis, self reported car and heavy vehicle traffic in front of the home, high education, non smoking and exposure to environmental tobacco smoke were associated with higher annoyance levels. At the centre level, adjusted means of annoyance scores were moderately associated with sulphur urban levels (slope 1.43 per $\mu g\ m^{-3}$, standard error 0.40, $r = 0.61$).

Conclusions: Annoyance due to air pollution is frequent in Europe. Individuals' annoyance may be a useful measure of perceived ambient quality and could be considered a complementary tool for health surveillance.

Key words: annoyance, air pollution, respiratory symptoms

I Introduction

Air pollution is a risk factor for respiratory and cardiovascular diseases[1;2]. It is now accepted that air pollution is an important issue in public health given its impact on long term mortality[3]. However, the assessment of exposure to air pollution is complicated. Most of the epidemiological studies that assess health effects of air pollution use central site measurements, in some cases weighted by the distance between participants' homes and a main road[4], or individual patterns of daily activity[5]. Another type of measure incorporating broader scopes and domains (such as quality of life or community values) is annoyance due to air pollution[6]. It is a subjective score, often used for measuring noise or odours[7], but rarely used for air pollution exposure. In Sweden, this measure has been incorporated in the National Environmental monitoring program and urban citizens' annoyance correlated with urban air pollution even if pollutant levels were well below thresholds[8]. Oglesby et al. have shown across eight Swiss towns and neighbourhoods within these areas that the aggregate group mean annoyance correlated with the air quality in the city or neighbourhood. In contrast, individual reporting of annoyance was only weakly associated with outdoor levels of air pollution[9]. Rotko et al. have shown that at the population level, the mean annoyance was correlated with mean $PM_{2.5}$ and NO_2 concentrations across six European cities, but individual annoyance was not associated with individual $PM_{2.5}$ or NO_2 concentrations[10].

Besides air quality, individual characteristics affect the reporting of annoyance, leading to substantial subjectivity of annoyance scores. In previous studies several variables such as gender, age, education or respiratory symptoms have been associated with annoyance due to air pollution but not consistently[11-14]. The rate of respondents highly annoyed by air pollution at home also varied across different European cities[15-17]. It is

not possible to generalize these results across cultures and countries as the previous studies were restricted to few areas.

The objectives of this study are to describe the personal and socio-demographic determinants of annoyance due to air pollution in a large international multicultural European study and to assess its association with central measurements of air pollution.

II Materials and Methods

Study population

The European Community Respiratory Health Survey (ECRHS) was conducted in twenty-eight urban centres of 11 Western European countries[18]. It was first conducted in 1991-3 and repeated in 1999-2001. The objective was to estimate the variation in the prevalence, exposure, risk factors and treatment of respiratory diseases, especially asthma, in middle-aged adults living in Europe. Centres were chosen based on pre-existing administration boundaries, their size and the availability of sampling frames. Participants were randomly selected from the populations aged 20-44 in 1991-3. The details of this project are described elsewhere[19;20].

This analysis is based on the second survey and includes all centres that used the annoyance question and data on 7867 participants from 25 centres in 12 countries (Figure 1). Sample size varied by centre from 123 in Turin (Italy) to 596 in Bergen (Norway). The response rate for this stage was 65.3%, ranging from 30.3% in Bordeaux (France) to 83.1% in Uppsala (Sweden).

Figure 1: Map of Europe with the centres participating in the European Community Respiratory Health Survey II (ECRHSII).

Description of variables

Annoyance due to air pollution was self-reported on an 11 point scale (0: no disturbance at all, 10: intolerable disturbance) through the following question: "How much are you annoyed by outdoor air pollution (from traffic, industry, etc) if you keep the windows open?" The overall response rate for this question was 97.9% among study participants. All determinants of annoyance have been collected within the same questionnaire.

The variables for the analysis were chosen based on previous studies[21-24]. Socio-demographic factors were age, sex, education (based on age at end of study and

categorized in tertiles) and socioeconomic class (based on occupation). The respiratory variables included in the analysis were wheezing, breathless while wheezing, wheezing without a cold, shortness of breath at rest (dyspnoea), shortness of breath while sleeping (night dyspnoea), cough in winter, phlegm during day or night in winter, phlegm during day or night in winter for more than three months, asthma attack in the last 12 months (current asthma), asthma treatment, rhinitis without a cold in the last 12 months (current rhinitis), and in addition having ever had asthma or rhinitis and season of the rhinitis. The life style factors were frequency of physical exercise, smoking and exposure to environmental tobacco smoke (ETS), defined as regular exposure to tobacco smoke at home and/or at work. Finally, the questionnaire asked about general as well as heavy vehicle traffic intensity in front of the home. This information was collected from a four-option question, where the options were no traffic, infrequent, frequent and constant traffic.

Air pollution measurements

Annual means of fine particulate matter ($PM_{2.5}$) (fine particles with a median size of 2.5μm aerodynamic diameter) and its elemental content were available for 21 centres from a 12-month measurement campaign. Sulphur represents a background portion of $PM_{2.5}$, mainly consisting of sulphate particles (SO_4^{2-}), which are oxidation products formed from sulphur dioxide (SO_2) emissions during long range transportation in the atmosphere. Concentrations measured in one location characterized the level of this long-range pollution for the city at large, and correlations between fixed-site monitors, home outdoor, and even personal concentrations are very high for S. Thus, it reflects the 'regional' air quality whereas other pollutants characterize more local emissions. We use the annual mean mass concentration of sulphur measured on fine particles with a median size of 2.5 μm aerodynamic diameter ($PM_{2.5}$). These measurements are

available for 21 centres from a 12 month measurement campaign described elsewhere[25-27]. In brief, between June 2000 and December 2001, at a central monitoring site, 7 days were sampled over a two-week period during each month, using identical equipment and procedures in each centre. S content on $PM_{2.5}$ filters was analysed using energy dispersive X-ray fluorescence spectrometry (ED-XRF). Both $PM_{2.5}$ and S concentrations are reported in $\mu g\ m^{-3}$.

Statistical analysis

The statistical analysis was performed in two steps. In a first step, personal determinants of annoyance were identified by univariate negative binomial regression, entering centre as a fixed effect if the p value from the test of heterogeneity was ≤ 0.10, and entering centre as a random effect if p was >0.10. The results are expressed as ratios of mean annoyance scores. Effect estimates were derived for each centre and heterogeneity across centres was examined using standard methods[28].

Negative binomial regression was also used for the multivariate model. The model was created in a forward procedure including variables with $p < 0.20$ in the crude analysis and then retaining the ones with $p < 0.10$. A backwards procedure resulted in the same selection of covariates. Socio-economic status and smoking were forced in the model, due to their association with annoyance in the bivariate analysis and to the social implications. The multivariate model was adjusted for centre.

In a second step, the data was analysed on the centre level, regressing the centre-wide average annoyance against the city mean regional air pollutant: $PM_{2.5}$ or S. The mean annoyance was calculated crudely initially and then adjusted for the variables identified previously as associated with annoyance in the multivariate analysis. The mean annoyance per centre was calculated using the mean of the predicted values from the negative binomial regression model in each centre. For the crude mean annoyance, the

negative binomial regression was univariate and for the adjusted mean the negative binomial regression was multivariate, including the co-variables of interest. The association of ambient $PM_{2.5}$ and S with both the crude and adjusted average annoyance at the centre level was measured with a linear regression model, weighted by centre's sample size. Thus, the crude model reflects a purely ecologic association. The adjusted models were controlled for all potential individual-level confounding variables, except the reported traffic density. The last model was also adjusted for the reported traffic density at home.

The analysis was done using STATA 8 (Stata Corporation, College Station, Texas, USA). The criterion for statistical significance was set at a p value < 0.05.

III Results

Overall, 3 406 (43%) participants reported no annoyance at all (0 on the scale), 3 656 (43%) reported low to moderate annoyance (1 to 5) and 805 (14%) reported high annoyance (6 or more). Only 489 (6%) individuals were very highly annoyed (8 to 10)[29]. The overall mean was 2.21 and the median 1.0. Table 1 shows the centres ordered by the mean level of annoyance, which ranged from 0.69 in Bergen (Norway) to 4.38 in Huelva (Spain). The percentage of participants reporting 6 or more on the annoyance scale varied from 2% in Reykjavik (Iceland) to 41% in Huelva. Reykjavik and Bergen scores were significantly lower than those in all other centres. In general, participants in the Northern European countries reported less annoyance. The annual means of $PM_{2.5}$ varied from 3.74 $\mu g\ m^{-3}$ in Reykjavik to 44.86 $\mu g\ m^{-3}$ in Turin. The annual means of S varied from 0.16 $\mu g\ m^{-3}$ in Reykjavik to 2.02 $\mu g\ m^{-3}$ in Verona (Table 1).

Table 1: Median, interquartile range and mean annoyance scores (from 0 to 10), percentage of subjects reporting high annoyance (≥ 6) and $PM_{2.5}$ and S levels in participating study centres.

Centre	n	p25%	p50%	p75%	Mean	Percent reporting high annoyance	Annual mean of $PM_{2.5}$ in $\mu g\ m^{-3}$	Annual mean of S in $\mu g\ m^{-3}$
Bergen	558	0	0	0	0.69	3	-	-
Reykjavik (RE)	460	0	0	1	0.71	2	3.74	0.16
Göteborg (GO)	489	0	0	1	1	4	12.62	0.90
Uppsala (UP)	516	0	0	1	1.01	5	10.40	0.75
Umeå (UM)	416	0	0	2	1.5	7	5.61	0.41
Bordeaux	165	0	0	3	1.82	10	-	-
Norwich (NO)	256	0	1	3	1.83	10	16.20	0.98
Pavia (PA)	192	0	0	3	1.84	13	35.27	1.78
Hamburg	303	0	1	3	1.92	10		
South Antwerp (SA)	294	0	2	3	2.1	10	20.78	1.45
Tartu (TA)	259	1	2	3	2.5	11	14.75	0.89
Oviedo (OV)	241	0	2	5	2.59	17	15.88	1.18
Erfurt (ER)	285	0	2	4	2.6	14	16.25	1.14
Galdakao (GA)	359	0	2	5	2.61	16	16.25	1.58
Grenoble (GN)	384	0	2	5	2.67	16	19.01	0.89
Montpellier	202	1	2	5	2.84	16	-	-
Verona (VE)	205	0	2	5	2.84	22	41.52	2.02
Ipswich (IP)	281	0	2	5	2.9	22	16.45	1.00
Albacete (AL)	294	0	3	5	3.1	19	13.13	1.01
Basel (BS)	446	0	2	5	3.11	24	17.42	1.04
Turin (TU)	123	0	3	6	3.3	25	44.86	1.83
Paris (PS)	425	1	3	5	3.33	25	17.81	1.08
Antwerp City (AC)	238	1	3	5	3.36	24	24.08	1.46
Barcelona (BA)	272	1	3	6	3.56	25	22.21	1.39
Huelva (HU)	204	2	5	7	4.38	40	17.29	1.56
Total	7867	0	1	4	2.21	14	19.12	1.17
- not measured								

For the individual variables, female gender, socio-economic class, all the respiratory outcomes, passive smoking and self-reported car and heavy vehicle traffic were associated with annoyance (Table 2). Age, education, exercise, smoking and season of the interview were not associated with annoyance. There was little evidence for hetergeneity across centres, except for sex (p value for heterogeneity = 0.083), high education (p = 0.058), non manual workers (p = 0.066) and self-reported car and heavy vehicle traffic (p < 0.001). Heterogeneity for sex did not follow any specific pattern; women in Umeå (Sweden), Norwich (UK), Pavia (Italy), Oviedo (Spain), Montpellier (France), Basel (Switzerland) and Antwerp City (Belgium) reported significantly higher

annoyance than men. In Ipswich (UK), Albacete (Spain) and Turin (Italy) they tended to report lower annoyance than men (Figure 2). Heterogeneity for high education and non-manual workers did not follow any specific pattern either. The association between annoyance and high education was statistically significant and positive only in Göteborg (Sweden). The association between annoyance and non-manual workers was positive and statistically significant in Uppsala (Sweden) and Verona (Italy) and negative in Basel. For all other centres, the associations were not statistically significant and the confidence intervals included the pooled estimate.

Figure 2: Crude ratios of mean annoyance scores comparing women with men by centre.

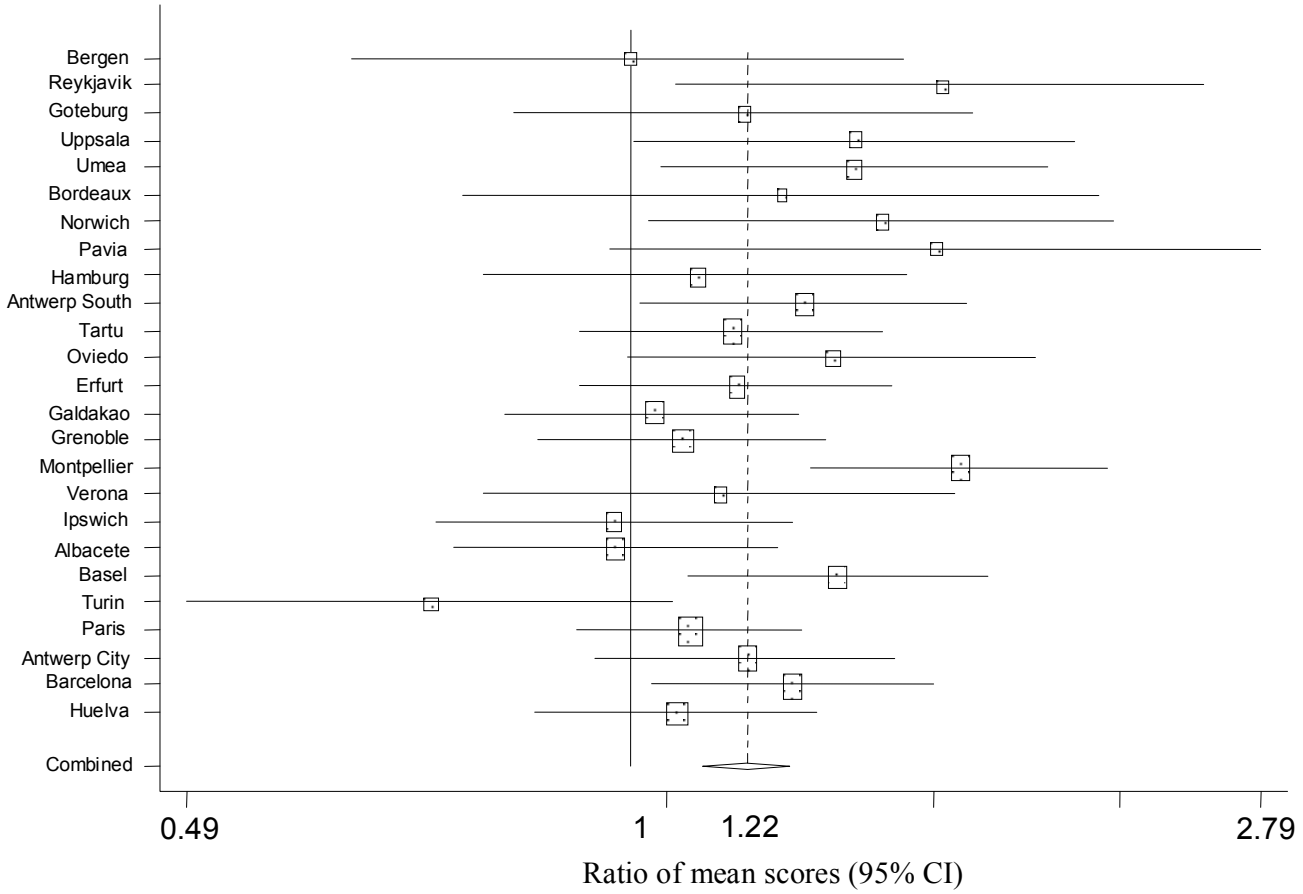


Table 2: Ratios of mean annoyance scores from univariate negative binomial regression and p values from tests of heterogeneity.

	Ratio of mean scores (95% CI)	p from tests for heterogeneity
Gender		
Men (reference)	1	
Women	1.22 (1.15 - 1.28)	0.083
Age (years)		
<35 (reference)	1	
35-39	0.91 (0.82 - 1.00)	0.821
40-44	0.98 (0.89 - 1.08)	0.988
45-49	1.01 (0.92 - 1.11)	0.964
>50	1.00 (0.90 - 1.10)	0.761
Education (age at end of education in years)		
<18 (reference)	1	
19-22	1.00 (0.94 - 1.07)	0.764
>23	0.98 (0.91 - 1.04)	0.058
Socio economic class		
Manual occupation (reference)	1	
Non-manual occupation	1.07 (1.00 - 1.15)	0.066
Others (e.g. housewives)	1.24 (1.11 - 1.39)	0.853
Respiratory symptoms		
No symptoms (reference)	1	
Wheezing	1.22 (1.14 - 1.32)	0.789
Wheezing and breathless	1.28 (1.16 - 1.41)	0.918
Dyspnea	1.46 (1.29 - 1.65)	0.355
Night dyspnea	1.25 (1.10 - 1.41)	0.760
Cough	1.28 (1.17 - 1.40)	0.858
Phlegm	1.36 (1.23 - 1.50)	0.315
Phlegm > 3 months	1.28 (1.14 - 1.45)	0.946
Ever asthma	1.16 (1.06 - 1.28)	0.572
Current asthma	1.24 (1.07 - 1.44)	0.820
Ever rhinitis	1.14 (1.07 - 1.21)	0.309
Current rhinitis	1.11 (1.04 - 1.18)	0.695
Exercise (days with exercise per week)		
≤ 3 (reference)	1	
4-5	0.99 (0.91 - 1.08)	0.938
6-7	0.98 (0.91 - 1.06)	0.970
Smoking		
Never (reference)	1	
Ex smoker	1.02 (0.94 - 1.09)	0.912
Current smoker	1.01 (0.94 - 1.08)	0.616
Passive smoking	1.10 (1.03 - 1.17)	0.893
Exposure to traffic		
No or infrequent traffic (reference)	1	
Frequent or constant car traffic	2.23 (2.10 - 2.36)	<0.001
Frequent or constant truck traffic	1.99 (1.89 - 2.10)	<0.001
Season of the interview		
Spring (reference)	1	
Summer	0.95 (0.87 - 1.04)	0.224
Fall	0.95 (0.88 - 1.03)	0.160
Winter	0.92 (0.84 - 1.00)	0.645

CI; confidence interval

Centre was entered as a fixed effect when p for heterogeneity was ≥0.10 and as a random effect when p for heterogeneity was <0.10.

The participants who reported high exposure to car traffic also tended to report higher annoyance: this association was statistically significant for all centres. Subjects from Northern centres tended to report higher annoyance when reporting high levels of car traffic than participants in Southern centres (Figure 3). Similarly, respondents who reported high levels of heavy vehicle traffic also tended to report greater annoyance. This association was statistically significant for all centres, except for Oviedo, Albacete and Huelva. The associations also tended to be stronger in Northern compared to Southern centres. In the multivariate analysis (Table 3), nocturnal shortness of breath, phlegm and rhinitis were the respiratory indicators significantly associated with annoyance, in addition to female gender, heavy traffic, high education, never smoking and exposure to environmental tobacco smoke.

Figure 3: Crude ratios of mean annoyance scores comparing frequent or constant exposure to car traffic with no or infrequent exposure by centre.

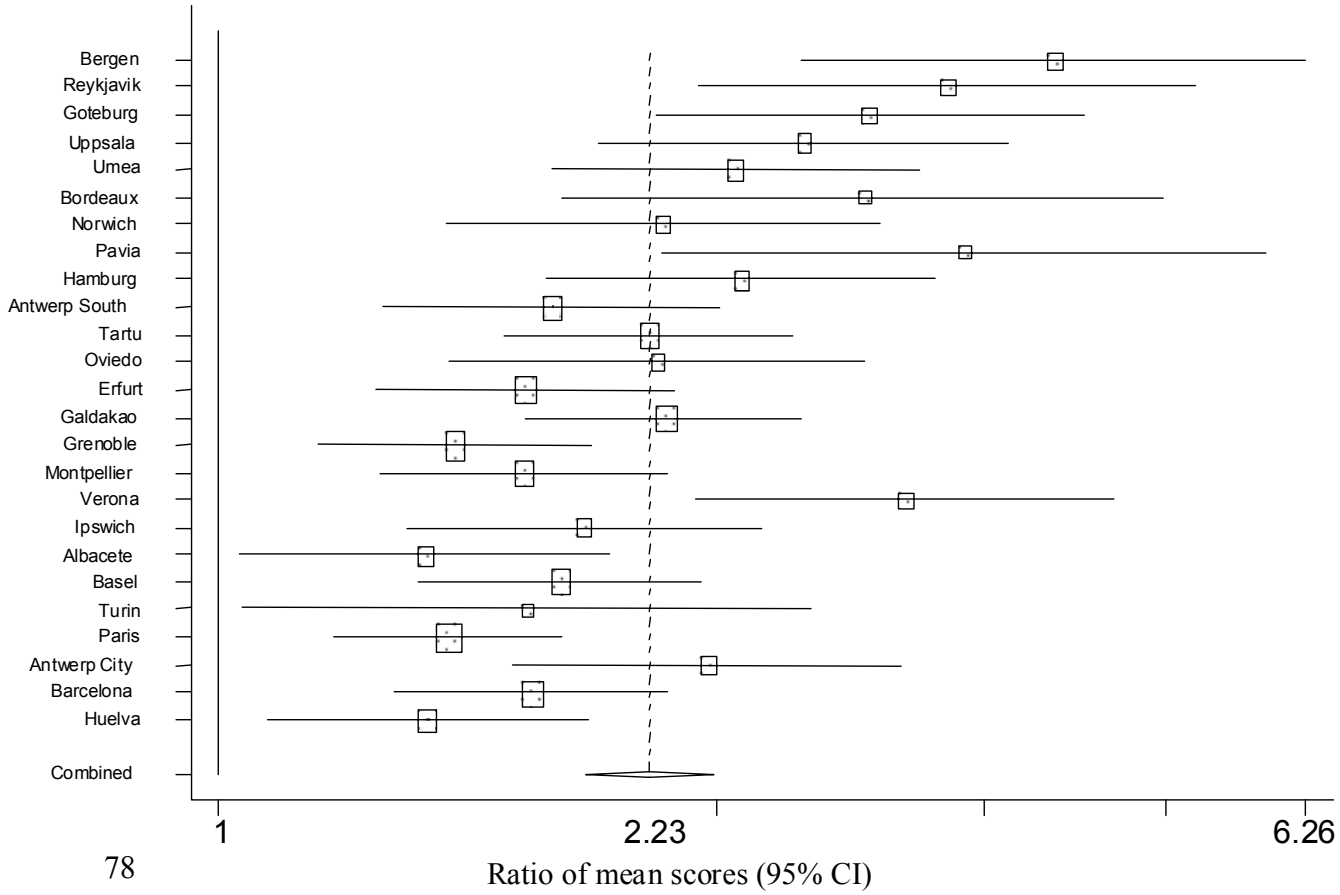


Table 3: Ratios of mean annoyance scores from multivariate negative binomial regression.

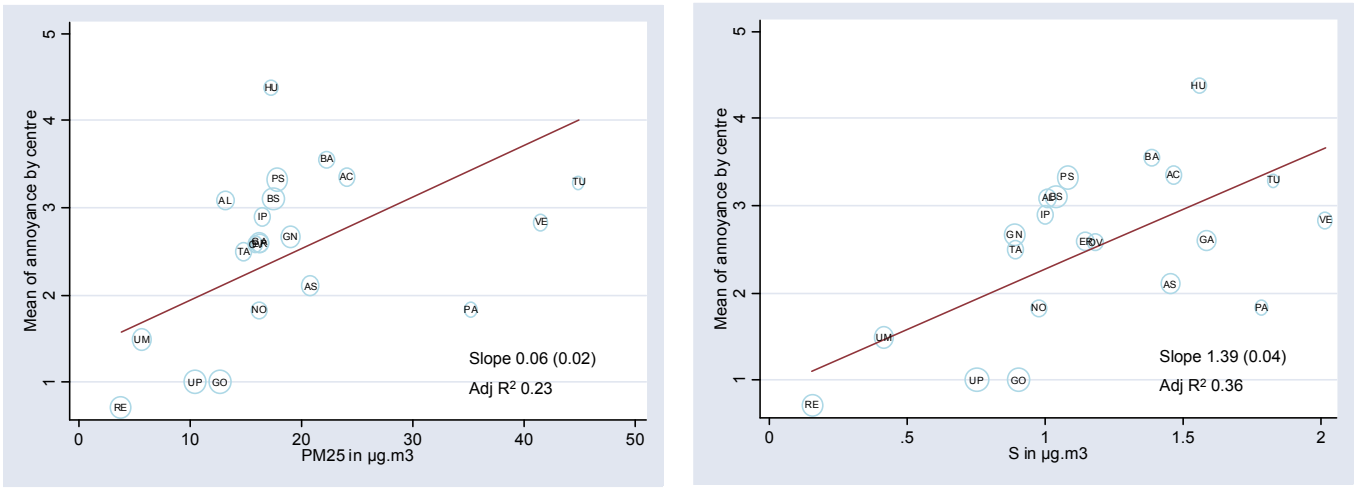
		Ratio of mean scores (95% CI)	
Gender			
Men (reference)		1	
Women		1.17	(1.10 - 1.24)
Socio economic class			
Manual occupation (reference)		1	
Non-manual occupation		1.01	(0.93 - 1.09)
Others (e.g. housewives)		1.07	(0.94 - 1.22)
Respiratory symptoms			
None (reference)		1	
Night dyspnea		1.33	(1.17 - 1.50)
Plegm		1.27	(1.15 - 1.40)
Ever rhinitis		1.07	(1.01 - 1.14)
Smoking			
Never (reference)		1	
Ex smoker		1.02	(0.95 - 1.09)
Current smoker		0.94	(0.87 - 1.01)
Passive smoking		1.10	(1.03 - 1.18)
Exposure to traffic			
No or infrequent traffic (reference)	1		
Frequent or constant car traffic	1.69		(1.58 - 1.82)
Frequent or constant truck traffic	1.48		(1.38 - 1.59)

CI; confidence interval
Multivariate model adjusted for all variables listed and centre

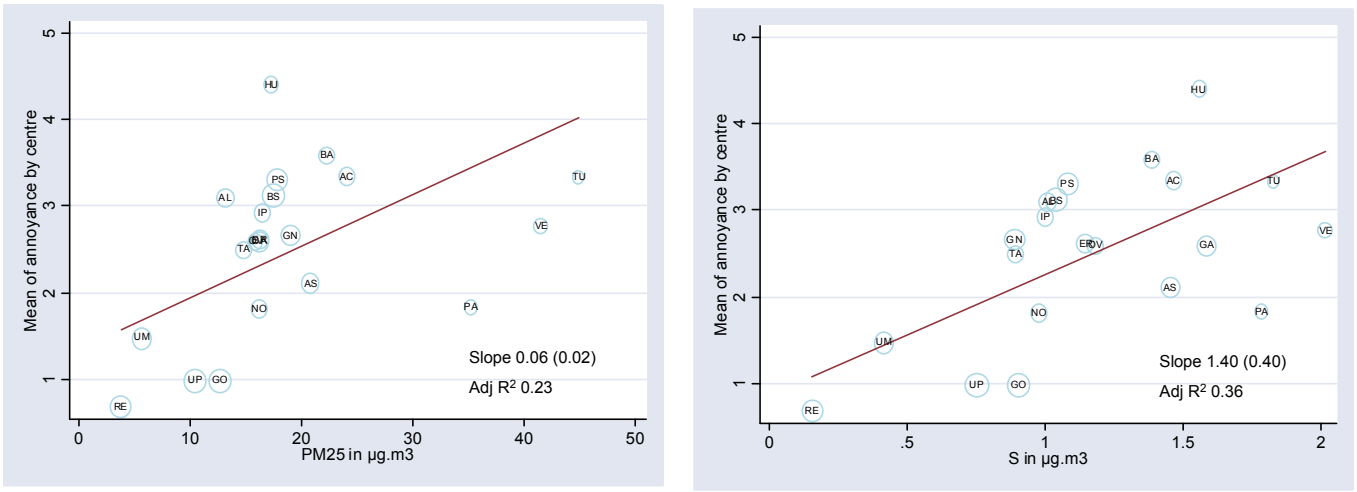
Figure 4 shows the association between the mean annoyance and $PM_{2.5}$ and S. The first panel illustrates the crude association, the second panel includes mean annoyance adjusted for all individual-level variables shown in Table 3, except traffic, and the third panel includes the mean annoyance adjusted for all variables including traffic. The association was similar in the three panels for the two pollutants. The scatter plots for $PM_{2.5}$ included three outliers from the Italian survey. After excluding the Italian data, results were as follows: slope 0.14 (SE 0.03) and R^2 0.54 for the crude model; slope 0.14 (SE 0.03) and R^2 0.54 for the adjusted model excluding traffic and slope 0.14 (SE 0.03) and R^2 0.54 for the adjusted model including the traffic variables. The models including the Italian surveys gave a slope of 0.06 (0.02) and R^2 0.25 (Figures 4 a to c).

Figure 4: Plots of mean annoyance scores against $PM_{2.5}$ and S levels at each centre and estimated change in mean of annoyance per one µg m^{-3} increase in $PM_{2.5}$ and S. The slope (standard error) and R^2 (adjusted for degrees of freedom) are shown. The size of circles indicates the weight of each centre in the regression analysis.

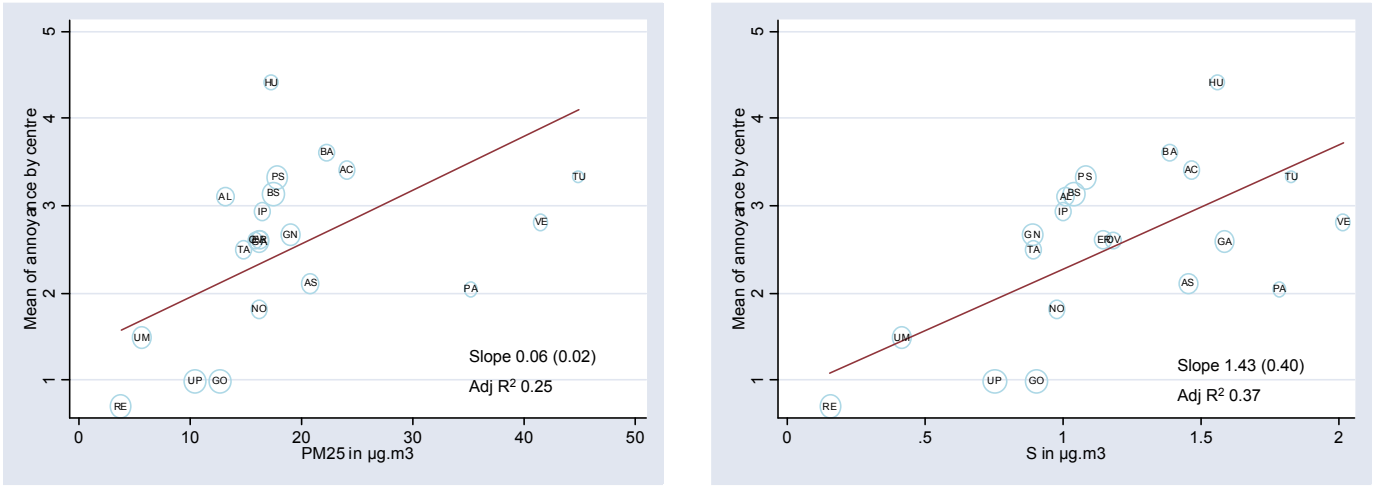
a) Mean annoyance versus $PM_{2.5}$ and S, crude



b) Mean annoyance versus $PM_{2.5}$ and S, individually adjusted for all the variables of table 3 except traffic



c) Mean annoyance versus $PM_{2.5}$ and S, individually adjusted for all the variables of table 3 including traffic



IV Discussion

Principal findings

This study highlights the importance of annoyance due to air pollution as 14% of the Europeans are highly annoyed by air pollution and more than half reported some degree of annoyance. Individual characteristics affect the reporting of annoyance, such as gender, socio-economic status, respiratory symptoms, exposure to environmental tobacco smoke and self-reported traffic.

Strengths and weaknesses of the study

Due to the international setting of this study, our data cover a variety of scenarios and include a large number of observations. Annoyance is in itself an interesting measure of well-being and our unique cross-European study indicates complex and heterogeneous associations between the perception of environmental quality and background measures of pollution.

The lack of home outdoor air quality measurements is a major limitation of our study. While self reported traffic density may be considered a marker for this missing information the limitation of this questionnaire-based information needs to be emphasized, as perception of traffic may determine the reporting of annoyance. Our air pollution measures reflected 'urban background' levels. The participants from the same centre were assigned the same level of pollution, however, only some of them live close to very busy streets. Thus, self-reported traffic intensity may serve as a proxy for additional air pollution (or annoyance) beyond what is due to background air pollution. In the analysis, using the individually adjusted mean of annoyance by centre, the association between air pollution and annoyance was very similar including or excluding traffic from the multivariate regression model.

In Texas, Brody et al. showed that the public perception of air quality was not correlated with actual measures of air quality, but it was very strongly influenced by individual factors such as setting, state identification and socioeconomic characteristics[30].

$PM_{2.5}$ is more affected by the location of the monitor while S is less related to the distance between the monitor and source of the pollutant[31]. In this study, the monitors from the three Italian centres were in busy streets, reflecting a traffic situation instead of the urban background. Thus, the most appropriate marker of urban background pollution, measured at a single monitor, is the S content. However, spatial heterogeneity of $PM_{2.5}$ is rather limited as well. Thus, as shown, whether we use S or $PM_{2.5}$ as markers of background pollution has little influence on the results.

Comparison with other studies

The general distribution of annoyance was different from those described in other studies, as the percentage of subjects reporting very high annoyance (more than 8 on the scale in the Swiss SAPALDIA study[32] or more than 7 in the EXPOLIS study, including Finland, Greece and Czech Republic[33]) is lower in this study. Also the percentage of subjects reporting no annoyance is higher. Annoyance varies widely across Europe, showing a gradient from North to South. In previous studies, Rotko et al. described that 6% of respondents were highly annoyed by air pollution at home in Helsinki, 7% in Athens, 3% in Basel, 4% in Milan, 6% in Oxford and 25% in Prague[34], in comparison to 18% in eight Swiss cities[35] and 5 to 17% in 55 selected Swedish urban areas[36]. The variables associated with annoyance in this study are quite consistent with the ones described previously, mainly for gender, socio-economic status and subjects with respiratory symptoms. Forsberg et al.[37] and Williams et al. [38;39] described that women, middle aged people and subjects suffering from respiratory symptoms reported higher scores at the same pollution level. Rotko et al. found that

women, non white-collar workers and those living downtown in Helsinki perceived annoyance more often at home but they found little differences for other variables, such as age, respiratory symptoms, smoking status or environmental tobacco smoke (ETS) exposure[14]. In a study of six European cities Rotko et al. found an association between air pollution annoyance and female gender, respiratory symptoms, sensitiveness to air pollution and living downtown, but not with age, education, smoking status or having children[40]. Our comparison of the city average annoyance and centre pollution level does not confirm previous multi-centre findings such as those from Switzerland[41]. The substantial cultural and environmental heterogeneity across ECRHS centres as compared to the more homogenous Swiss population sample may partly explain this discrepancy.

Interpretation of determinants of annoyance

Several studies observed higher annoyance scores among women[14;42-44] and some have argued that women are in general more sensitive to environmental risks[45]. It has been proposed that women have more environmental conscience, and some authors have suggested that women in general have a better sense of smell than males[46;47]. However, it is still unclear why women could be more affected by air pollution[48;49] and our data reveal differences across cities with men reporting higher annoyance in some centres. We hypothesize that in some cities women may spend more time at home[50-52], thus having a better perception of the home environment. Adult women in the EXPOLIS study spent more time at home on average, from 2 and a half hours more in Athens to 10 minutes less in Prague[52]. It will be necessary to use qualitative and quantitative methods to gain a better understanding of the difference between men's and women's risk perception[53].

Although not surprising, the reason why subjects with respiratory indicators report higher scores of annoyance is unclear. It could be the fact that having respiratory symptoms makes them more sensitive and vulnerable to irritant substances such as air pollution[54]. Another explanation could be that symptomatic subjects, in general, spend more time at home. Subjects with respiratory symptoms could also be more likely to associate air pollution with a risk of respiratory disease, or be more aware of the risks of air pollution and therefore overstate their actual personal level of annoyance[55]. However, it is of interest that none of the asthma-related symptoms were associated with annoyance in the multivariate analysis. In the bivariate analysis, only "ever asthma" and "have presented an asthma attack in the last 12 months" were associated with annoyance but the associations were not very strong perhaps due to the improvement of asthma treatment relative to previous studies, which showed that asthmatic subjects are more sensitive to air pollution[56].

Socio-economic status was only associated with annoyance in the crude analysis. Non-manual workers tended to report more annoyance but this association was only marginally significant. The non-classified subjects tended to report higher annoyance than the manual workers. This group consisted mainly of housewives and students, as they tend to spend more time at home during the day, when there is more traffic, it is expected that they become more annoyed by air pollution.

The fact that smokers are less likely to report high levels of annoyance can be explained by the fact that smokers tend to have a lower perceived risk of health-related problems and are also less concerned about their health[57]. Another explanation could be that they are used to high smoke exposures and are less aware of ambient air quality.

As opposed to smokers, those exposed to environmental tobacco smoke tended to report greater annoyance, which could be due to the fact that they are more sensitive to air quality [58].

In general, annoyance was associated with reported traffic density at home, both for cars and heavy vehicles, but associations were heterogeneous. Southern centres tended to report higher levels of annoyance when reporting high traffic frequencies. Despite the fact that these individuals generally experience less traffic, they may be more sensitive to traffic, or they may be closer to streets or live in street canyons in some of the densily populated Southern cities of ECRHS. Although regional pollution was in general associated with average annoyance, we observed substantial scatter across these cities and countries. Annoyance at home most likely reflects local (traffic) pollution rather than the regional air quality. To test this hypothesis, we also adjusted for the reported traffic density at home, which may capture both local traffic density and the perception thereof. However, results changed only marginally with substantial cross-city variation. As a general pattern, people living in polluted cities reported, on average, a higher annoyance due to air pollution, but it is necessary to interpret that correlation cautiously as mean annoyance varied across communities with very similar ambient air quality.

Implications for policymakers

On the basis of our results, we caution against the use of community mean annoyance as a surrogate for regional air pollution. Although this may be appropriate across communities of similar cultural and environmental conditions, 'annoyance' appears to be much more complex in a cross-cultural international context since annoyance is a subjective measure. It represents the subjectivity of the participant and incorporates dimensions such as dread, fear in the face of the unknown or anxiety. Annoyance due to noise has been related to physical and psychological conditions[59-62]. Similar studies

have not been done for air pollution annoyance. Aggregate Public Health indicators which include air pollution and residential noise have been proposed to assess the health of a population[63]. Also, some authors have shown that people are concerned with air pollution[64-66] and have proposed that to fully evaluate the impact of air pollution on health, it is necessary to not only assess the chemical aspect but also the circumstances, including the social ones, of the subject[67]. Many factors have to be taken into account when assessing the relationship between air pollution levels such as air pollution perception and beliefs on air pollution risks[68]. Air pollution might trigger annoyance by physical or psychological mechanisms. The former would include acute symptoms directly caused by air pollution. It has been recognised that air pollution is associated with headache, rhinitis, cough, eye irritation [69-71]. Subjects might attribute these to air pollution and therefore report annoyance. On the other hand people may be aware of the risks of air pollution[72;73] from which they cannot usually escape. This may cause frustration and lead to higher annoyance.

The individual's perception of air pollution is also a key issue in the development of new policies of risk assessment and management. Risk perception is a complex matter that includes social, political and cultural aspects[74] and annoyance due to air pollution is only one of the aspects related to air pollution risk perception. Thus, we conclude that individuals' annoyance due to air pollution, although not valid as a measure of true air quality, may be a useful measure of perceived ambient quality. It can easily be monitored in surveys, across Europe, and may put environmental policies into perspective of people's perception and help locate populations with the biggest needs for environmental changes.

Unanswered questions and future research

Despite the large size of this study and its international setting, we did not find a strong association between annoyance and air pollution measurements. Objective characterisation of environmental exposures would be necessary to fully disentangle individual, social, cultural and environmental determinants of annoyance or perceived air quality at home. Given the complex link between health, well-being, social factors, the environment and personal choices, prospective studies, including personal or home-based air pollution measurements, may be of particular value.

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Association between annoyance and individual's values of NO_2 in a European setting.

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Association between annoyance and individual's values of NO_2 in a European setting

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Abstract

Introduction: Annoyance due to air pollution has been proposed as an indicator of exposure to air pollution. Our aim was to asses the geographical homogeneity of the relationship between annoyance and modelled home based NO_2 measurements.

Methods: The European Community Respiratory Health Survey II (ECRHSII) was conducted in 2000-01, in 25 European centres in 12 countries. Modelled air pollutants were obtained in 20 cities. For this analysis outdoor residential NO_2 from 4753 subjects (from 37 in Tartu to 532 in Antwerp) were used. Annoyance due to air pollution was self-reported on an 11 points scale (0: no disturbance at all, 10: intolerable disturbance). Demographic and socioeconomic factors, smoking status and presence of respiratory symptoms or disease were measured through a standard questionnaire. Negative binomial regression was used.

Results: Median NO_2 concentration was 27 $\mu g.m^{-3}$ (from 10 in Umea to 57 in Barcelona). The mean of annoyance was 2.5 (0.7 in Reykjavik to 4.4 in Huelva). NO_2 was associated with annoyance (Ratio of the mean score 1.26 per 10 $\mu g.m^{-3}$, 95% Confidence Intervals 1.19-1.34). The association between NO_2 and annoyance was heterogeneous among cities (p for heterogeneity < 0.001).

Conclusions: Annoyance is associated with home outdoor air pollution but with a different strength by city. This indicates that annoyance is not a valid surrogate for air pollution exposure. Nevertheless, it may be a useful measure of perceived ambient air quality and could be considered a complementary tool for health surveillance.

Key words: annoyance, air pollution, NO_2, Europe

I Introduction

Assessment of individual's exposure to traffic related air pollution is complicated. Personal or home outdoor measurements are not easily feasible in large epidemiological studies and tend to be very expensive. Modelling presents an alternative; but adequate information is not always available on source emissions or from environmental measurements.[1] It has been suggested that annoyance due to air pollution reported through a questionnaire could be used as an indicator of exposure to air pollution.[2;3] Several studies have shown a moderate to good association between central levels of air pollution and annoyance but they also concluded that personal characteristics were stronger determinants than the actual levels of air pollution.[4-10] Few studies have assessed the association between NO_2 exposure at individual level and annoyance due to air pollution. Oglesby et al. suggested that annoyance could not replace home based measurements, as annoyance was strongly influenced by personal factors and they also suggested that even adjusting for all the personal determinants would not be enough as they found interactions between NO_2 and individual's variables.[11] Rotko et al. did not find an association between home outdoor NO_2 and annoyance due to air pollution while at home when doing the analysis at individual level, they only find an association at population level.[12] In a previous study, we showed the determinants of annoyance in the European Community Respiratory Health Survey II (ECRHSII) population and we found a moderate association between annoyance and central measurements of $PM_{2.5}$ and its Sulphur content, although heterogeneous across centres.[13] Annoyance is assessed for the local environment around the house which is not captured by centrally measured background pollutants. At that time home outdoor measurements of air pollution were available in a subgroup only. We have now linked modelled NO_2 home outdoor concentrations for the residence of the majority of the subjects. This allows us

to assess the association between air pollution and annoyance due to air pollution, at the individual level in a larger population.

The objective of this study was to assess the association between reported annoyance due to air pollution and home outdoor levels of NO_2 in 20 cities from 10 countries, and investigate the geographical homogeneity thereof.

II Materials and Methods

Study population

The ECRHS was carried out in twenty-eight urban centres, in 11 European countries. It was first conducted in 1991-3 and repeated in 1999-2001. Centres were chosen based on pre-existing administration boundaries, their size and the availability of sampling frames. Subjects were randomly selected from the populations aged 20-44 in 1991-3. A sub sample of symptomatic subjects was also recruited. The details of this project study are described elsewhere.[14;15]

This analysis was based on the second survey, including all the subjects from the random samples with modelled home outdoor NO_2 who had answered the annoyance question. When the modelled NO_2 was not available, home outdoor measurements were used if obtained. 4753 (4399 with modelled NO_2 and 354 with measured home outdoor NO_2) subjects in 20 cities in 10 countries were included. Sample size varied by centre from 37 in Tartu (Estonia) to 532 in Antwerp (Belgium). Ethical approval was obtained for each centre from the appropriate institutional or regional ethics committee, and written consent was obtained from each participant.

Description of variables

Annoyance due to air pollution was self-reported on an 11 point scale (0: no disturbance at all, 10: intolerable disturbance) through the following question: “How much are you

annoyed by outdoor air pollution (from traffic, industry, etc) if you keep the windows open?". The other variables used in this analysis were sex, age, night shortness of breath, chronic phlegm, ever rhinitis, socio-economical status (based on occupation), smoking (never, ex, current) and exposure to environmental tobacco smoke (ETS). Self reported traffic was also associated with annoyance but it was not used in this analysis since it is closely related to NO_2.

Modelled NO_2 measurements from APMoSPHERE

Modelled NO_2 derived from the EU-funded APMoSPHERE (Air Pollution Modelling for Support to Policy on Health and Environmental Risks in Europe). NO_2 has been widely used as a marker for traffic-related air pollution. As part of APMoSPHERE 1-km-resolution emission maps of several pollutants, including NO_2, were developed for the then member states (EU15). Estimates were obtained by disaggregating national emissions estimates, categorised by sources of air pollution (SNAP categories), to the 1km level on the basis of relevant proxies (e.g. population density, road distribution, land cover).[16] Modelling of NO_2 concentrations was then done using focal sum techniques, in a GIS, to relate emissions within concentric zones around each monitoring site to the monitored concentrations. Models were developed using monitoring data from 714 background sites for 2001, drawn from the EU Airbase database. Validation was conducted by comparing predictions with observations for a separate set of 228 sites ($r^2 = 0.60$).

Where modelled NO_2 estimates could not be provided, home outdoor measurements were used if available. That was the case for 3 cities that were/are not in the European Community (Reykjavik, Tartu and Basel resulting in 287 subjects), for the subjects in Umea that did not live in the city centre and were not geocoded due to local reasons

(117 subjects) and for some cases in UK (25 subjects) and Spain (5 subjects) for whom the address was not clear or missing.

Home outdoor NO_2 measurements

Measurements of NO_2 as a marker for local tail pipe emissions were made at the homes of a subset of participants. At this individual level, outdoor (at the kitchen, or bedroom when kitchen was not available, window) and kitchen indoor NO_2 concentrations were collected during a 14 day period in 16 centres during 2001, involving around 2050 households of subjects who did not move house during the follow up. After about six months this procedure was repeated in 40% of the households. Values below limits of detection were set at half the detection limit (0.34 μg.m-3) and values above 150 (maximum 180) μg.m-3 were set to 150 μg.m-3. The passive samplers (Passam AG, Switzerland) were analysed in a central laboratory. For subjects with two measurements the mean of the two was calculated. Home outdoor NO_2 measurements were used in this analysis when modelled NO_2 measurements were not available.

Statistical analysis

Negative binomial regression was used to assess the association between annoyance and NO_2. The multivariate model used was the same as that previously applied to analyse annoyance for this population.[17] The variables included in the original model were sex, socio-economical status, night shortness of breath, chronic phlegm, rhinitis, smoking status, exposure to ETS and self reported car and heavy vehicles traffic. However self reported traffic was not included in the model used here, as traffic is closely related to NO_2 (and data on road traffic emissions are employed in the APMoSPHERE models). Annoyance and the other variables associated with it in the multivariate model were tested to see if subjects with NO_2 measurements were different from those without

measurements from the ECRHSII population. Wilcoxon-Mann-Whitney test was used for annoyance score and chi square test for categorical variables. NO_2 was analysed as a continuous variable, in quartiles and dichotomously (below and above the median). The results are expressed as ratios of the mean annoyance scores. Effect estimates were derived for each centre and area and heterogeneity across cities was examined by using standard methods for random-effects meta-analysis. To help measure how well the estimates capture the variability of the annoyance score, we used the pseudo R^2 given by the software, which is analogous to the R^2 of the ordinary logistic regressions. The pseudo R^2 presented here was the inverse of the likelihood of the full model over the likelihood of the model including only the constant. The analysis was made using STATA 8. The criterion for statistical significance was set at a p value < 0.05.

III Results

Central medians of NO_2 levels varied from 9.75 $\mu g.m^{-3}$ in Umea (Sweden) to 57.32 $\mu g.m^{-3}$ in Barcelona (Spain). In general, northern centres had lower levels of NO_2. In table 1, centres are ordered from North to South and data shows the distribution of NO_2 home outdoor levels means per centre.

The distribution of annoyance per centre is reported in table 1 and the means ranked from 0.7 in Reykjavik (Iceland) to 4.38 in Huelva (Spain). The percentage of subjects highly annoyed (6 or more in the scale) varied from 1 in Reykjavik to 40 in Huelva. A North to South trend in reported annoyance was observed.

Table 1: Description of outdoor NO_2 (median and interquantile range) and description of annoyance (mean and porcentaje of highly annoyed), per city.

Centre	N	NO_2* in percentiles			Annoyance	
		p25	p50	p75	Mean	Percent ≥ 6
Reykjavik (RE)	82	7.30	12.25	19.20	0.70	1
Umeå (UM)	268	4.88	9.75	12.47	1.63	9
Upssala	487	11.27	15.45	19.75	1.04	5
Tartu (TA)	37	19.30	22.20	26.20	2.54	11
Goteborg	318	23.41	26.67	28.74	1.04	4
Norwich (NO)	236	22.50	25.40	27.05	1.86	10
Ipswich (IP)	244	24.90	26.10	28.00	2.95	23
Antwerp	532	22.99	27.83	32.93	3.36	24
Erfurt	83	19.61	24.48	25.84	2.90	18
Paris	424	49.05	50.46	52.57	3.34	25
Basel (BS)	88	29.23	34.35	38.75	3.57	30
Grenoble	382	25.41	30.80	31.45	2.69	16
Verona (VE)	205	23.87	27.54	29.43	2.84	22
Pavia (PA)	192	15.36	19.31	23.72	1.84	13
Torino (TU)	73	35.90	38.33	40.59	3.62	29
Oviedo (OV)	139	24.13	30.48	32.09	2.55	17
Galdakao (GA)	359	19.89	25.50	33.02	2.61	16
Barcelona (BA)	256	53.45	57.32	59.19	3.61	25
Albacete (AL)	144	28.32	29.75	31.81	3.35	24
Huelva (HU)	204	29.68	33.42	33.70	4.38	40
Total	4753	19.89	27.10	32.93	2.48	16.73

* Including 4399 modelled + 354 measured home outdoor NO_2

The association between NO_2 and annoyance was positive and significant, disregarding the NO_2 categorization or the level of adjustment. When categorizing the NO_2, the estimates increased in accordance to NO_2 quartiles (table 2).

Table 2: Ratio of mean annoyance scores from negative binomial regression.

	Crude		Adjusted by centre		Adjusted*	
	RMS	95% CI	RMS	95% CI	RMS	95% CI
NO_2 increase per 10 µg.m^{-3}	1.29	(1.25 - 1.33)	1.27	(1.21 - 1.35)	1.26	(1.19 - 1.34)
NO_2 in quartiles	1.58	(1.42 - 1.76)	1.38	(1.21 - 1.58)	1.38	(1.20 - 1.60)
	2.06	(1.85 - 2.29)	1.60	(1.40 - 1.84)	1.53	(1.30 - 1.78)
	2.53	(2.27 - 2.81)	1.84	(1.58 - 2.15)	1.85	(1.55 - 2.19)
NO_2 > 27 µg.m^{-3}	1.78	(1.65 - 1.91)	1.32	(1.20 - 1.45)	1.29	(1.16 - 1.44)

RMS ratio of the mean annoyance score
* sex, ses, night shortness of breath, chronic phlegm, rhinitis, smoking, passive smoking, centre

Figure 1 shows the centre-specific adjusted estimates. The p-value for heterogeneity was below 0.001. Table 3 shows the specific crude and adjusted estimates and the pseudo R2 of each model for each centre. For the adjusted analysis the association was positive and significant in Umea, Uppsala, Antwerp, Grenoble, Torino and Huelva; positive but not significant in Reykjavik, Goteborg, Norwich, Ipswich, Paris, Basel, Pavia, Oviedo, Galdakao and Barcelona and negative but not significant in Tartu, Erfurt, Verona and Albacete. The general pseudo R^2 for the crude model was 0.13 and the

pseudo R^2 distribution within cities varied from 0 to 0.024 for the crude model and from 0.006 to 0.104 in the adjusted model.

Table 3: Ratio of mean annoyance scores from negative binomial regression per each center

	Crude*			Adjusted*†		
	Ratio of mean score	95% CI	R^{2} **	Ratio of mean score	95% CI	R^{2} **
Reykjavik	1.23	(0.66 - 2.29)	0.003	1.11	(0.57 - 2.18)	0.062
Umea	**1.73**	**(1.14 - 2.64)**	0.007	**1.70**	**(1.06 - 2.73)**	0.026
Uppsala	**1.57**	**(1.16 - 2.13)**	0.007	**1.57**	**(1.14 - 2.17)**	0.027
Tartu	1.27	(0.68 - 2.38)	0.004	*0.88*	*(0.35 - 2.25)*	0.104
Goteburg	1.14	(0.67 - 1.94)	0.000	1.09	(0.63 - 1.88)	0.015
Norwich	**1.78**	**(1.11 - 2.84)**	0.007	1.60	(0.89 - 2.85)	0.032
Ipswich	1.25	(0.85 - 1.84)	0.001	1.29	(0.83 - 1.99)	0.006
Antwerp	**1.89**	**(1.61 - 2.23)**	0.024	**1.96**	**(1.63 - 2.35)**	0.035
Erfurt	0.88	(0.56 - 1.38)	0.001	*0.89*	*(0.50 - 1.58)*	0.037
Paris	*1.08*	*(0.99 - 1.18)*	0.002	1.08	(0.98 - 1.18)	0.014
Basel	1.16	(0.83 - 1.60)	0.002	1.32	(0.86 - 2.03)	0.020
Grenoble	**1.74**	**(1.45 - 2.08)**	0.021	**1.62**	**(1.35 - 1.96)**	0.030
Verona	1.03	(0.69 - 1.55)	0.000	*0.87*	*(0.55 - 1.39)*	0.016
Pavia	*1.60*	*(0.93 - 2.75)*	0.004	1.65	(0.83 - 3.28)	0.024
Torino	1.55	(0.83 - 2.88)	0.005	**2.38**	**(1.31 - 4.33)**	0.108
Oviedo	1.19	(0.80 - 1.76)	0.001	1.37	(0.86 - 2.16)	0.023
Galdakao	*1.16*	*(0.99 - 1.35)*	0.002	1.11	(0.91 - 1.34)	0.007
Barcelona	1.11	(0.98 - 1.26)	0.002	1.10	(0.96 - 1.26)	0.016
Albacete	1.07	(0.70 - 1.62)	0.000	*0.99*	*(0.61 - 1.59)*	0.015
Huelva	**1.58**	**(1.16 - 2.15)**	0.008	**1.80**	**(1.23 - 2.65)**	0.036
All Fixed	**1.26**	**(1.19 - 1.32)**	0.013	**1.24**	**(1.18 - 1.32)**	0.034
All Random	**1.32**	**(1.18 - 1.49)**	NA	**1.33**	**(1.17 - 1.52)**	NA

bolded estimates have a p-value <0.05
italics estimates have a p-value <0.10
* p value for heterogeinity < 0.001
** pseudo R^2 of the whole model

† sex, ses, night shortness of breath, chronic phlegm, rhinitis, smoking, passive smoking, centre

The association between annoyance and NO_2 stratified by gender and by respiratory symptoms is presented in table 4. All the subgroups showed a similar association and in all the cases the pseudo R^2 was low, around 0.03. Stratifying by atopy gave similar results; the pseudo R^2 being 0.04 in atopics and 0.03 in non-atopics.

	All				For females				For males				Without any respiratory symptoms				With any respiratory symptom			
	Ratio of mean score	95% CI		R^{2**}	Ratio of mean score	95% CI		R^{2**}	Ratio of mean score	95% CI		R^{2**}	Ratio of mean score	95% CI		R^{2**}	Ratio of mean score	95% CI		R^{2**}
Crude	1.29	(1.25 -	1.33)	0.0132	1.28	(1.23 -	1.34)	0.01	1.30	(1.24 -	1.37)	0.01	1.30	(1.22 -	1.38)	0.01	1.28	(1.23 -	1.33)	0.01
Adjusted per centre	1.27	(1.21 -	1.35)	0.0281	1.32	(1.23 -	1.42)	0.03	1.20	(1.11 -	1.30)	0.03	1.38	(1.24 -	1.53)	0.03	1.23	(1.15 -	1.31)	0.03
Fully adjusted*	1.26	(1.19 -	1.34)	0.0338	1.31	(1.20 -	1.42)	0.04	1.22	(1.11 -	1.33)	0.04	1.41	(1.25 -	1.58)	0.03	1.21	(1.13 -	1.29)	0.03

*sex, ses, night shortness of breath, chronic phlegm, rhinitis, smoking, passive smoking, centre

** pseudo R^2 of the whole model

Table 4: Ratio of mean annoyance scores from negative binomial regression. Stratified.

IV Discussion

Annoyance due to air pollution was associated with home outdoor NO_2 measurements; nevertheless this association was different among cities. The estimates were very weak even in the centres with the strongest associations, and were even negative in some cities. No clear geographical pattern could be observed. No specific subgroup of subjects who could better predict NO_2 with annoyance was found.

One of the strengths of this study was the large number of participating cities across Europe, allowing us to compare the heterogeneity of associations between NO_2 and annoyance across different European countries. Another advantage was that it included measurements of NO_2 estimated (or measured) at the place of residence, thus allowing the association with annoyance to be analysed at the individual level. While NO_2 per se may not cause annoyance, it is a widely used surrogate of traffic-relate pollutants and, thus, is expected to correlate with traffic emissions that may be more easily identified as a bad smell. For annoyance due to air pollution, to our knowledge, only three previous studies have used individual-level air pollution concentrations.[9;18;19]

An issue that has been raised previously about the association between annoyance due to air pollution and air pollution is that the question itself has limitations in its phrasing. On the one hand, it concerns annoyance caused by outdoor air pollution whilst indoors; this is likely to be influenced by the frequency with which the subjects open their windows, as well as the proportion of time spent indoors and general ventilation conditions. Assuming that subjects in colder (northern) countries are less likely to open their windows; we would expect weaker associations in northern countries. This was, however, not the case: the association between annoyance and air pollution showed no clear geographic pattern. The estimates, as well as the pseudo R^2, for each centre were instead very heterogeneous. It is also important to note that the inclusion in the

multivariate model of the variable “Do you sleep with the window open in winter?”, as well as the variable assessing the frequency of such events, did not alter the estimate of the association between annoyance and NO_2. In stratified analyses, the estimate was similar in subjects sleeping with the window open to those who do not, and even tended to be slightly smaller in the former. To sleep with the window open was associated with annoyance only in the crude model; once centre was added into the model, the association disappeared. The season of the interview was not associated with annoyance, nor with the association between annoyance and NO_2.

Another weakness of this study is that the sub-sample for whom NO_2 values were available was not the same as that without them. Subjects with NO_2 tended to be more annoyed by air pollution. They also included more females and more people in formal employment (as opposed to others such as housewives or students), had more rhinitis, were less likely to be current smokers and reported more traffic than the subjects without NO_2 values. The reasons for these discrepancies are not clear, since a high proportion (70%) of participants in the random sample of ECRHSII had NO_2 values. The main determinant of exposure estimation was the ability to geocode the address, which in principle has nothing to do directly with the personal characteristics of the subjects. There were, however, possible biases in Umea and Goteborg, where only participants living in the city centre could be geocoded.

Most of the studies investigating association between annoyance and air pollution have found a correlation between both, using central, personal modelled and/or individual concentrations of pollutants. They have also usually concluded that personal characteristics also play a big role in the rating of annoyance. To our knowledge, however, no previous studies have compared associations between countries.

Forsberg at al., for example, showed an association between annoyance due to air pollution and central NO_2 concentrations. The correlation coefficient between the percentage of subjects reporting annoyance per city or town and the six month average NO_2 was around 0.60. They found a better correlation for subjects living in urban areas than for the ones living in residential areas.[20] Williams and Bird showed that perception of air pollution was not a reliable indicator of the actual levels when using the measurements from the nearest monitoring station in Greater London. They did not compare among different cities but they showed that inside the same city, subjects living in urban areas were more disturbed than subjects living in suburban areas.[21] Klaeboe et al. found an association between environmental annoyance and three months mean of modelled NO_2 in Oslo. Subjects tended to have more complaints or higher levels of annoyance when the levels of NO_2 were higher.[9] Oglesby et al. found a significant association between high annoyance due to air pollution and estimated home outdoor NO_2 in 8 Swiss cities. However, the association was not significant when they used the annoyance score. The crude correlation between annoyance score and estimated home outdoor was $r = 0.36$ and NO_2 explained 7.5% of the annoyance variance. They also suggested that subjects could rate annoyance differently from one area to another within the same country.[22] Rotko et al found a very high correlation between annoyance due to air pollution in traffic and home outdoor NO_2 concentration when aggregating the results by city ($r=0.99$). When assessing the association individually, it was significant but the crude model only explained 13% of the annoyance variance. They had individual level NO_2 measurements for four cities in Europe but they did not compare between the cities.[23] In a previous publication we assessed the association between annoyance due to air pollution and air pollution characterized at one central monitor instead of the residential location. We found a

moderate association that was heterogeneous among centres.[24] Now, in this study we show how the relation between annoyance and air pollution also differed by geographical areas even using individual determinations. The association is heterogeneous and the levels of NO_2 explained very little of the annoyance variance at individual level, as reported previously.

Even if home outdoor NO_2 and annoyance due to air pollution are associated, we do not recommend the use of annoyance as a surrogate for personal exposure to traffic-related air pollution. The general pseudo R^2 for the crude model was low and the pseudo R^2 distribution within cities varied. Only a small part of the NO_2 variation can thus be predicted on the basis of annoyance. The correlation is only partly explained by the levels of the pollutants and the personal characteristics. We were not able to identify a subgroup of subjects who would better predict the NO_2 in comparison with the total population, although we selected women and/or subjects with respiratory symptoms where one could plausibly argue that those subjects tended to be more annoyed by air pollution.[25] Another reason why we do not recommend the use of annoyance as an air pollution indicator is its heterogeneity. The estimates varied from negative to positive association without any discernable geographical pattern. To interpret a pooled estimate would be incorrect.

The fact that the association between annoyance and NO_2 varies from city to city suggests a socio-cultural influence. The importance of personal, social and cultural factors in influencing risk perception has long been well-established.[26] Bickerstaff explained how social and cultural factors could influence perception of air pollution. The main conclusion was probably that the perception of risk takes into account numerous factors including social, political and cultural ones, and that there is no a set of variables that could predict the risk perception at group level.[27] Olofsson and

Öhman showed that personal characteristics, including political affiliation or education, could predict environmental concern but the addition of general beliefs, such as beliefs about science or view of nature, increased predictability. They also showed that the individual factors related to environmental concern were not the same and did not have the same predictive power between the two geographical areas they studied (North America vs. Scandinavia).[28] Dietz et al. investigated whether individual characteristics and/or beliefs could explain their environmental willingness to act. They found no clear association and that environmental participation was not predictable.(29) Annoyance is thus subjective, and not all the annoyance can be explained by measurable variables. However that subjectivity does not take away its importance, as it reflects the subjects' feelings. Also it has been suggested that annoyance per se could have health effects. Subjects are aware of health effects of air pollution and are concerned about it, even when the levels are in accordance with the guidelines.[30;31] Lercher et al. found an association between annoyance and respiratory symptoms not explained by air pollution concentrations and suggested that the perception of polluted air could trigger annoyance and symptoms even when air pollution levels are below the guidelines.[32] It has also been suggested that a negative impression of the general environment of the neighbourhood was associated with a lower health quality.[33;34]

Policy makers might take into account the annoyance due to air pollution as a direct outcome of interest. While this and other studies ultimately confirm that annoyance is not a valid maker of air pollution exposure, it is important in its own right as it integrates individual perception, feeling of security and health problems. It may also influence trust in government and the regulatory authorities.[35] Its standardized measurement is simple and it could be easily added to environmental monitoring and health tracking surveys.

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Air pollution and asthma in ECRHS.

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Air pollution and asthma in ECRHS

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Short title: Air pollution and asthma in ECRHS

Abstract

We studied the association between urban background particle pollution, self reported traffic intensity at home, nitrogen dioxide (NO_2) measured outside home and five symptoms of current asthma analysed as a continuous score (ranges from 0 to 5) as well as asthma incidence.

Persons aged 25-44 years were randomly selected (1991-1993) and followed up to 10 years later, 2000-2002 (European Respiratory Health Survey (ECRHS I+II). ECRHS II included standardized particle pollution measurements taken during one year in 21 centres across 10 countries, and individual measurements of NO_2 for a subset of participants (16 centers). In total 4284 persons were at risk in the asthma incidence analysis. Since particles were measured at city level and other variables were reported individually, hierarchical models were used.

Urban background levels of pollution were not correlated with asthma outcomes. However, self-reported traffic intensity at home was associated with higher asthma scores and a risk for new onset of asthma. NO_2 at home outdoors was positively associated with the score with some evidence for larger effects among atopics (ratio of mean scores 1.19 per 10 $\mu g/m^3$, 95% CI = 1.04-1.36).

This study provides preliminary evidence that local traffic-related pollutants may both aggravate and induce asthma in adults.

Key words: air pollution, asthma, incidence, severity

I Introduction

It is well known from time-series studies that fluctuations in air pollution levels are associated with short-term effects on asthmatics[1]. Worsening of asthma symptoms, emergency visits and hospitalizations are in several studies correlated with short-term concentrations of air pollutants such as particles and ozone. A few studies have focused on ambient air quality and asthma incidence in children, but only one investigation focused on new onset of asthma in adults. That recent study from Sweden reported a non-significant positive association between living close to high traffic flows and asthma incidence in adults[2]. Else, evidence of adverse effects of air pollution on asthma outcomes and of a potential asthmogenic role of traffic-related local pollutants are by and large based on studies in children[3-20]. In adults, traffic related pollutants have been associated with the prevalence of cough, bronchitis and COPD rather than with asthma [21-25]. However, an Italian study found indications of an association between NO_2 and asthma prevalence in young adults when climate was adjusted for[26], and among US Veterans residence near a major road made persistent wheeze more prevalent[27]. One study found health care use for asthma in adults associated with traffic volume[28], while similar studies in children have been both positive[29-31] and negative[32,33].

Air pollutants may not only trigger symptoms in asthmatics and amplify the inflammatory reactions in the airways, but in addition promote allergic disease[34-36]. In animal as well as in human experiments, air pollutants, especially diesel exhaust particulates, are able to trigger or amplify an IgE-response. Brief exposures to street levels of NO_2 (500 µg/m3) appears to prime circulating eosinophils and enhance the eosinophilic activity in sputum in response to inhaled allergens[37]. Pollutant-induced

oxidative stress could promote airway inflammation and, consecutively, hyper responsiveness which may be one path to development of asthma. Atopy and a family history of asthma may reflect varying susceptibility to air pollutants[2, 18-20], but this needs to be further investigated. Associations with air pollution have in some studies been different between sexes[3, 4, 15, 17, 19, 38], however no firm conclusions can yet be drawn.

Despite a fast growing number of air pollution studies very little is known about the effect of particles and vehicle exhaust on asthma severity and incidence in adults. The ECRHS has shown that the course of asthma can be graded using a score based on the occurrence of asthma symptoms[39, 40]. There is no threshold in the association between increasing number of asthma symptoms and any of the markers of asthma severity or main risk factors of asthma, suggesting that symptoms of asthma are possibly best analyzed as a continuous asthma score in epidemiological studies. Thus, the aim of this study is to investigate whether asthma incidence and asthma related illness using this novel score are associated with urban background particle pollution, indicated with $PM_{2.5}$ mass concentration or sulfur content of $PM_{2.5}$. Moreover, we investigate whether these asthma outcomes associate with traffic-related pollution at home outdoors. These pollutants are poorly characterized with urban background pollution with contrasts in people's exposure originating mostly from differences within rather then between cities. Thus we use self reported residential traffic intensity and NO_2 concentrations measured at home outdoors.

II Materials and Methods

Study population

Persons aged 25-44 years were randomly selected from the population for the European Respiratory Health Survey (ECRHS I) carried out in 1991-1993[41]. The follow-up (ECRHS II) took place during the period 2000-2002 and included also standardized fine particle pollution ($PM_{2.5}$) measurements over one year in 21 of the ECHRS centres from 10 countries, analysis of elements and oxidative properties, and individual measurements of nitrogen dioxide for a subset of participants from 16 centers[42-44]. The follow-up of the random ECRHS I sample included from these centres leads to a sample of 3232 males and 3592 females (mean response rate = 65.3%). Both surveys included initial screening questionnaire, extensive interviewer led questionnaire, skin prick test, blood test for IgE, spirometry and methacholine challenge test.

Asthma variables

The *asthma score* used in this study is a modification of a score earlier developed using data from ECRHS[39]. The authors concluded that symptoms of asthma are possibly best analysed as a continuous asthma score, since there is no threshold in the association between increasing numbers of asthma symptoms and any of the markers of severity of asthma or the main risk factors. The original score was based on answers to eight questions, were three included the term "asthma". The modified score consists of a sum of the positive answers to the other 5 questions dealing with symptoms during the last 12 months, *i.e.* this simplified score ranged from 0 through 5[40]. The positive answers to these questions meant that the following problems were present during the last 12 months: wheeze and breathlessness, feeling of chest tightness, attack of shortness of breath at rest, attack of shortness of breath after exercise, and, woken by attack of shortness of breath. In contrast to the binary responses to the usual asthma questions, the score characterizes asthma as a continuum, thus captures asthma severity. In

addition, the score is expected to increase the power of a study in comparison with a dichotomous definition. It has shown that the score has a good predictive ability for occurrence of markers of asthma at follow-up, as well as for identifying risk factors[40]. For comparison purposes, we also evaluated the association of pollution with each symptom separately.

The asthma score was used for all subjects as well as for subsets; those with/without ever asthma, with/without family history of asthma or atopy, in atopics/non-atopics, non-smokers, and in males/females.

Cumulative incidence of asthma has been studied among participants in ECRHS II who in ECRHS I answered *no* to whether they have ever had asthma. There were 4284 persons at risk. However, 108 out of 208 reported at the follow up (ECRHS II) their first asthma attack to have occurred at an age less their age at inclusion in ECRHS, when they denied having asthma. Another 18 asthmatics did not give any information on age at first attack. However, 46 % out of these 122 persons did not report any respiratory symptoms during the last 12 months asked for in ECRHS I. 40% of the rest of new the cases were according to ECRHS I free of respiratory symptoms the last 12 months. Due to this inconsistency in the questionnaire responses, we use two definitions of new cases of asthma. First we use all 208 new cases, second we accept as 'new asthma' only those with a reported age at first attack falling between ECRHS I and the follow up. The simple definition may at least be a valid measure for "onset of adult symptomatic asthma", while the more strict definition may be closer to 'true incidence' in terms of first time expression of asthma.

The level of current asthma symptoms analysed as a continuous score has been studied in all participants as well as in only those reporting ever asthma in ECRHS II. All the

questions on asthma were answered by 6731 subjects. Full information on the individual covariates used in our models exists for 4586 persons.

Cumulative incidence was also studied stratified by sex, family history of asthma or allergy, and by atopy and in non-smokers. In addition, the analysis was restricted to those having the same residence at baseline and at the follow up.

Air pollution

Air pollution was characterized in two ways. First, particle concentrations were used to characterize the rather homogenously distributed 'urban background pollution' ($PM_{2.5}$ and sulfur content of $PM_{2.5}$). Exposure contrasts are thus assumed to originate from comparisons across communities. Second, traffic related pollution outside the residence was used to integrate contrasts in exposure that originate from differences in local emissions, thus, within communities.

Each study centre (N=21 in 20 cities) operated a fixed monitoring site to estimate the annual mean of $PM_{2.5}$ in a central location. In all centers the mass concentration of $PM_{2.5}$ was measured for one year to derive an annual average. The methods and city specific results have been described elsewhere[42]. Standardized technique and similar equipments (the Basel $PM_{2.5}$ sampler from BGI, Inc.; Gelman Teflo filters) were used in all centres and a single central laboratory and one technician was responsible for weighing the filters. Sulfur content on $PM_{2.5}$ is particularly homogenously distributed across urban areas, thus well suited to characterize urban background pollution. Thus, elemental composition of $PM_{2.5}$ was assessed on all filters using dispersive X-ray fluorescence spectrometry (ED-XRF). Elemental composition and also oxidative properties of the $PM_{2.5}$ are already published[43,44]. In four centers the measurement site was located within 15 meters of the main street (Pavia, Turin, Verona and Antwerp

City). Although sulfur is unlikely to be heavily affected by local sources[43], we also performed sensitivity analyses without these centers to test for the influence of monitor location.

The assessment of individual-level exposure to traffic-related pollution relied on two approaches, namely a questionnaire, and NO_2 measurements.

Self-reported exposure

Traffic intensity outside the house was reported separately for cars and heavy vehicles (never, seldom, frequently or constantly), and the answers from these two questions were combined to a four category variable for which the highest category "constant" needs the answer constantly for at least one question, and at least frequently for the other. The lowest category "never" (taken as reference) means that the answer to both questions was never or that the answer was never for one type of vehicles and seldom for the other type.

Measured NO_2-levels at home

For a subset of participants (1634 persons from 16 centers) we implemented a home-based measurement protocol using nitrogen dioxide (NO_2) as a marker for motor vehicle emissions outdoors (and also gas use indoors). 1270 persons in this subgroup had information on all covariates used in adjusted analyses. Diffusive samplers (Passam AG, Switzerland) were placed outside the kitchen window where the NO_2 concentration was measured during a 14-day period. Fore some individuals (n=667) this was repeated a second time. Samplers were stored refrigerated and subsequently analyzed centrally [42].

The subgroup with measured NO_2 concentration at home was representative with regards to asthma and self reported traffic. There was no difference in the prevalence of asthma ever (10 vs. 9 %, p= 0.22) or atopy (28 vs. 26 %, p=0.13) between participants with NO_2 data and those without, and persons with NO_2 measurements reported constant car traffic outside their kitchen only slightly more often than the rest of the participants in the 16 centers with home measurements (25 vs. 22 %, p= 0.01).

Statistical analysis and covariates

We used hierarchical models to adjust for the effect of covariates and to evaluate the relation to self-reported traffic intensity at home at the individual level, and to examine the association with particle pollution with exposure data at center level[45-46].

As the core set of covariates we included sex, age, atopy (IgE > 0.35), family history of asthma or atopy, smoking (no, former, current), occupational exposure (none, low, high), social class (5 categories based on the ISCO coding of the occupational history), and gas cooking (mainly gas vs. others). These risk factors of asthma outcomes were retained in models regardless of their significance. Stratified sub-group analyses included all these covariates but the stratification variable.

The asthma score is modeled using a negative binominal distribution. For individual level variables we model the ratio of the mean scores together with 95 % confidence intervals (95% CI) and for centre level variables the ratio of the mean scores with the 80 % interval relative change (IRC), that is, for air pollutants the mean, the lower and the upper limit of the estimated effect per unit change in the concentration. In a sensitivity analysis we also studied the five symptoms from the asthma score separately using logistic regression. For NO_2 the effect of a 10 $\mu g/m^3$ higher concentration is reported.

For the categorical variable "traffic flow" the lowest category "never" is used as the reference category.

For the analysis of cumulative incidence the model is based on the Bernoulli distribution, and the length of the follow-up period for each subject was adjusted for in the regression model. From the incidence study we present the odds ratio with 95% CI for individual level variables and the interval odds ratio, covering the middle 80 % of the odds ratio, associated with one $\mu g/m^3$ increase in the annual mean concentration for particulate pollutants.

Due to the smaller number of participants with home outdoor NO_2 measurements we were unable to conduct the incidence analyses in this subgroup. Individual level NO_2 was thus only used to study relations with the asthma score applying logistic regression. In these models adjustments were also included for centre and for the season from which values originated (spring, summer, autumn, winter).

In the analysis of relations to self-reported traffic intensity and individual NO_2 concentration at home outdoors we tested for heterogeneity between centers using standard methods for random-effects meta-analysis[45].

Evaluation of selection bias due to loss to follow-up

Prior to the main analysis we assessed the patterns of response rates within and across centers. Centre-specific response rates correlated negatively with the average levels of fine particle mass (r=-0.55). However, the loss to follow up (non-response) at centre level did not significantly correlate with the prevalence of "asthma ever", nor with incidence.

Another problem would be if a selective loss to follow (dependent on disease status) was associated with air pollution, then loss of incident cases may follow the same

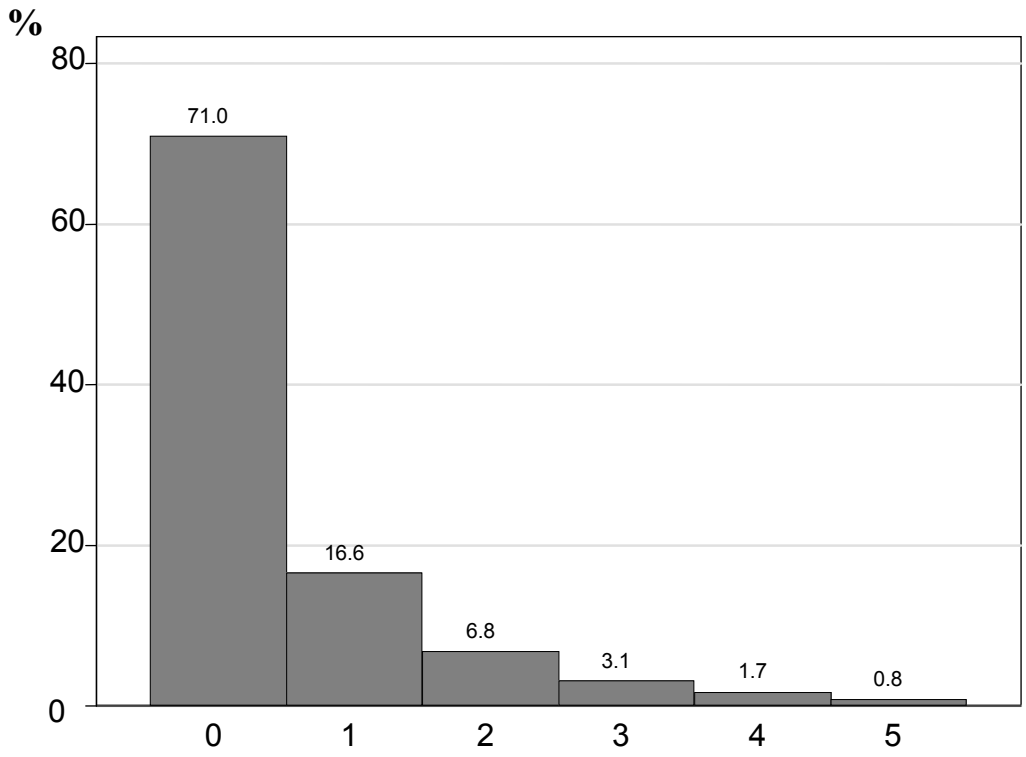
pattern. To test this we estimated the ratio of loss to follow up between asthmatics and non-asthmatics in ECRHS-I. These were not correlated with particle pollution.

III Results

Asthma score

The distribution of the asthma score was skewed, and almost 71 % of the study subjects reported none of the asthma symptoms and scored 0 (figure 1). The mean score was 0.51 and the standard deviation 0.97, so the negative binominal regression model which allows for extra-Poisson variation is appropriate for modelling this score.

Figure 1. Distribution of the asthma score based on 5 symptom questions from the ECRHS II (%), all centres.



There was no association between urban background particle concentration and asthma score in the adjusted model, ratio of the mean scores per unit change in S and PM2.5 was 1.00 (80% IRC 0.62-1.62) and 0.89 (0.56-1.41), respectively (table 1). Excluding the four centres with PM measurements within 15 meters of the main street (Pavia, Turin, Verona and Antwerp City) did not significantly change the null results for $PM_{2.5}$. After excluding those centers the ratio of the mean scores per unit change in PM2.5 was 1.01 (80% IRC 0.64-1.60). Neither was there any significant difference in the relative change between total study population and any of the studied subgroups, and, thus no association between the asthma score and the centre-specific level of PM2.5 and S in any of the subgroups.

Table 1. Multivariate associations (ratio of the mean scores and 95% confidence interval) between asthma score and individual characteristics as well as center-specific levels of PM2.5 and S, respectively (total population; N=4586).

Individual characteristics	Ratio (95% CI)		
Age at II (ref. ≤ 35)			
35-40	1.11	(0.92 -	1.32)
40-45	1.08	(0.90 -	1.29)
45-50	1.12	(0.93 -	1.34)
>50	1.22	(1.02 -	1.47)
Females	1.24	(1.10 -	1.40)
Social Class (ref. I-II)			
III non-manual	1.26	(1.10 -	1.45)
III manual	1.07	(0.82 -	1.40)
IV-V	1.47	(1.17 -	1.85)
Unclassifiable	1.42	(1.10 -	1.83)
Atopy	1.69	(1.50 -	1.90)
Family history of asthma or atopy	1.43	(1.27 -	1.60)
Smoking (ref. Never)			
Former	1.11	(0.97 -	1.28)
Current	1.36	(1.20 -	1.56)
Cooking done mainly with gas	1.09	(0.95 -	1.25)
Any occupational exposure (ref. None)			
Low	0.92	(0.80 -	1.05)
High	1.00	(0.80 -	1.26)
Traffic (ref. None)			
Seldom	0.85	(0.72 -	0.99)
Frequent	1.11	(0.95 -	1.30)
Constant	1.32	(1.15 -	1.52)
Centre characteristics	Ratio (80% IRC)		
S (per $\mu g/m^3$)	1.00	(0.62 -	1.62)

$PM_{2.5}$ (per $\mu g/m^3$)	0.89	(0.56 -	1.41)
	1.01*	(0.64 -	1.60)

* Excluding Antwerp City, Pavia, Turin, and Verona centres (N=4048)

Table 2 shows asthma score by centre and reported traffic exposure at home.

On average subjects reporting constant traffic scored 0.63 (range from 0.24 to 0.96). Among asthmatics (ever asthma) reporting constant traffic (n=158) the mean score was 1.91 (range from 0.83 to 3).

Table 2. Asthma score, mean (SD), by centre and reported traffic exposure at home.

	Reported Traffic at home frontdoor											
	Never			Seldom			Frequent			Constant		
Centre	No.	Mean	(SD)	No.	Mean	(SD)	No.	Mean	(SD)	No.	Mean	(SD)
South Antwerp	114	0.33	(0.78)	107	0.31	(0.65)	44	0.52	(1.09)	73	0.47	(1.00)
Antwerp City	47	0.77	(1.16)	82	0.33	(0.72)	57	0.46	(0.98)	108	0.51	(0.95)
Erfurt	131	0.48	(0.96)	59	0.44	(0.88)	46	0.35	(0.53)	51	0.57	(1.04)
Barcelona	106	0.43	(0.84)	44	0.34	(0.71)	42	0.40	(0.77)	75	0.60	(1.10)
Galdakao	152	0.30	(0.70)	42	0.14	(0.42)	57	0.46	(1.04)	108	0.34	(0.71)
Albacete	70	0.57	(0.89)	64	0.53	(0.82)	78	0.85	(1.27)	96	0.77	(1.04)
Oviedo	78	0.77	(1.29)	38	0.58	(1.03)	54	0.54	(1.02)	70	0.91	(1.21)
Huelva	45	0.69	(1.14)	27	0.81	(1.11)	61	0.80	(1.29)	70	0.96	(1.30)
Grenoble	189	0.54	(0.96)	76	0.51	(1.04)	49	0.57	(0.91)	68	0.78	(1.22)
Paris	146	0.76	(1.13)	97	0.65	(0.94)	64	0.69	(1.07)	109	0.67	(0.98)
Pavia	128	0.42	(0.93)	22	0.27	(0.55)	22	0.50	(0.91)	20	0.50	(1.00)
Torino	29	0.28	(0.84)	31	0.23	(0.56)	26	0.27	(0.78)	37	0.54	(1.26)
Verona	94	0.34	(0.84)	31	0.19	(0.40)	49	0.31	(0.74)	27	0.56	(1.15)
Ipswich	99	0.78	(1.07)	78	0.69	(1.01)	52	0.83	(1.22)	60	0.92	(1.14)
Norwich	113	0.72	(1.11)	59	0.61	(0.97)	36	0.72	(1.14)	48	0.46	(1.01)
Reykjavik	229	0.41	(0.78)	77	0.30	(0.67)	71	0.41	(0.77)	77	0.51	(0.85)
Goteborg	266	0.36	(0.92)	112	0.29	(0.67)	56	0.43	(0.87)	54	0.24	(0.55)
Umea	199	0.40	(0.92)	79	0.29	(0.64)	69	0.51	(1.01)	66	0.58	(1.07)
Uppsala	264	0.36	(0.86)	78	0.41	(0.89)	77	0.42	(0.95)	88	0.65	(1.30)
Basel	244	0.45	(0.97)	84	0.42	(0.78)	55	0.49	(1.12)	63	0.81	(1.42)
Tartu	105	0.57	(1.20)	49	0.31	(0.80)	45	0.58	(1.23)	60	0.72	(1.29)

In the adjusted model, the ratio of the mean scores associated with reporting constant traffic vs. the reference category was 1.32 (95% CI= 1.15-1.52), without significant

heterogeneity across centres. The difference in ratio between men and women was negligible. Among the 1751 participants with a family history of asthma or atopy, the ratio of the mean scores associated with constant traffic tended to be somewhat higher, 1.42 (95% CI= 1.15-1.76), than in subjects without a family history of asthma or atopy (1.27; 95% CI= 1.05-1.54), but the interaction was not statistically significant. Among the 1266 subjects with atopy at ECRHS II associations were larger then among non-atopics (ratio= 1.51; 95% CI= 1.20-1.91) for 'constant traffic' as compared to 1.24 (95% CI= 1.03-1.48). In contrast, those reporting "ever asthma" in ECRHS II had similar associations as those without a history of asthma at ECRHS II. Sex or smoking status did not seem to modify the associations with reported traffic.

In the subset with home outdoor measurements of NO_2, a 10 μg/m3 increase in NO_2 was associated with a non-significant ratio of the mean scores of 1.03 (95% CI= 0.96-1.10) (Table 3). The effect of NO_2 reached statistical significance among the 350 participants with atopy, for which a 10 μg/m3 increase in NO_2 resulted in a ratio of the mean scores of 1.19 (95% CI= 1.04-1.36). Among those reporting ever asthma, the ratio of the mean scores tended to be larger as well (1.11; 0.98-1.26 for a 10 μg/m3 increase in NO_2).

Table 3. Associations (ratio of the mean scores and 95% confidence interval per 10 $\mu g/m^3$ increase in NO_2) between NO_2 level at home outdoors and asthma score among all subjects and in subgroups.

	N	Ratio	(95% CI)		p-value
All					
Crude‡	1601	1.00	(0.94 -	1.08)	0.89
Adjusted§	1270	1.03	(0.96 -	1.10)	0.44
Subgroups					
Males	575	1.02	(0.93 -	1.11)	0.74
Females	695	1.03	(0.93 -	1.15)	0.58
Family history of asthma or atopy					
No	850	1.05	(0.96 -	1.15)	0.26
Yes	420	1.02	(0.91 -	1.14)	0.78

Atopy					
No	920	0.98	(0.90 -	1.07)	0.64
Yes	350	1.19	(1.04 -	1.36)	0.01
Ever asthma at ECRHS-II					
No	1134	0.99	(0.91 -	1.07)	0.77
Yes	135	1.11	(0.98 -	1.26)	0.09
Never smokers	572	0.96	(0.83 -	1.10)	0.56

‡ Adjusted for season and centre
§ Also adjusted for age, gender, social class, atopy, family history of asthma or atopy, smoking, cooking done mainly with gas, and any occupational exposure

Results for the five separate symptoms were similar to those for the score. There was no correlation between adjusted symptom prevalence's and urban background PM2.5 or S. However, the odds ratio for reporting frequent traffic vs. the reference category (none) ranged from 1.26 to 1.55 and was significant for all 5 symptoms but attack of shortness of breath at rest, with woken by attack of shortness of breath as the symptom most associated with constant traffic. In the subset with home outdoor measurements of NO_2, there were positive but non-significant associations between NO_2 and for 4 out of 5 symptoms in the entire group, and for all 5 symptoms in participants with atopy. In the latter group the association with attacks of shortness of breath after exercise was significant, where a 10 µg/m3 increase in NO_2 resulted in an odds ratio of 1.50 (95% CI= 1.15-1.95).

Incidence

Incidence varied a lot between centers, ranging from 0 to 6 new cases per 1000 person years, as cumulative incidence from 0 to 5 % (table 4). There was no association between urban background particle concentration and the cumulative asthma incidence across communities using the simple definition of incident cases, the odds ratio per unit change in S and $PM_{2.5}$ was 1.00 (80% IOR= 0.63-1.59) and 0.96 (80% IOR= 0.57-1.62), respectively (table 5). With the more strict definition of incident cases the odds ratio per unit change in S and $PM_{2.5}$ was 1.00 (80% IOR= 0.37-2.68) and 0.94 (80%

IOR= 0.39-2.30), respectively (table 5). Excluding the four centres with PM measurements within 15 meters of the main street did not significantly change the null results for $PM_{2.5}$. Neither were there any significant difference in the odds ratios between the total study population and any of the studied subgroups, and, thus no association between the cumulative asthma incidence and urban background levels of particles.

Table 4. Asthma "onset" according to the simple definition (a) and incidence according to the strict definition including a reported age at first attack within the follow up (b), per centre and in total.

	(a)				(b)			
Centre	No. at risk	Cases	follow-up (years)	Incidence (*1000 person-years)	No. at risk	Cases	follow-up (years)	Incidence (*1000 person-years)
Tartu	164	1	6.95	0.88	163	0	6.99	0.00
Pavia	92	1	8.36	1.30	91	0	8.45	0.00
Paris	248	8	7.76	4.16	240	0	8.02	0.00
Turin	83	3	8.15	4.44	80	0	8.45	0.00
South Antwerp	249	6	9.60	2.51	244	1	9.79	0.42
Verona	144	5	8.49	4.09	140	1	8.73	0.82
Antwerp city	180	4	8.98	2.47	178	2	9.08	1.24
Barcelona	158	10	8.28	7.64	150	2	8.72	1.53
Galdakao	273	6	8.46	2.60	271	4	8.52	1.73
Umea	240	18	7.89	9.51	226	4	8.38	2.11
Basel	280	11	10.02	3.92	275	6	10.20	2.14
Erfurt	238	13	8.85	6.17	230	5	9.16	2.37
Reykjavik	340	21	8.39	7.36	326	7	8.75	2.45
Uppsala	291	16	8.28	6.64	281	6	8.58	2.49
Ipswich	177	8	8.23	5.49	173	4	8.42	2.75
Huelva	148	7	8.17	5.79	145	4	8.34	3.31
Goteborg	242	18	8.56	8.69	232	8	8.92	3.86
Grenoble	219	13	8.65	6.87	214	8	8.85	4.23
Albacete	204	13	8.09	7.88	200	9	8.25	5.45
Oviedo	153	10	7.90	8.28	150	7	8.06	5.79
Norwich	161	16	8.28	12.00	153	8	8.71	6.00
All centres	4284	208	8.46	5.74	4162	86	8.71	2.37

The odds ratio associated with reporting constant traffic (vs. seldom or no traffic) was 1.51 (95% CI= 1.05-2.19) with the simple definition of incident cases (table 5). In the subgroup with the same residence during the follow up period (n= 2133), the odds ratio was 1.84 (95% CI= 1.07-3.19). When the analyses were repeated with the more strict incidence definition there were no obvious associations between self-reported traffic at

home and cumulative incidence. However, in the subgroup with the same residence during the follow up period (n= 2066), the odds ratio for constant traffic was almost as high as before; 1.74 (95% CI= 0.751-4.022).

Table 5. Multivariate association (odds ratio and 95% confidence interval) between cumulative incidence and individual variables as well as center-specific levels of PM2.5 and S, respectively among all subjects and subjects who did not change residence between ECRHS I and II.

	All			Same residence		
Individual characteristics	OR (95% CI)			OR (95% CI)		
Age at II (ref. ≤ 35)						
35-40	0.84	(0.52 -	1.34)	1.00	(0.56 -	1.78)
40-45	0.99	(0.63 -	1.55)	1.33	(0.74 -	2.37)
45-50	0.99	(0.62 -	1.56)	1.18	(0.59 -	2.35)
>50	0.97	(0.61 -	1.55)	1.30	(0.62 -	2.71)
Females	2.21	(1.57 -	3.10)	2.46	(1.54 -	3.95)
Social Class (ref. I-II)						
III non-manual	1.64	(1.11 -	2.43)	1.46	(0.88 -	2.43)
III manual	1.77	(0.87 -	3.64)	1.51	(0.53 -	4.27)
IV-V	2.84	(1.58 -	5.11)	2.41	(1.04 -	5.60)
Unclassifiable	1.70	(0.86 -	3.39)	0.57	(0.13 -	2.63)
Atopy	3.53	(2.62 -	4.74)	3.44	(2.24 -	5.28)
Family history of asthma or atopy	1.59	(1.18 -	2.13)	1.82	(1.19 -	2.77)
Smoking (ref. Never)						
Former	1.31	(0.93 -	1.84)	1.28	(0.77 -	2.12)
Current	1.07	(0.75 -	1.52)	1.26	(0.76 -	2.09)
Cooking done mainly with gas	1.08	(0.77 -	1.53)	1.54	(0.94 -	2.53)
Any occupational exposure (ref. None)						
Low	0.85	(0.59 -	1.23)	0.87	(0.53 -	1.43)
High	1.04	(0.57 -	1.90)	0.94	(0.40 -	2.18)
Traffic (ref. None)						
Seldom	1.24	(0.83 -	1.85)	1.50	(0.86 -	2.62)
Frequent	1.14	(0.74 -	1.75)	1.51	(0.84 -	2.75)
Constant	1.51	(1.05 -	2.19)	1.84	(1.07 -	3.19)
Centre characteristics	OR (80% IOR)			OR (80% IOR)		
S (per $\mu g/m^3$)	1.00	(0.63 -	1.59)	1.00	(0.57 -	1.74)
$PM_{2.5}$ (per $\mu g/m^3$)	0.96	(0.57 -	1.62)	0.95	(0.54 -	1.67)

In general, the effect of frequent traffic tended to be stronger in females (p-value for interaction $p<0.10$). In females the odds ratio was 1.67 (95% CI= 1.06-2.64) for constant traffic, and in males it was 1.24 (95% CI= 0.63-2.41). With the strict definition

the odds ratio in females was 1.48 (95% CI= 0.76-2.90) for constant traffic, and in males 0.83 (95% CI= 0.26-2.67).

The association of reported constant traffic cumulative incidence was significant only in non-atopics using the simple definition, with an odds ratio of 1.78 (95% CI= 1.06-2.99). The pattern was the same using the strict definition, but the odds ratio became non-significant; OR = 1.33 (95% CI = 0.62 – 2.9). Stratified for family history of asthma or atopy, the odds ratio associated with constant traffic were positive, non-significant in both categories, with a tendency for a higher effect in those without a family history.

IV Discussion

This is to our knowledge the first study on asthma symptoms and asthma incidence in adults investigating both the effects of urban background pollution and of local traffic-related pollutants. Neither asthma symptoms during the past 12 months as a continuous score nor the incidence of asthma was associated with the urban background level of pollution. In contrast, self reported traffic correlated significantly with both the asthma score and adult onset of asthma while the association of home outdoor NO_2 with asthma score was significant only among atopics. These results must be put in context of exposure assessment and various strength and limitations of our study.

Across and within-community contrasts

The use of a continuous asthma score is a novel approach to characterize the cumulated 'acute conditions' among asthmatics, experienced during the last 12 months. Given that we characterized background and local pollution for approximately the same period, and given that acute effects of air pollution on asthma symptoms have been well

established[1], the differences in our results across versus within communities is of particular interest.

We emphasize that background pollution levels are unable to characterize contrasts in exposure that originate from living or working at different locations within communities, which greatly vary with regard to proximity to local sources of pollution, such as traffic. Most ECRHS communities are large with many subjects living far away from the central monitor. Moreover, ignoring the most extreme cities, the three ECHRS centers with the lowest $PM_{2.5}$ levels (Reykjavik, Iceland; Umeå, Uppsala, Sweden), and the three Italian cities would reduce the range in ambient $PM_{2.5}$ to only 12.5 µg/m3. Thus, this raises the serious question whether (true unknown) exposure levels may vary as much within communities as they do across communities. While some pollutants, such as sulfate, show low spatial variability within a city, traffic pollutants such as NO_2 and to greater extent ultrafine particles, show large variability within cities and cannot be well described by a central monitoring station (48-50) where home based measurements or models are needed[51]. Using NO_2 as the marker of within-community contrasts of exposure, one can demonstrate the heterogeneity in exposure within communities. In fact, among our 16 centers with home outdoor measurements, only 44% of the NO_2 variance is explained between centres with the rest being due to differences between residential locations within cities. For the 10 mid-range centres within-city contrasts explained even 98% of the variance. In other words, a simple cross-community comparison is destined to fail if these pollutants are relevant. The approach may only work under the very narrow hypothesis that only those 'background pollutants' with very low spatial variation were asthmogenic while other constituents would not matter. This hypothesis is not very plausible, and in fact, several more recent

studies point in the direction that traffic-related pollutants, marked with NO_2 or measures of proximity, do correlate with asthma symptoms. Our null findings in the cross-community comparison are consistent with others such as SAPALDIA[22] where bronchitis symptoms, but not wheezing or other asthma symptoms were correlated with the community background level of pollution.

The null findings across Europe also highlight inherent limitations of comparisons across very diverse locations with substantial heterogeneities in a range of factors that affect the occurrence of asthma symptoms, including climate, diet, health care systems, treatment attitudes, and even the interpretation of questionnaires in different languages and cultures. None of these factors can be easily controlled in the cross-community comparisons and several are correlated with background pollution which showed a strong North-South gradient within ECRHS. An Italian multi-centre study gives a vivid example of the need to control such aggregate level characteristics[26]. They found a cross-community association between NO_2 and asthma symptoms only in an analysis stratified by North and South Italian centers whereas the comparison across all centers suggested a negative association. ECRHS, while apparently the largest cross-European multi-centre study has not a sufficient number of centers within comparable socio-cultural or geographic areas to stratify the cross-community analyses.

Asthma incidence

The incidence of asthma in adults is poorly investigated in general, and in particular with regard to the contribution of air pollution. We found inconsistency in participants answers about their asthma history, namely a large group of persons that denied having asthma in ECRHS I who in ECRHS II had asthma and reported a first attack at an age less than in ECRHS I. More than 85 percent of them scored 0 on the asthma score in

ECRHS I, and at least felt so free from symptoms that they reported not to have asthma. Possibly, when they later have been diagnosed with asthma, they may have realized that episodes earlier in life probably could have been asthma attacks. It would mean that the true incidence is overestimated with the simple definition. On the other hand, air pollutants may also determine the risk for an "onset" of symptomatic asthma in persons that have been free from the disease for years.

Our findings of traffic-related pollution contributing to asthma incidence are in line with a recent Nordic study[2]. Unfortunately, our subsample with measured NO_2 was too small to investigate the associations with asthma incidence. Thus, we rely on reported traffic which must be interpreted with caution. As reviewed by Heinrich et al[51], reported traffic may be rather problematic and a source of systematic bias as both, exposure and health status are based on questionnaires. Subjects with asthma or symptoms may be more aware of traffic or more likely to perceive it as a nuisance, thus systematic bias toward larger estimates cannot be ruled out.

The lack of pollution measurements from the entire follow up period is a limitation that may have affected the incidence analyses in particular. New cases occurred throughout the follow-up while our exposure characterization relates to the last year. Although trends in air pollution are often spatially correlated across areas, this simplification might be less true across the very large European geographic area. A full assessment of trends is not possible due to the lack of comparable long-term monitoring networks. However, based on data available in several cities, one can conclude that changes in air quality differed across European areas, introducing heterogeneity in these trends which is likely a source of random misclassification with biases toward null findings.

The incidence study may also be subject to response biases as we lost many participants since the beginning of the study. Our analysis revealed that the centre-specific response

rate correlated negatively with the average levels of fine particle mass. However, the loss to follow up (or non-response) at centre level did not significantly correlate with the prevalence of "asthma ever", nor with incidence. Moreover, loss to follow-up among asthmatics as compared to non-asthmatics did not correlate with the level of urban background pollution. Thus, we do not believe that the incidence results were subject to bias by centre specific response patterns. Our findings suggest similarities with the increasing number of studies conducted in children, suggesting a potential causal role of air pollution in the development of this complex disease. Asthma incidence among school children in Japan was associated with the level of NO_2 measured in the vicinity of included schools[3]. More studies have found asthma or asthma-like symptoms such as wheeze in children correlated to markers of traffic-related pollution and/or the NO_2-level close to[4-7] or in the place of residence[8,9]. In a large Taiwanese study of school children from 22 areas, the NO_x-level was significantly associated with asthma prevalence[10]. Some studies have found associations with asthma using modeled levels of NO_2[11,12] or other indicators of high traffic exposure (e.g., high counts, proximity to major roads)[12-20]. However, generalize to adult onset asthma needs to be shown as asthma phenotypes and risk patterns may change across life time.

Pollutants and susceptibility

Toxicological studies in animals and humans show that traffic pollutants such as diesel particles and NO_2 damages the epithelial cells, amplify the inflammatory reactions in the airways and trigger an IgE-response[35-37]. Time-series studies also consistently find short-term effects of particles on respiratory and asthma admissions[1]. Our findings using the novel asthma score are in line with this.

Epidemiological studies in children have found respiratory problems including wheeze and asthma to be more common in areas with higher emissions from road traffic[3-20]. Studies of traffic pollution and asthma incidence are rare. An incidence-based case-referent study from Sweden found an association with NO2 measured outside the residence, significant only in atopics[2]. An Italian prevalence study found indications of an association between urban background NO2 and asthma in young adults when climate was adjusted for[26], and among US Veterans persistent wheeze was more prevalent for persons living close to a major road[27]. We found in our study no association between urban background particle concentration and asthma incidence, but for persons reporting constant traffic the odds ratio (vs. the reference category) was 1.84 (95% CI= 1.07-3.19) if they had the same residence during the follow-up period and somewhat lower for the total study population. Stratified for atopy, this association was stronger and statistically significant only among non-atopics, in contrast with the findings by Modig et al who found the association between asthma incidence in adults and NO2 at home only in atopic persons[2], as did Zmirou et al for early traffic exposure and childhood asthma[20].

It is interesting to see that results for the asthma score were stronger among those with atopy. While the literature is not consistent among children, evidence in adults is sparse. Heredity for asthma or atopy as well as being allergic increases the risk for developing asthma. However, it is not clear how atopy or heredity may modify the effect of air pollutants on asthma risk or severity. Our findings of asthma severity during the last 12 months and traffic related pollution are, however, in line with experimental evidence showing amplification of allergic symptoms with exposure to vehicle exhaust[52]. Other studies have seen stronger associations in children without parental asthma[18,19].

It has been observed in several of these studies that the effect of traffic pollution at home was larger in girls[3,4,15,17,19,34], but the explanation is not obvious. Home exposures may be more relevant for girls if they have less exposure elsewhere, or girls may be more susceptible for these pollutants. In our study, the association between incidence and self-reported traffic tended to be stronger in females as well. However, reporting of traffic and traffic annoyance also differs by sex, and women may spend more time around homes. Both factors would lead to stronger associations in women.

V Conclusions

For the novel asthma score we found an association both for subjectively reported high traffic exposure in the entire study population and for home NO_2, although significant only in atopics. For cumulative incidence we found an association only for subjectively reported exposure using the simple definition of incident cases. With the more strict definition and less many incident cases no significant association remained. The statistical power in this study was insufficient to investigate associations with objective measures of local pollution. Given the importance of severity of illness among asthmatics and the need to understand the causes of adult onset of asthma, more studies are needed on this subject. Of particular interest will be investigations of susceptibility factors including sex, atopy, or genes that affect the association between air pollution and asthma severity and incidence in adults. Traffic pollutants seem to be of particular interest, and individually and objectively assessed exposure levels are required to appropriately investigate these hypotheses.

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Home outdoor NO_2 and new onset of asthma in adults.

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Home outdoor NO2 and new onset of asthma in adults

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Abstract

Objective. The aim of this study is to investigate the association between modelled background levels of traffic-related air pollution at the subjects' home addresses and asthma incidence in a European adult population.

Material and methods. Adults from the European Respiratory Health Survey (ECRHS II) were included (N=4878 from 20 cities). Subjects' home addresses were geocoded and linked to outdoor NO2 estimates, as a marker of local traffic related pollution, from the 1-km background NO2 surface modelled in APMoSPHERE (Air Pollution Modelling for Support to Policy on Health and Environmental Risk in Europe). Asthma incidence was defined as reporting asthma ever in the follow-up but not in the baseline. An alternative variable to define new asthma was also used: a score (0 to 5) based on positive answers to symptoms reported for the last 12 months: wheeze / breathlessness, chest tightness, dyspnoea at rest, dyspnoea after exercise, and woken by dyspnoea. Models were adjusted for age, gender, socio-economic status, family history of asthma and/or atopy, smoking and centre.

Results. A positive but non-significant association was found between NO2 and asthma incidence (RR 1.28 95% CI 0.99-1.87) per 10 µg.m-3. NO2 was positively associated with the asthma score in subjects with no asthma and no symptoms at baseline (ratio of the mean asthma score (RMS) 1.14 95%CI 0.99-1.31 per 10 µg.m-3). Results were homogenous among centres (p value for heterogeneity 0.472), but the score findings appeared to be stronger among those with atopy (RMS 1.54 95%CI 1.13-2.09).

Conclusions. In adults, traffic related pollution might intervene in asthma incidence. The use of the asthma score offers an alternative to investigate asthma aetiology in adults.

Key Words: Asthma, NO2, air pollution, asthma incidence

I Introduction

An acute association between air pollution and asthma visits, hospitalizations and even mortality has been established in numerous studies[3-17]. In children air pollution has also been associated with asthma incidence[18-22]. Few studies have investigated new onset of asthma and air pollution in adults. In the ASHMOG study, in a highly selected population in California, Abbey et al. found a positive but not significant association between asthma incidence and particulate matter[23] while McDonnell et al. reported an increased risk of asthma incidence for an increase in ozone only in males[24]. These studies, however, were based on central measurements with no characterization of exposure to local traffic-related pollution, which may play a role in the onset of childhood asthma[21]. Mödig et al, in a case-control study in Sweden, suggested that living close to high traffic roads could be associated with asthma incidence while NO2 was only associated with asthma incidence in atopic adults[25]. The poor accuracy of the exposures based on data from central monitoring sites could decrease the effect estimates in previous studies[26]. In the European Community Respiratory Health Survey (ECRHS), in a previous analysis the assessment of the association between home outdoor NO2 (as a surrogate of traffic) and asthma incidence was limited due to the low number of subjects having individual measurements[27]. The use of modelled estimates of home outdoor NO2 concentrations offers now the opportunity to investigate the hypothesis in a far larger population sample (around 5,000 subjects). The aim of this study was to assess the association between NO2, used as a marker of traffic-related, air pollution, and new onset of asthma in adults.

II Materials and Methods

Study population

The ECRHS was carried out in 28 cities in 11 Western European countries. It was first conducted in 1991-3 (ECRHS I) and repeated in 1999-2001 (ECRHS II). Centres were chosen based on pre-existing administrative boundaries, their size and the availability of sampling frames. Subjects were randomly selected from the populations aged 20-44 in 1991-3. Both surveys included a main questionnaire, skin prick test, IgE determination in blood samples, spirometry and methacholine challenge test. The details of this project study are described elsewhere(28;29). A total of 6001 participants (45% of males) in the 20 centres measuring air pollution were followed-up (around nine years later, during the years 1998-2002). Among them 4523 (75%) subjects had an assigned home NO2 value (modelled). Of those 4523 subjects, 4465 had no missing information in any of the respiratory symptoms and 3921 had full information for all the covariates used in the adjusted models. Ethical approval was obtained for each centre from the appropriate institutional or regional ethics committee, and written consent was obtained from each participant.

Definition of asthma and population at risk

New cases of asthma were those who developed asthma between ECRHS I and ECRHS II. They were defined as subjects answering positively to the question: "Have you ever had asthma?" in ECRHS II among those subjects who answered 'no' to asthma ever in ECRHS I (n = 4185). We also performed a stricter analysis considering cases the subjects who answered yes to asthma ever in ECRHS II and reported age of onset of asthma between both surveys.

In addition, an alternative variable to measure asthma incidence was used with a 5 points score (defined by Pekkanen et al.[30] and modified by Sunyer et al.[31] in the ECRHS population) among subjects who answered no to asthma ever, no current asthma, no asthma medication and no asthma symptoms in ECRHS I (n=3177) . The score consisted of the sum of the positive answers to five questions on asthma symptoms but without the term "asthma" in the phrasing in order to avoid biases. The 5 questions used in the score were: breathless while wheezing in the last 12 months, woken up with a feeling of tightness of chest in the last 12 months, attack of shortness of breath at rest in the last 12 months, attack of shortness of breath after exercise in the last 12 months and woken by an attack of shortness of breath in the last 12 months. The other 3 items used in the original score were asthma ever, current asthma and asthma medication. This score proved to have high predictive ability, reinforcing its utility as a measure of asthma in longitudinal studies. Furthermore, it has shown the strength of analysing asthma as a continuum in the general population. The asthma score thus provides a simple and powerful solution for the analysis of risk factors of asthma in epidemiological studies[30;31].

Other variables

Total serum IgE and specific IgE to cat (e1), house dust mites (Dermatophagoides pteronyssinus d1), Cladosporidium as indicator of mould (g6) and timothy grass were determined using the Pharmacia CAP system (Pharmacia, Uppsala, Sweden). Atopy was defined as a result >0.35 kUA.L-1 for any specific IgE.

The other variables used in this analysis were sex, age, socioeconomic class (based on occupation), smoking (never, ex, current), family history of asthma and/or atopy

(mother or father), cooking mainly with gas, any occupational exposure and season of the interview.

Modelled NO2 concentrations with APMoSPHERE

NO2 has been widely used in epidemiological studies as a marker for traffic-related air pollution[32-34]. As part of the APMoSPHERE project 1-km-resolution emission maps were developed for the then member states (EU15) by disaggregating national emissions estimates, categorised by sources of air pollution (SNAP categories), to the 1km level on the basis of relevant proxies (e.g. population density, road distribution, land cover)[35]. The NOx emission map was then used as the basis for modelling NO2 concentrations using focal sum techniques, in a GIS. The model provides estimates of concentrations by calibrating the distance-weighted sum of the emissions (tonnes/km/year) in concentric annuli (circles) around each monitoring site to the monitored concentrations (ug/m3). Models are developed by setting the weight of the innermost annulus to 1, and each successively outer annulus (to a maximum of 11 km) to Wa-1/2 (where Wa-1 is the weight of the next, inner annulus). Weights for each of the annuli were then incrementally adjusted, from the second annulus outwards, under the rule that Wa≤Wa-1, and the correlation with the monitored concentrations recomputed, until R2 was maximised. The resulting regression model was then used to convert the sum of the weighted emissions to a concentration (in ug/m3). Models were developed using monitoring data from 714 background sites for 2001, drawn from the EU Airbase database. Validation was conducted by comparing predictions with observations for a separate set of 228 reserved background sites (r2 = 0.60). The resulting model was converted into a kernel file (with weights for each annulus) which was then moved across the entire EU to produce a 1 km gridded map of concentrations.

Finally, the NO2 at the place of residence of each subject was obtained by intersecting the point locations of residence with the air pollution map.

Statistical analysis

The association between asthma cases and NO2 was assessed using logistic regression to give odds ratios (OR). For the subjects who had a date of onset of asthma between both surveys, the association between NO2 and asthma incidence was tested with multivariate Cox regression calculated in hazard's ratios and expressed in relative risks (RR). The age at the first survey was considered as the beginning of the follow-up, while the age of asthma diagnosis or age at the second survey was considered as the end of the follow-up.

Due to the asthma score distribution, negative binomial regression was used to assess the association between asthma score and NO2. The multivariate model used was the same as that already defined in this population for asthma. NO2 was analysed as a continuous variable as GAM modelling depicted the association with NO2 without any parameterisation. The results of the negative binomial regression were expressed in Ratio of the Mean asthma Scores (RMS).

Effect estimates were derived for each centre and heterogeneity across cities was examined by using standard methods for random-effects meta-analysis, both for asthma and asthma score.

The asthma variable, asthma symptoms and asthma score were tested to see if subjects with NO2 values (N = 4523) were different from those from the same centre who were missing NO2 data (N = 2478). Chi square test was used for the asthma variable and asthma symptoms, and the Wilcoxon-Mann-Whitney test was used for the asthma score.

The analysis was made using STATA 8.2. The criterion for statistical significance was set at a p value < 0.05.

III Results

Table 1 shows the distribution of NO2 levels per centre ordered from north to south. Medians of NO2 levels per centre varied from 12.34 µg.m-3 in Umeå to 57.13 µg.m-3 in Barcelona, with a gradual increase from north to south. Around 10% of the subjects reported to have had asthma ever, ranging from 4% in Galdakao to 17% in Norwich. From 2 to 9% reporting no asthma at baseline reported asthma in the follow up.

Table 1: Description of outdoor NO2 (median and interquantile range), asthma and asthma score per city

Centre	N	NO2 in percentiles			Asthma		Asthma score*		
		p25	p50	p75	Asthma Ever %	Asthma ever in ECRHS II but no asthma in ECRHS I	all subjects mean (sd)	Score only in subjects with asthma score ≥ 1 in ECRHS II	Score at ECRHS II in subjects with no asthma and no symtpoms in ECRHS I
Umeå	152	10.63	12.34	13.87	15.79	7.97	0.40 (0.97)	1.90 (1.27)	0.19 (0.60)
Upssala	484	11.27	15.45	19.75	11.57	4.52	0.45 (1.00)	1.95 (1.20)	0.22 (0.67)
Goteborg	317	23.41	26.69	28.82	12.30	7.07	0.39 (0.87)	1.67 (1.03)	0.16 (0.44)
Norwich	224	22.80	25.40	27.00	16.96	9.09	0.64 (1.08)	1.82 (1.08)	0.31 (0.66)
Ipswich	245	24.90	26.10	28.00	13.47	3.77	0.75 (1.09)	1.82 (0.96)	0.49 (0.82)
Antwerp	637	22.98	28.26	33.27	5.65	2.30	0.43 (0.89)	1.69 (1.00)	0.25 (0.61)
Erfurt	83	19.61	24.48	25.84	6.02	3.70	0.46 (0.89)	1.46 (1.03)	0.41 (0.90)
Paris	432	49.05	50.46	52.57	15.51	3.99	0.70 (1.04)	1.66 (0.98)	0.37 (0.76)
Grenoble	382	25.41	30.80	31.45	13.35	5.49	0.59 (1.02)	1.74 (1.05)	0.33 (0.74)
Verona	205	23.87	27.54	29.43	11.71	3.28	0.34 (0.82)	1.62 (1.06)	0.19 (0.56)
Pavia	192	15.36	19.31	23.72	7.29	3.85	0.42 (0.89)	1.65 (1.05)	0.21 (0.57)
Torino	73	35.90	38.33	40.59	9.59	4.41	0.34 (0.92)	2.08 (1.24)	0.17 (0.65)
Oviedo	139	24.13	30.48	32.09	6.47	3.01	0.70 (1.14)	1.76 (1.19)	0.39 (0.76)
Galdakao	360	19.89	25.50	33.02	4.17	2.58	0.32 (0.74)	1.58 (0.87)	0.21 (0.62)
Barcelona	254	53.45	57.13	59.03	8.66	5.79	0.46 (0.88)	1.68 (0.91)	0.25 (0.62)
Albacete	144	28.32	29.75	31.81	7.86	3.01	0.71 (1.03)	1.72 (0.89)	0.35 (0.69)
Huelva	204	29.68	33.42	33.70	7.84	5.10	0.83 (1.23)	1.89 (1.20)	0.53 (0.91)
Total	4523	20.00	27.20	33.02	10.33	4.44	0.52 (0.98)	1.74 (1.05)	0.28 (0.68)

** 4465 subjects as 58 with missing in at least one variable of the score

All the associations between asthma ever and NO2 were higher than one, although they did not reach statistical significance (p > 0.05) (Table 2). The OR of having asthma per each 10 ug.m-3 increase of NO2 was 1.25 (95% Confidence Intervals (CI) 0.955-1.627). Of the subjects reporting not having asthma ever in ECRHS I and having asthma ever in ECRHS II, 175 provided information on age of asthma onset, and only 90 reported age

of the onset between both surveys. Only 76 of these cases had information on all the covariates used in the adjusted model. Among them, the relative risk of developing asthma per each increase of 10 μg.m-3 was 1.30 (95% CI 0.87-1.94) using Cox modelling. No difference was observed by sex. No further analyses were conducted due to the lack of power.

Seventy percent of the subjects scored 0. Among those who scored more than 0, 17% scored 1, 7% scored 2, 3% scored 3 and 3% scored more than 3 symptoms. The most common symptom was attack of shortness of breath after exercise, which was reported by 17% of all the participants and by 59% of the subjects who scored one or more. The mean asthma score was 0.51, with a range from 0.30 in Reykjavik to 0.83 in Huelva. A north-south gradient could be observed in the mean of the asthma score. However, as expected, the gradient for asthma ever was in the opposite direction (Table 1).

A significant association between asthma score and NO2 was found; the estimates increased after adjusting for centre and further increased when adjusting for all the covariates, though the statistical significance became borderline (Table 2).

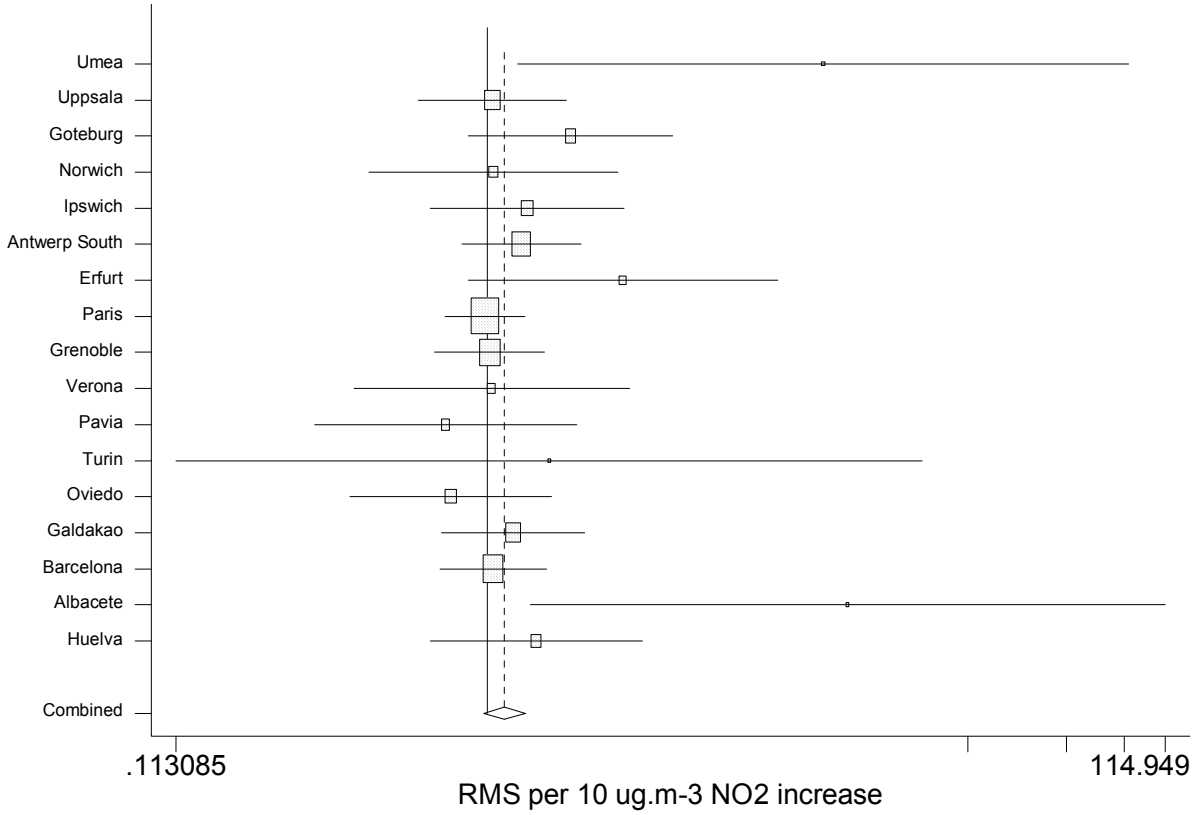
Table 2: Odds Ratios (OR) and Ratio of the Mean Score (RMS) per each 10 ug.m-3 increase of NO2

*Fully adjusted means adjusted is age, gender, SES, smoking, family history of asthma and/or atopy cooking mainly done with gas, any occupational exposure and season of the interview

bolded estimates have a p-value<0.05 *italics* estimates have a p-value<0.10

For both asthma ever and asthma score, no statistical difference was found between men and women; nevertheless the estimates were higher in women. In addition, for the asthma score, estimates tended to be higher in subjects who did not move between both surveys. Estimates were also higher in subjects with atopy and mainly in subjects with atopy for cat allergens. Results were homogenous among all the centres in both the crude and the adjusted analysis (Figure 1).

Figure 1: Crude ratios of mean asthma scores in ECRHS II per each 10 ug.m-3 NO2 increase by centre in subjects with no asthma no respiratory symptoms in ECRHS I
p value for heterogeinity 0.390



IV Discussion

This study suggests a positive association between asthma incidence in adulthood and NO2, albeit not significant, with similar findings across Europe. The significant results based on the novel asthma score very much support the incidence-based analyses. This is to our knowledge the first time that the asthma score has been used in an air pollution

cohort investigation and the interpretation of the results requires careful discussion. First, however, the strengths and limitations of the exposure assessment are addressed.

By geocoding home addresses of ECRHS participants we were able to assign an ambient NO2 concentration derived from the APMOPSPHERE map to each subject on an individual basis. The APMOSPHERE map, however, has a spatial resolution of 1x1km and was modelled on the basis of annual mean concentrations measured only at background sites (the traffic sites were not included). It therefore does not necessarily capture the spatial and temporal contrasts in exposure due to very local emissions or dispersion patterns such as those occurring in street canyons. Asthma incidence or prevalence studies in children have usually used more local markers of exposure such as living within 50 or 100 meters of busy roads; thus a direct comparison with our results is limited. Nevertheless, in line with the studies of children, our data suggest a potential role of traffic related pollution in the onset of asthma among adults. The findings were of borderline significance and our inability to characterise exposure contrasts on a finer spatial scale may have contributed to loss in statistical power.

The cities in ECRHS have different characteristics that could affect the precision of the APMoSPHERE-based modelled NO2. For example population density varied from 47 inhabitants.km-2 in Umea to 24 783 inhabitants.km-2 in Paris[36]), meaning that in Umea 47 subjects have the same assigned value of NO2 while in Paris almost 25 000 subjects have the same assigned value of NO2. However, it is of note that we found no indication of heterogeneity of effects across these cities. Power to detect such heterogeneities was, however, limited.

We observed significant associations between pollution and the asthma symptom score. The interpretation of this finding may be challenging for various reasons. The score

comes with several advantages as compared to a dichotomous definition of onset of asthma. As previously shown, it may be a valuable instrument to reduce misclassification bias due to dichotomization of asthma[30;31]. The use of a continuous measure also increases the power to detect risk factors, a notion supported by our findings. Overall, the score has been demonstrated to be very powerful in the assessment of asthma risk factors[31]. Results using asthma ever (i.e., a dichotomous definition) and asthma score were in the same direction.

The score, however, is based on reported symptoms which are well known expressions of the acute variation in respiratory health among asthmatics, furthermore the symptoms are reported for the last 12 months. In light of the inherently variable phenotype of asthma, the change in the score may not necessarily reflect the incidence of a chronic condition but rather the performance of respiratory health during the past 12 months. If one interprets the symptoms as a measure of the (acute) respiratory performance during the past 12 months rather then incidence of a chronic condition, our finding with the score reflects a strong confirmation of air pollution affecting the performance among people with respiratory health problems, including those with asthma.

In contrast to another analysis[27], we restricted our analysis to subjects without doctor diagnosed asthma nor any symptoms at baseline. Thus, subjects reporting scores of 1 and higher may indeed be considered 'incident cases' of a previously unapparent condition. However, Sunyer et al have shown substantial change in the score, with many subjects losing or gaining symptoms[31]. As a consequence, it may be particularly questionable to consider those with a change from no disease at baseline to a very low symptom score as 'incident cases'. We thus performed a further analysis (data not shown) considering those with only one symptom at follow-up as non-cases. Next, we required at least 2 symptoms, and in a final analyses at least 3 symptoms to be

considered a ‘new case’. The effect estimates gradually increased, strongly suggesting that the ‘new onset’ asthma score findings were driven mainly by those most symptomatic at follow-up. This ‘high score’ phenotype has been shown to be particularly strongly associated with doctor diagnosed asthma. These results support the use of the ratio of the mean asthma score per unit increase in NO2 as a measure of aetiology of new asthma[31].

While the score findings clearly support the incidence data, we recognise that the asthma score does not replace measures of ‘doctor diagnosed asthma’. In adults, however, the definition of ’asthma‘ remains a challenge and the score clearly complements attempts to better understand the aetiology of this disease, independent of secular trends in the labelling of ‘asthma’ by the community of physicians. In a previous publication within the ECRHS, Chinn et al have shown that from ECHRS I to II the prevalence of asthma increased while the prevalence of symptoms did not, suggesting a change over time in the diagnosis or treatment of asthma[37].

Our previous analysis had much less power as modelled NO2 concentrations were not available but only measurement data among a limited subgroup[27]. Thus, we could not use the score as a measure of ‘incident asthma’ but investigated the association between the score at ECRHS II and NO2 at home outdoors among a subgroup only, and irrespective of the presence or absence of symptoms at baseline.

A minor issue is the differences between the populations with and without modelled NO2 values. Asthma ever in ECRHS II had the same distribution in both populations. The asthma score was different for subjects with or without NO2 (p-value 0.065), being smaller for the ones without NO2. The significance of that difference, however, is borderline and the distribution of all the symptoms included in the score were similar in both populations (lowest p-value for the 5 symptoms 0.203).

Finally, one has to acknowledge that NO2 is considered a marker of traffic related air pollution rather then the 'culprit pollutant', although NO2 may play an interacting role in combination with other pollutants prevalent in the urban air[33].

Our study adds to a very small and inconclusive literature about the role of air pollution in adult onset asthma. Previously, within the ASHMOG project, several publications reported an association between asthma incidence and ozone, as well as particulate matter. The subjects came from a highly selected adult population of residentially stable, non-smoking, non-Hispanic whites. All were Seventh-day Adventist from California recruited in 1977 and followed-up in 1982 and 1992. To assess air pollution exposure, the researchers assigned an average of interpolated values based on the subject's zip codes at home and work, using measurements from fixed site monitors. The 8-h average ozone (from 9 am to 5 pm) was found to be associated with a risk in men of developing asthma, after 10 years (RR = 3.12; CI = 1.61-5.85)(38) or 20 years (RR = 2.09; CI = 1.03-4.16 for an interquantile range increase)(24). A separate analysis reported a positive but not significant association with particulate matter (RR = 1.30, CI = 0.97-1.73)[23].

In a matched incidence case-control study carried out in a single city (Luleå, Northern Sweden), NO2 was measured at subject's home and traffic flow was determined using land road maps. A positive but not significant association between asthma incidence and high traffic flow was found (OR = 2.4, 95%CI = 0.9-6.2); with NO2 an association was only observed in subjects with a positive skin-prick test (OR = 1.2, 95%CI = 1.0-1.3 per each µg.m-3 increase)[25].

Unlike the ASHMOG study we found an association in both women and men, with higher estimates in women. In addition, as in Mödig's paper, we also found higher effect in atopics. Our estimates were smaller than in the Swedish paper, i.e. Swedish

study reported an OR of 1.2 per μg.m-3 increase of NO2 and in our study we found 1.2 per 10 μg.m-3 increase of NO2. This large difference could be due to the different design between the two studies. For example, asthmatics identified in the general population may have milder symptoms compared to those recruited in the Swedish study by doctors. Our finding of much larger (i.e. ~5 times larger) albeit non-significant results for incidence of 'high asthma score' (4 or 5) is in line with this notion. It could be assumed that their cases were more severe and better defined than ours, identified in the general population using a questionnaire. Another reason could be that they used home-based measurements of NO2 which led to a bigger exposure range.

Most of the experimental studies looking at the mechanisms of lung damage caused by air pollution have used diesel exhaust or ozone exposure. They have mainly sought and explained acute effects. The mechanisms by which air pollution could cause asthma exacerbations are mainly explained by oxidative stress and the inflammation in the upper and lower respiratory tract[39-46]. It has also been proposed that diesel exhaust particles could interact with allergens increasing the allergic response[47]. The way in which air pollution could cause asthma incidence are less clear but could additionally involve allergic sensitization[42;48;49]. In the absence of an agreed animal model for asthma, the study of the mechanisms of long-term exposure to air pollutants is limited and investigations using a combination of epidemiological and toxicological approaches may be needed.

We attempted to identify more susceptible sub-populations based on sex, body mass index, SES, (data not shown) and atopy. While no interactions were statistically significant, we found noticeably higher estimates for the asthma score – but not onset of doctor diagnosed asthma - among atopics. The estimates were more than double in cat sensitive subjects, which is in accordance with previous studies. Traffic related air

pollution, but not urban background pollution[50], has also been associated with atopy[51]. It has been suggested that reactive pollutants may prime sensitization to allergens[25;51]. Regarding specific pet allergens, McConnell et al. found that the association between air pollution and asthma prevalence in children was higher among those having a dog, but not a cat[52]. Adult onset asthma may, in part, be a different phenotype from that observed among children. The reason why in our analysis the association of the symptoms score was higher in subjects sensitive to cat allergens is unclear, and may need further investigation.

V Conclusion

An association was found between a marker of traffic related air pollution and asthma incidence in European adults; however a longer follow-up would be necessary to confirm the finding and further investigate potential factors of susceptibility such as atopy and other conditions. While open questions remain in the interpretation of the symptoms score, the use of this continuous asthma outcome offers a tempting alternative to investigate asthma aetiology in adults.

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Source-specific $PM_{2.5}$ and urinary levels of Clara cell protein CC16. The ULTRA study.

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Source-specific $PM_{2.5}$ and urinary levels of Clara cell protein CC16.

The ULTRA study

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Abstract:

Introduction: We have previously reported that outdoor levels of fine particles ($PM_{2.5}$, diameter <2.5 μm) are associated with urinary CC16, a marker for lung damage, in Helsinki, Finland, but not in the other two ULTRA cities (Amsterdam, The Netherlands, and Erfurt, Germany). We now evaluated whether $PM_{2.5}$ from specific sources would be more strongly associated with CC16 than (total) $PM_{2.5}$. In addition, we compared two source apportionment methods.

Methods: We collected biweekly spot urinary samples over six months from 121 subjects with coronary heart disease for the determination of CC16 (n=1251). Principal Component Analysis (PCA) was used to apportion daily outdoor $PM_{2.5}$ between different sources. In addition, Multilinear Engine (ME) was used for the apportionment in Amsterdam and Helsinki. We analyzed associations of source-specific $PM_{2.5}$ and $PM_{2.5}$-absorbance (i.e. absorption coefficient), an indicator for combustion originating particles, with log(CC16/urinary creatinine) using multivariate mixed models in STATA.

Results: CC16 was associated with the same-day levels of absorbance (pooled estimate 0.6% change, Standard Error (SE) 0.3%, for an increase of 1×10^{-5} m^{-1} in absorbance) and $PM_{2.5}$ from soil (2.3%, SE 1.0%, for an increase of 1 $\mu g/m^3$ in $PM_{2.5}$ from soil). However, the latter association was driven by extreme values. Correlations between source-specific $PM_{2.5}$ determined using either PCA or ME were in general high. Associations of the source-specific $PM_{2.5}$ with CC16 were in general statistically less significant when ME was used.

Conclusions: The present results suggest that $PM_{2.5}$ from combustion and possibly from soil lead to increased epithelial barrier permeability in lungs.

Key words: $PM_{2.5}$, absorbance, Source specific $PM_{2.5}$, Clara cell CC16

I Introduction:

It is now generally accepted that air pollution, mainly particulate matter (PM), has negative impacts on health, including the health of the respiratory system[1]. However, PM is a mixture of several components from different sources and it is still far from clear which components and sources of PM are mainly responsible for the health effects, although there is abundant evidence on the harmful effects of vehicular emissions[2]. Several studies have also suggested that particles from combustion sources in general are harmful[3;4].

Clara cell protein CC16 is a protein secreted by non-ciliated bronchiolar cells. It has been used as a biomarker of lung epithelial permeability as it can easily been determined in serum or urine. It has been hypothesized that the presence of CC16 in serum is an indicator of rupture in the epithelial barrier of the lungs. Due to its small size and its water-solubility, CC16 is eliminated by glomerular filtration and therefore can be found and measured in urine[5]. In a previous study, urine CC16 was associated with the daily variation of $PM_{2.5}$ in Helsinki, Finland, but not in the other two ULTRA study centres (Amsterdam, The Netherlands, and Erfurt, Germany)[6]. In the present study, we aim to test if using source-specific $PM_{2.5}$ will shed light on the reasons for that heterogeneity.

Determination of PM sources can be done by various methods. Hopke et al.[7] have shown that overall there is a high correlation across analysis methods/researchers for major sources. In this study we have applied source apportionment results obtained by two independent researchers using different source apportionment methods for two cities (Amsterdam and Helsinki).

Our aims were to test if source-specific $PM_{2.5}$ or $PM_{2.5}$-absorbance, an indicator for combustion originating particles, would be more strongly associated with CC16 than

(total) $PM_{2.5}$. In addition, we compare results from two different source apportionment methods applied in both Amsterdam and Helsinki

II Materials and Methods:

Study population

This project took place in the context of the ULTRA (Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air) study. ULTRA was a European study, carried out in three cities: in Amsterdam (The Netherlands) from November 1998 to June 1999, in Erfurt (Germany) from October 1998 to April 1999 and in Helsinki (Finland) from November 1998 to April 1999. The main objective of ULTRA was to study the effects of air pollution in a high risk subgroup of patients with cardiovascular disease. In each city, elderly subjects with stable coronary heart disease were followed with biweekly clinic visits for six months. The visits were scheduled to be always on the same weekday and hour of the day for each subject. During each visit a clinical examination was performed, which included a collection of a urinary sample. The details of the methods as well as the standard operative procedures (SOPs) used in the study can be found elsewhere[8].

In Amsterdam, 37 subjects were recruited, and 47 in both Erfurt and Helsinki. The characteristics of the population are described in previous publications[6]. Summarizing, 27%, 7% and 43% were females in Amsterdam, Erfurt and Helsinki, respectively. The mean age was 71 years in Amsterdam, 65 in Erfurt and 68 in Helsinki. Fifty percent of the subjects had any respiratory disease in Amsterdam, 40% in Erfurt and almost 70% in Helsinki. All subjects were current non-smokers, and in Amsterdam and Erfurt the majority (around 75%) and in Helsinki half of them were ex-smokers. Around 15%

were regularly exposed to ETS at home during the study in Amsterdam and Erfurt, but none in Helsinki.

Urinary CC16

The urinary samples were collected during the visit or just before the visit at home. Mid-stream samples were required to avoid contamination by prostatic secretions. All the samples were analysed in the same laboratory by automated latex immunoassay. CC16 and creatinine were determined in all the samples. The coefficient of variation between the duplicate samples was 22.6% for ln(CC16) and 4.6% for urinary creatinine. Subjects with CC16 below the limit of detection (CC16<1µg/L) at every visit were excluded: 4 subjects in Amsterdam, 1 in Erfurt and 5 in Helsinki, all were females.

Air pollution and source apportionment

$PM_{2.5}$ and gaseous pollutants were monitored at a central outdoor site[8]. Locations of the monitors were chosen to be representative of urban background air pollution in each city. $PM_{2.5}$ filter samples (from noon-to-noon) were collected daily with a single stage Harvard Impactor, and samples were weighted to determine mass concentrations. After weighing, the blackness of the filters was assessed using a reflectometer and the values were converted into the absorption coefficients, a surrogate for elemental carbon. The methods as well as quality control measures have been reported elsewhere[9].

All $PM_{2.5}$ filters were analyzed for elemental composition with energy dispersive X-ray fluorescence spectrometry[10].

The sources of $PM_{2.5}$ were resolved using two methods. The first one, described by Vallius et al.[10] for this same data, consisted of Principal Component Analysis (PCA) and multivariate regression to identify and quantify the different sources of $PM_{2.5}$.

"Non-elemental" variables (gases and ultrafine particles) were also taken into account to identify sources. Four days with outlier concentrations were excluded from source analyses in Amsterdam and Helsinki, and six days in Erfurt. Six $PM_{2.5}$ source categories were identified in Amsterdam, four in Erfurt and five in Helsinki.

The other method used for $PM_{2.5}$ source apportionment was Multilinear Engine (ME)[11], in which the source compositions and contributions were analyzed using a 2-way model. All sources were constrained to have only positive values for components[11], and no sample was allowed to have negative source contribution. The error estimates of the observed data were used for scaling. As ME analysis were done mainly for another purpose, i.e. to compare outdoor, indoor and personal $PM_{2.5}$ sources, and there was no indoor and personal data in Erfurt, we only have the results of ME for Amsterdam and Helsinki. Ultrafines or gases (except NO) were not included in the ME as such data were not available from indoors. Six sources were identified in both cities.

For all the sources, lags 0 to 3 as well as the average of lags 0 to lag 4 were assessed. Lag 0 was defined as the concentration from the noon of the previous day to the noon of the day of the visit.

Statistical analysis

The logarithms of the CC16 levels, divided by urinary creatinine to account for diuresis, were used in analyses. Centre-specific basic models were built first considering the long-term time trend, temperature (lag 0-3), relative humidity (lag 0-3), barometric pressure (lag 0-3) and the weekday of the visit(6). Generalised Least square (GLS) linear mode in Stata 8.2, considering subject-effects as random ones, were performed. All the source-specific $PM_{2.5}$ concentrations determined with the same method were added in the same model as they were largely uncorrelated. The pooled effect estimate

was calculated as a weighted average of the centre specific estimates using the inverse of the centre specific variances as weights. The heterogeneity between centres was tested with X^2 test[12].

Stratified analyses were done by subjects with or without any respiratory disease. Extreme values were excluded in sensitivity analyses: the extremes were defined as values above the 98 percentiles of the concentration distributions

III Results

With PCA, six sources were identified in Amsterdam, five in Helsinki, and four in Erfurt. ME was applied only in Amsterdam and Helsinki, and identified six sources in both cities. The main sources in all cities were Traffic and Secondary PM (Table 1).

Effects of source-specific PM2.5 (estimated with PCA) and absorbance

In the pooled analyses, there was a statistically significant association between the absorbance of $PM_{2.5}$ filters and CC16 at lag 0 (Table 2). A suggestive association at lag 0 was observed in all cities (Figure 1).

The only other significant pooled association was between CC16 and $PM_{2.5}$ from soil source at lag 0 (Table 2). A significant association at lag 0 was observed in Erfurt while in the other cities the associations were less evident (Figure 2). $PM_{2.5}$ or other sources were not associated with CC16 in the pooled analyses.

Table 1: Descriptive statistics for total and source-specific PM2.5 and absorbance

	Amsterdam				Helsinki				Erfurt			
N (days)	223				164				156			
	5th	50th	95th	% of $PM_{2.5}$	5th	50th	95th	% of $PM_{2.5}$	5th	50th	95th	% of $PM_{2.5}$
$PM_{2.5}$	6.0	16.8	47.0	100	5.2	10.7	25.8	100	6.1	16.3	62.3	100
Absorbance	0.6	1.5	3.4	NA	1.0	1.9	3.6	NA	0.8	2.0	5.1	NA
Secondary												
PCA	-5.0	5.1	21.8	34	-1.0	5.5	15.9	50	-1.7	5.4	31.9	38
ME	0.0	5.9	21.9	41	0.0	4.2	14.4	42	NA	NA	NA	NA
Oil												
PCA	0.2	1.6	5.9	13	0.0	1.3	4.2	13	-	-	-	-
ME	0.0	2.0	6.4	16	0.0	1.7	5.1	16	NA	NA	NA	NA
Traffic												
PCA	1.2	6.1	20.4	13	0.8	2.6	6.5	23	0.3	7.0	18.4	34
ME	0.1	1.2	9.6	13	0.0	0.5	1.8	5	NA	NA	NA	NA
Industry/Urban												
PCA	-7.1	-0.5	9.2	26	-	-	-	-	-6.9	-1.6	24.7	6
ME	0.3	3.1	16.1	23	0.0	2.6	10.9	28	NA	NA	NA	NA
Soil												
PCA	0.0	1.4	3.6	1	-0.3	0.4	2.2	5	0.5	2.7	13.8	19
ME	0.1	0.3	0.6	2	0.0	0.4	1.5	4	NA	NA	NA	NA
Salt												
PCA	-0.2	0.2	1.8	4	0.1	0.8	2.3	7	-	-	-	-
ME	0.0	0.3	2.8	6	0.0	0.2	1.8	4	NA	NA	NA	NA
Unidentified												
PCA	-5.7	0.5	8.3	4	-3.4	0.2	3.5	2	-7.3	0.1	8.5	3
ME	-3.7	-0.1	6.5	2	-3.0	0.1	4.1	2	NA	NA	NA	NA

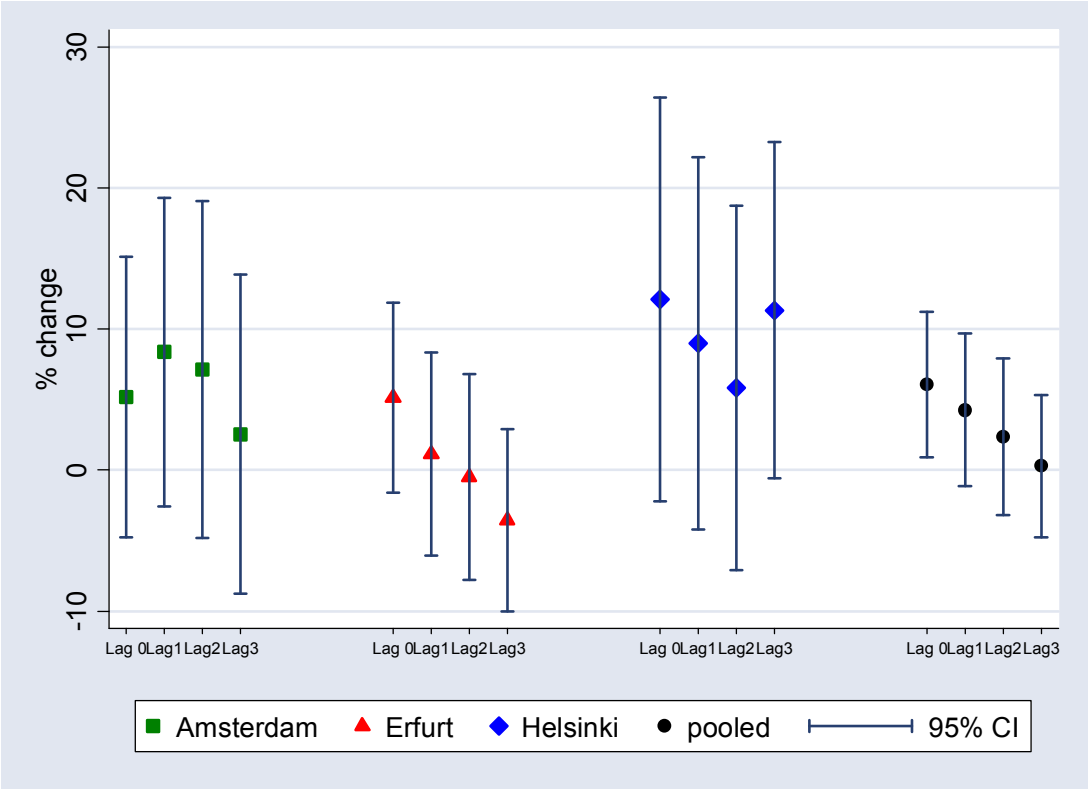
$PM_{2.5}$ and its sources are expressed in ug.m^{-3}, absorbance in $m^{-1}.10^{-5}$
5th, 50th and 95th refers to the percentiles
% of $PM_{2.5}$ refers to the percentage of the source that contributes to the total PM2.5 mass
- Not identified
NA Not applicable

Table 2: Pooled estimates (3 cities) for the associations between source-specific PM2.5 estimated with PCA and CC16

	Lag 0		Lag 1		Lag 2		Lag 3		5 days average	
	%	SE	%	SE	%	SE	%	SE	%	SE
$PM_{2.5}$	0.3	0.2	0.3	0.2	0.2†	0.2	-0.1†	0.2	0.3†	0.3
Absorbance	**6.1**	**2.6**	4.3	2.8	2.4	2.8	0.3†	2.6	7.2†	4.4
Secondary	-0.2	0.3	0.3	0.3	0.2	0.3	-0.3†	0.3	-0.1†	0.4
Oil*	0.2	1.9	2.0	2.0	1.7	2.2	-1.1	2.0	0.9	4.0
Traffic	0.4	0.6	0.5	0.6	0.6	0.7	0.0	0.6	1.4†	1.0
Industry/Urban**	0.3	0.4	0.3	0.4	-0.1	0.4	-0.2	0.4	0.0	0.7
Soil	**2.3**	**1.0**	0.7	1.3	2.1	1.7	0.1	1.5	2.7	2.0
Salt*	5.5	5.2	2.6	5.2	-3.6	5.2	7.5	5.3	10.3	9.7
Unidentified	0.5	0.5	0.1	0.5	0.2†	0.5	0.5	0.5	0.3	0.8

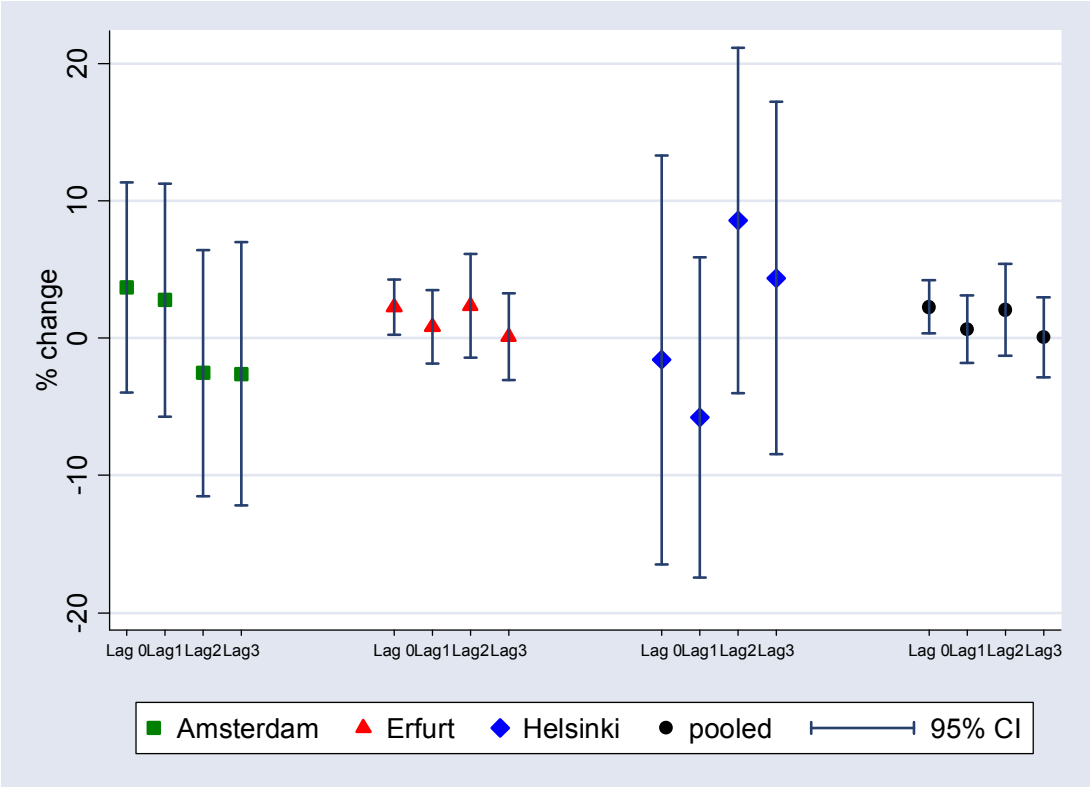
* Only Amsterdam and Helsinki
** Only Amsterdam and Erfurt
% refers to percenta change in CC16 per 1ug.m-3 (source specific) PM2.5, 1*10-5 absorbance
bolded estimates have a p-value<0.05
italics estimates have a p-value<0.10
† p value for heterogeneity < 0.10

Figure 1: City-specific effect estimates (per 1 m-1*10-5) for the associations between absorbance and CC16.



Vertical lines indicate 95% confidence intervals.

Figure 2: City-specific effect estimates (per 1 µg.m-3) for the association between soil (estimated with PCA) and CC16.



Vertical lines indicate 95% confidence intervals.

The association at lag 0 between absorbance and CC16 got weaker when extreme values were excluded (% change = 4.8, SE = 2.9, p-value = 0.099). Among subjects with chronic lung disease the associations between absorbance and CC16 were slightly weaker (% change = 4.9, SE = 4.1, p-value = 0.235) than among other subjects (% change = 6.6, SE = 3.5, p-value = 0.066).

When stratifying for respiratory disease, the association at lag 0 between soil and CC16 was similar among subjects with any respiratory disease (% change = 2.2, SE = 2.2, p = 0.316) than among the subjects without (% change = 2.1, SE = 1.1, p = 0.060) or than in the total population. When excluding the high values of the soil source the association disappeared (% change = 1.1, SE = 1.4, p = 0.455). Among those with any chronic lung disease, soil was significantly associated with CC16 at lag 2 (% change = 7.6, SE = 2.8, p = 0.008) but when excluding outliers the estimate decreased and the association was no more significant (% change = 3.8, SE = 3.31, p = 0.254). In subjects without respiratory disease, no association at lag 2 between soil and CC16 was found even without excluding high values (% change = -1.0, SE = 2.2, p = 0.644).

Comparison of source apportionment methods (PCA & ME) in Amsterdam and Helsinki

The correlation coefficient between $PM_{2.5}$ and absorbance was around 0.70 in both cities (Table 3). For Amsterdam the sources with the highest correlation with $PM_{2.5}$ were Secondary (r = 0.62) when using PCA and Industry/Urban (r = 0.79) when using ME. For Helsinki the best correlations coefficients were found with Secondary (r = 0.82 when using PCA and r = 0.61 when using ME).

Table 3: Spearman's correlation coefficients between source-specific and total PM2.5 and absorbance, and the source-contributions to PM2.5

		Amsterdam			Helsinki			
		PM2.5	Absorbance	Same source*	PM2.5	Absorbance	Same source*	Urban/industry ME
PM2.5		1						
Absorbance		0.73	1		0.70	1		
Secondary	PCA	0.62	0.11	0.88	0.82	0.46	0.81	0.42
	ME	0.71	0.25		0.61	0.18		
Oil	PCA	0.18	0.13	0.95	0.35	0.24	0.91	0.26
	ME	0.22	0.09		0.41	0.28		
Traffic	PCA	0.50	0.87	0.91	0.26	0.74	0.81	0.56
	ME	0.47	0.84		-0.05	0.44		
Industry/Urban	PCA	0.27	0.30	0.55	NA	NA	NA	NA
	ME	0.79	0.72		0.57	0.76		
Soil	PCA	-0.14	-0.09	0.83	0.19	0.14	0.91	0.24
	ME	0.04	0.16		0.11	0.31		
Salt	PCA	0.04	0.01	0.83	0.19	0.07	0.55	0.12
	ME	0.14	0.12		-0.05	-0.02		
Unidentified	PCA	0.18	0.01	0.92	0.17	0.04	0.76	0.39
	ME	0.13	0.02		0.22	0.09		

* correlation between the same source but estimated with the two different methods

Rather similar $PM_{2.5}$ source contributions were estimated using PCA and ME, an exception being Traffic in Helsinki (Table 1). 'Traffic' in PCA corresponded to 'Traffic' plus 'Industry/Urban' in ME. In the ME model, no negative source contributions were allowed and the weights of extreme values were decreased. Thus it tended to give smaller variances. Spearman correlations between $PM_{2.5}$ sources estimated either with PCA or ME were in general high (Table 3). In Amsterdam, the Spearman coefficients ranged from 0.55 for Industry/Urban to 0.95 for Oil, in Helsinki from 0.55 for Salt to 0.91 for Oil combustion. In Helsinki, the PCA method did not identify an Industry/Urban source. The PCA source showing the highest correlation with the ME Industry/Urban source was Traffic (r = 0.56).

Table 4 shows the associations of source-specific $PM_{2.5}$ estimated with PCA and ME with CC16 for Amsterdam and Helsinki. Overall, effect estimates obtained using PCA and ME were rather similar, but fewer significant associations were observed when using ME. Five-day average of traffic-$PM_{2.5}$ was associated with CC16 in both centres, but only when PCA was used for the apportionment. In Helsinki, when adding 'Traffic'

to 'Industry/Urban' in ME, the estimate for the 5 day average was 10.5% (SE 3.8%) per 1 $\mu g/m^3$ of $PM_{2.5}$.

Table 4: Associations between source-specific PM2.5 (estimated with PCA and ME) and CC16 in the 2 cities

Oil												
PCA	0.3	2.2	0.6	2.8	-1.0	4.5	-0.3	3.8	3.5	3.4	8.8	9.1
ME	-0.4	1.9	0.3	2.4	-2.7	3.8	0.3	4.0	-0.1	3.7	5.7	7.6
Traffic												
PCA	0.8	0.8	1.4	0.9	**3.0**	**1.4**	2.9	3.6	-1.3	3.1	**17.6**	**8.1**
ME	0.6	1.6	2.4	1.8	3.6	3.1	1.8	13.7	-15.2	14.1	30.4	28.6
Industry/Urban												
PCA	0.2	0.7	0.4	0.9	-0.8	1.6	NA	NA	NA	NA	NA	NA
ME	0.4	1.0	0.6	1.2	1.6	2.0	2.6	2.0	1.8	1.6	**10.4**	**3.8**
Soil												
PCA	3.7	3.9	-2.5	4.6	3.2	8.2	-1.6	7.6	8.6	6.4	6.9	12.0
ME	23.5	31.3	-14.1	46.9	-2.5	62.3	-3.9	13.8	9.1	12.1	-0.4	26.9
Salt												
PCA	0.4	7.6	-6.8	7.9	8.7	13.1	10.5	7.4	-0.9	7.1	12.5	15.1
ME	2.0	4.5	-5.6	5.1	4.7	9.2	11.8	9.6	2.1	9.3	15.3	16.9
Unidentified												
PCA	-0.1	0.8	0.2	0.8	-0.2	1.1	3.7	2.3	**6.2**	**2.3**	0.0	5.1
ME	0.2	1.3	0.5	1.0	1.5	1.6	4.1	3.0	*4.0*	*2.2*	-1.7	4.3

% refers to percentage change in CC16 per 1ug.m-3 (source specific) PM2.5, 1*10-5 absorbance **bolded** estimates have a p-value<0.05
italis estimates have a p-value<0.10

IV Discussion

We found a positive association between CC16 and the same-day level of $PM_{2.5}$-absorbance, an indicator for combustion originating particles, in the three European cities. In the source specific analysis, only crustal $PM_{2.5}$ was associated with CC16. In general, source-specific $PM_{2.5}$ concentrations determined by PCA and ME were highly correlated.

In previous studies, CC16 has been associated with ozone air pollution. It has been used as a marker of lung damage in epidemiological as well as in experimental air pollution studies[13-15]. We found previously limited evidence on the effects of particulate air pollution on CC16[6]. In the current study, we used the same patient data and found an association between CC16 and the same-day value of absorbance which is a surrogate

for elemental carbon, and consequently is used as a marker for combustion, especially for particles from diesel engines[16]. The result is consistent with our previous finding in the same study population: absorbance was associated with the occurrence of ST segment depression, an indicator for myocardial ischemia[4].

Relatively few studies have assessed the associations between source apportioned PM and health effects. All those have suggested that PM from various combustion sources, including traffic, are related to health. In 1987, Ozkaynak and Thurston observed that particles from industrial sources and from coal combustion were associated with mortality but not soil particles[17]. As part of the Harvard Six Cities Study, $PM_{2.5}$ and coarse particles were monitored at centrally from 1979 to 1988. They found an increase daily mortality related to traffic and coal combustion. Crustal particles were not associated with increase mortality[3]. In Phoenix, mortality data was obtained from Arizona Center for Health Statistics and $PM_{2.5}$ chemical composition from a central local monitoring station for the 1995-1997 period. Cardiovascular, but not total, mortality was associated with $PM_{2.5}$ from combustion and secondary[18]. In New Jersey, mortality was positively associated with traffic combustion, oil combustion and sulfate although not consistently within the three different sites studied[19].

To our knowledge, there is only one previous study that has evaluated respiratory health in association with source-specific $PM_{2.5}$. In Helsinki, 78 asthmatic adults were followed daily for six months with peak expiratory flow measurement and symptom records. Penttinen et al. observed that $PM_{2.5}$ attributable to long-range transport were positively, and soil-derived $PM_{2.5}$ negatively, associated with peak expiratory flow, suggesting that local combustion generated particles were harmful for respiratory endpoints. No source specific $PM_{2.5}$ was associated with any respiratory symptom[20].

It has been suggested that the combustion sources cause inflammation in the airways[21]. The most recognized mechanisms on how particulate air pollution could damage the lungs are inflammation and oxidative and nitrosative stress, as well as mithocondrial damage and even apoptosis[22-25].

Previous studies that have assessed the association of soil with health have produced inconsistent results. Soil particles mainly go to the coarse size fraction (PM from 2.5 to 10 μm); a recent review paper has questioned the harmfulness of the fraction[26]. Some studies have found positive association between dust storms or resuspended road dust and respiratory health[27;28] while some others have not[29;30]. In the pooled analyses, we found an association between CC16 and $PM_{2.5}$ from soil. However, not all city-specific estimates were positive and the results seemed to be driven by extreme values. Thus, drawing definite conclusions about the harmfulness of soil particles is difficult.

Hopke et al.[7] conducted an inter-comparison of different source apportionment methods and found a very high correlation between different methods and researchers. Our results are in concordance with that: sources between both methods were in general highly correlated. However, although both PCA and ME identified 6 sources in Amsterdam, in Helsinki PCA did not identify the Industry/Urban source. Some of the particles linked to traffic by PCA seemed to be related to industry/urban source by ME. This illustrates the difficulty of quantifying the fraction of particles caused by vehicular emissions in the absence of specific markers for traffic exhausts. In Amsterdam Traffic was the source with the highest correlation with Absorbance disregarding the method used. In Helsinki only Traffic identified with PCA showed a high correlation with absorbance, while Urban/Industries was the ME source most related with absorbance.

In the analyses of health effects, the estimates derived in PCA and ME analyses were similar in size when they were significant in PCA, but they were far from significant in ME. This is probably due to the smaller variation in source-specific $PM_{2.5}$ concentrations obtained using ME. Two studies in the US have compared the inter-method variability between source apportioned $PM_{2.5}$ mass and mortality. In Washington, they found that the variability of the relative risk across researcher and across method was smaller than the variability across sources or lag, even when the source apportionment was done by different groups[31]. In Phoenix, they obtained similar results[32]. Nevertheless, in both cases they concluded that further research was still needed to obtain more accuracy in the source apportionment methods.

V Conclusions:

The analyses of source-specific $PM_{2.5}$ helped to enlighten earlier heterogeneous results with $PM_{2.5}$ but did not completely solve it. $PM_{2.5}$ from combustion might lead to an increase in the lung's epithelial barrier permeability. The association with soil is less clear, seems driven by extreme values and maybe only due to chance.

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XI Discussion

This thesis was undertaken in the context of three large European projects forming overall a rich dataset that gave the opportunity to look at the complex problem of air pollution from various perspectives.

1. Main findings and limitations

1.1 Exposure assessment

In epidemiology, the majority of the studies use central measurements as a measure of exposure to air pollution among participants. This strategy assumes that all the subjects in a certain area are exposed to the same levels or the same variations, which are those from central monitoring stations. In order to accurately assess the adverse effects of air pollution, it is important to validate that assumption. Several studies have shown that personal and central outdoor air pollution were correlated, but most of those studies took place in Northern Europe or in the U.S[120-123].

In this thesis, the temporal relationship between outdoor and personal $PM_{2.5}$, carbon (measured indirectly trough light absorbance of the $PM_{2.5}$ filter) and sulphur content among post-myocardial infarction patients was assessed for the first time in a Southern European country. Personal $PM_{2.5}$ concentrations were higher than central outdoor concentrations, even after excluding days with exposure to passive smoking. Personal carbon levels were also higher than outdoor levels, but the two were very similar after excluding passive smoking. Personal sulphur levels were similar to the central ones. Outdoor and personal concentrations of sulphur, but not $PM_{2.5}$, were correlated cross-sectionally, concentrations of absorbance only after excluding days with passive smoking. In longitudinal analyses, outdoor and personal levels of both carbon and sulphur were significantly associated; for $PM_{2.5}$ the association was weaker.

The reason why the correlation for $PM_{2.5}$ was not as good as for carbon or sulphur could be due to the fact that $PM_{2.5}$ has more indoor or personal sources that are not measured by central monitoring stations[124], but the findings are important because they support the use of central measurements to assess the personal exposure to outdoor air pollution

from combustion sources, such as traffic, in a study on short-term effects of air pollution.

However, the results cannot be generalized to the whole population as the study was conducted in myocardial infarction survivors who are older and have different activity patterns[121;125-127], but it has been shown that subjects with cardiovascular disease are probably more susceptible to air pollution effects, therefore it is also important the assess exposure in such populations[128;129]. Furthermore, the results could not be generalized to studies on chronic effects of air pollution where the geographical variability within the same area plays a major role.

In this thesis, an alternative way to assess air pollution exposure was conducted using self reported annoyance due to air pollution. In a first step the determinants of annoyance were described, afterwards the association between annoyance and central measurements of air pollution was assessed.

High annoyance was reported by 14% of the subjects. The individual characteristics associated with annoyance were gender, SES, exposure to passive smoking, respiratory symptoms, and self-reported traffic. On the other hand, moderate and heterogeneous associations between the perception of environmental quality and background measures of pollution were found.

The determinants of annoyance found in this study are in accordance with those described in previous studies[130-133], and were quite homogeneous between all the centres. The moderate association with $PM_{2.5}$ or sulphur, but specially its heterogeneity discourages its use a marker of central air pollution.

As a further step, the association between home outdoor levels of NO_2, a marker of traffic-related air pollution, and annoyance was assessed. Both variables were collected at individual level. Annoyance did not explain the NO_2 variability even after adjusting for individual variables. Annoyance reflects many personal characteristics that are not always measurable. However, we recommend its use as a marker of perceived ambient air pollution, as it reflects subjects' opinion on the environment[134].

1.2 Respiratory health effects

Association between traffic-related air pollution and asthma has been studied. It has been shown that air pollution is associated with asthma worsening; however most of the studies were conducted in children[135-137]. In addition, the role of traffic-related air pollution in the new asthma onset is still unclear.

In the present study, asthma incidence or asthma symptoms were not associated to background levels of air pollution measured centrally. In contrast, self-reported traffic was associated with both asthma symptoms and asthma incidence. A positive but not significant association between measured home outdoor NO_2 and asthma symptoms was observed; such association became significant in atopics.

The reason why background levels of air pollution are not associated with asthma is probably due to misclassification. All the subjects living in the same centre were assigned the same value of air pollution, thus the intercommunity variability is not taken into account.

When assigning individual modelled values of NO_2 to the previous population an association between incidence of asthma and air pollution was strongly suggested which is a novel finding in adults. The use of the score to assess long-term risk factors was proposed to overcome misclassification and power problems[138;139], the results support the previous findings. The use of the largest epidemiological study of asthma in adults, and the effort to use new constructs to define asthma, might explain why this has been found for the first time.

However, two essential limitations arose, first the use of asthma score as a surrogate for asthma incidence; it has not been validated and furthermore the symptoms were only reported for the last 12 months, thus it is not easy to separate the acute effects from the new onset. Second, the modelled NO_2 used in this analysis was not designed for health studies and it is not very precise[115].

In the third paper of this section, a positive association between CC16 and the same-day level of absorbance, an indicator for combustion-originating particles, was found. In the $PM_{2.5}$ source-specific analysis, only soil $PM_{2.5}$ was associated with CC16.

The association found between absorbance and CC16 is concordant with previous studies that have shown that particles from combustion sources can cause inflammation in the airways[51;140;141] and supports the association with new asthma in adults.

2. General discussion and implications

2.1 Exposure assessment

Epidemiology needs accurate exposure in order to assess correctly the associations between the exposure and the effects. The exposure can be measured, modelled or classified based on questionnaire[34]. The personal monitoring of air pollution is probably the most accurate way to assess exposure, but it is usually expensive and very laborious[37]. Furthermore personal monitoring is probably not feasible for long periods of time. The validation of other tools, such as central monitoring or modelling for example, is needed to improve the exposure assessment. After ULTRA[26;122] and now MOCHILA, it has now been shown that central measurement of absorbance, and to lesser extent $PM_{2.5}$, can be used in longitudinal epidemiological studies to evaluate short-term exposure in Southern, Central and Northern Europe.

For NO_2, studies are less consistent: some have found a good correlation between personal and outdoor levels of NO_2[142] while others show a poor correlation between them[143;144]. An explanation could be that background central monitoring stations do not capture the very high levels of NO_2 that can be found close to the traffic sources due to the fact that NO_2 has a low dispersion, unlike $PM_{2.5}$[145;146]. Another reason could also be the high individual variability because of the indoor sources, mainly the use of gas appliances.

It is important to note that personal measurements probably reflect worse actual exposure from outdoor origin that central outdoor measurements, this because of the indoor sources. This thesis focuses on outdoor air pollution; although we acknowledge the relevance of indoor air pollution. $PM_{2.5}$ and NO_2 from indoor sources could also have adverse health effects. On the one hand, the characteristics of the indoor $PM_{2.5}$ have not often been described. In a recent study it was shown that probably around 40% of the indoor carbon came from outdoor sources[147]. Furthermore the correlation between indoor and outdoor particles from combustion sources is usually high[122;148],

and it has been shown that probably the most harmful source of $PM_{2.5}$ is combustion[149;150]. On the other hand, NO_2 is the same from indoor or outdoor sources, but the role of NO_2 per se in causing adverse health effects is still unclear and in epidemiology it has been mainly used a marker of traffic-related air pollution.

The exposure assessment based on questionnaires can also be very useful but their validity depends on too many variables. Questionnaires used to assess air pollution exposure have shown little reproducibility[151]. The present study contributes to the existing knowledge on questionnaire-based exposure with the annoyance studies concluding that annoyance is not a good surrogate for air pollution exposure.

It is also important to differentiate between two concepts; short term and long term exposure. The short term exposure refres to the study of the acute effects due to air pollution and the long term exposure for the chronic effects. The assessment of the longitudinal correlations between personal and central levels aims to validate the use of daily or hourly variations in the central air pollution concentrations in order to assume that variations at individual levels are the same (as in MOCHILA or ULTRA). The assessment of cross- or spatial-correlations between central and personal concentrations aims to validate the use of central concentrations of air pollution for long periods of time (as an average exposure for years or decades) in order to assume that the subjects have been exposed to such concentrations (as in ECRHS). While it seems that for the short-term studies, central measurements can be used to assess personal exposure, for cohort studies there is still work to be done. The use of central concentrations would imply that all the subjects living in the same city or area will be assigned the same levels of exposure which is unlikely to be true. An alternative to such studies could be modelling that would combine, besides the variables commonly used, more personal variables such as place and length of residence or activity patterns.

The future steps in air pollution exposure assessment include validating the exposure assessment for long term studies. Due to the emergence, since the 90's, of evidence showing that air pollution also has effects at low concentrations and in long term[7;12] studies assessing exposure in the long term would be very valuable for epidemiological research. Those should not only focus on $PM_{2.5}$, they could also include gases as it has been suggested that gases play a role as surrogates for other pollutants[152] and ultrafine

particles. There is growing evidence showing that ultrafine particles may play an important role in adverse health effects[153;154].

2.2 Respiratory health effects

It is accepted that air pollution has adverse health effects on the respiratory system[14], however there are still questions to be answered as for example; which source of air pollution is harmful, or what are the effects of air pollution on long term exposure, or if air pollution is associated with the onset of new diseases or only with exacerbations of pre-existing diseases.

Asthma is adulthood is an ill-defined disease with a list of aetiological factors, basically studied in occupational epidemiology. So far, air pollution has been rarely involved in its aetiology. The observed role of air pollution on inflammation and oxidative stress at pulmonary level is consistent with our findings of a role of air pollution on asthma incidence. Probably the size of our study and the use of valid markers of air pollution measurements might explain that we find for the first time an association.

In the present thesis, an association between asthma and NO_2 was found. However NO_2 is used as a marker of traffic-related air pollution rather than for being a harmful substance per se. Experimental studies assessing the effect of NO_2 in humans are inconsistent and usually the effects are only found in asthmatics and/or at high doses[88;102;155-158], even though some of those studies have found that NO_2 could interact with other pollutants enhancing the cellular damage in the lungs[91]. The utility of knowing which sources are the ones associated with adverse health effects has implications in policy management. Policies could have a more straightforward and directed approach.

The association between absorbance and Clara cell CC16 protein supports the finding that traffic-related air pollution is associated with lung damage. CC16 is a protein that is used as a marker of rupture in the epithelial barrier of the lung[159;160]. Absorbance is a surrogate of elemental carbon which comes from combustion. Even when there are other sources of combustion, as indoor burning, industry and energy production, it has

been suggested that traffic contributes significantly to the total carbon found in $PM_{2.5}$[161-165].

We have now found evidence for the adverse health effect of combustion particles in general and specifically from traffic; however, soil particles could also be harmful as suggested in this study by the association found between CC16 and soil. The soil particles mainly go to the coarse fraction and health effects associated with them are inconsistent[11;166;167]. One of the reasons for the inconsistencies in relation to soil, i.e. coarse particles, may be that personal exposure to such particles has not been adequately assessed until now. Coarse particles are the ones with more spatial variability and the use of personal measurements might shed a light on that issue.

Summarizing, the implications of the present work are diverse and they embrace mainly two different aspects: epidemiological research and public health point of view. Both have consequence in policies.

The findings support the use of central measurements to assess personal exposure to air pollution from combustion sources in Southern Europe. Combustion sources contribute substantially to the total PM; therefore the use of central measurements is adequate to assess short term effects of traffic-related air pollution. In addition, as it has been shown in this study, traffic-related air pollution is associated with asthma exacerbations and probably with asthma onset, even at the levels that actually exist. Traffic-related air pollution is also associated with lung damage, supporting the previous findings. Thus, new policies should address that issue and regulate traffic in urban areas. Furthermore, these findings may support the fact that population should not be located close to high traffic sources, or at least not susceptible populations (elderly or children). Schools and day care centres should be move further away from such sources.

On the other hand, annoyance due to air pollution has been shown not to be a good marker of air pollution and is not recommended to assess air pollution exposure. However policy makers might take it into account the annoyance due to air pollution as a direct outcome of interest. Annoyance is important in its own right as it integrates individual perception, feeling of security and health problems. It may also influence trust in government and the regulatory authorities. Its standardized measurement is

simple and it could be easily added to environmental monitoring and health tracking surveys.

XII Conclusions

The main conclusions from this thesis are:

- Daily levels of absorbance and sulphur of outdoor central measurements are good surrogates for personal exposure in a Mediterranean setting in studies on short-term effects; however for $PM_{2.5}$ other indoor and/or personal sources have to be taken into account.
- Self-reported annoyance is not a valid maker of air pollution exposure
- Self-reported annoyance as an environmental biomarker for public hralth surveillance is valuable in its own right as it integrates individual perception, feeling of security and health problems
- Traffic-related air pollution increases asthma symptoms in adults
- An association between traffic-related air pollution and new asthma onset in adults is strongly suggested
- $PM_{2.5}$ from combustion might lead to an increase in the lung's epithelial barrier permeability

Traffic-related air pollution is a major source of total air pollution in urban settings. Adequate tools to assess its exposure are still needed, for both long term and short term effects. Traffic-related air pollution is an important risk factor for respiratory morbidity and mortality. It is associated with asthma and its effect in the long term needs to be further investigated, as it seems that besides the association with asthma exacerbation, it could also play a role in new onset of asthma. The findings presented in this study support a stricter control of air pollution, furthermore subjects are annoyed by air pollution even when levels are low which is important as annoyance per itself reflects subject's belief and fears.

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ANNEXE I

1. Commentary to the "Annoyance due to air pollution in Europe"

Linking Particulate Matter and Sulfur Concentrations to Air Pollution Annoyance: Problems of Measurement, Scale, and Control

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Linking Particulate Matter and Sulfur Concentrations to Air Pollution Annoyance: Problems of Measurement, Scale, and Control

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Jacquemin et al. address an important topic in the field of epidemiology and public health by increasing understanding of the triggers of air pollution annoyance across 25 population centers in 14 countries in Europe. No study, however commendable, is without its limitations and this one is no exception. We offer a commentary of their article "Annoyance Due to Air Pollution in Europe" as a means to enhance future study of air pollution perceptions. Our assessment focuses on three elements of their research: 1) measurement of the dependent variable, air pollution annoyance; 2) problems associated with the spatial scale used to estimate air pollution exposure; and 3) the exclusion of statistical controls routinely used in the risk perception literature.

Measuring Air Pollution Annoyance

A potential problem with the measurement of the dependent variable is the restriction of the question of air pollution annoyance to the specific condition of keeping a window open. By this restriction, Jacquemin et al. are measuring how annoyed or disturbed a person is by outdoor air pollution when indoors. Not surprisingly, under this unusually specific condition, 43 percent of respondents score their level of outdoor air pollution annoyance at zero.

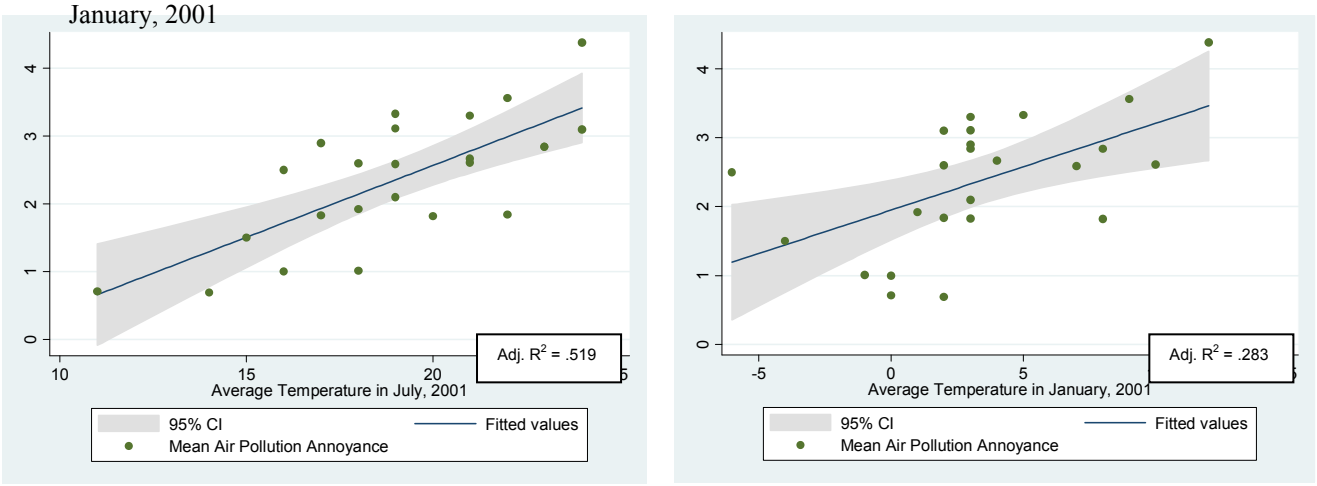
Jacquemin et al. also report that respondents from Northern European cities have substantially lower levels of air pollution annoyance. This variance in air pollution annoyance by city is partially explained by data on fine particulate matter ($PM_{2.5}$) and sulfur (S) concentrations. For example, figure 4a in their manuscript illustrates the relationship between mean air pollution annoyance scores and $PM_{2.5}$ and S levels for each city. For every unit increase ($\mu g\ m^{-3}$) in $PM_{2.5}$ and S, we observe a modest

increase in mean annoyance scores. Adjusted R^2 values in "crude" models are .23 for $PM_{2.5}$ and .36 for S.

Testing relationships between objective measures of air pollution and subjective reports of annoyance is perfectly reasonable. However, the construction of the question to derive annoyance scores may contaminate this effort. Recall, respondents are asked to indicate their level of annoyance with outdoor air pollution when indoors. Observed responses in air pollution annoyance may be driven by restrictions of the question. Indirectly, the question may be measuring how frequently an individual selected at random opens his/her window to the outside world.

We illustrate our point with data. First, we presume that the likelihood a person opens his/her window to the outside world is partially determined by the average temperature of the in which city he/she resides. All things held equal, we also presume that persons in colder climes such as Northern Europe are less likely to open their windows. To illustrate how the open window restriction may contaminate the measurement of outdoor air pollution annoyance, we collected average temperature data in the months of January and July (in degrees Celsius) for all 25 cities for 2001. Following Jacquemin et al., we generate two "crude" scatter plots (see Figure 1), with mean annoyance scores on the vertical axis and average temperature measures on horizontal axes. Like Jacquemin et al., we also derive an adjusted R^2 for both linear models.

Figure 1: Scatter Plots of Mean Air Pollution Annoyance Scores against mean Temperature in July and January, 2001



The results show that air pollution annoyance scores (as estimated by the question) increase as average temperature increases. The variance explained in mean annoyance scores by average temperature in July performs considerably better than the air pollution measures assembled by Jacquemin et al. Next, we perform regression tests (excluding the three Italian outlier cities of Pavia, Verona, and Turin, as done by Jacquemin et al.) to see how well air pollution measures of $PM_{2.5}$ and S hold up with the inclusion of temperature data. Results show that both estimates of air pollution disappear with the inclusion of a measure of average temperature in July (see Table 1).

Table 1: OLS Regression Models for Mean Air Pollution Annoyance

	b	95 % CI	*b*	95 % CI
Variables				
Constant	-1.728* (0.879)	-3.613 to 0.157	-1.543 (.994)	-3.674 to 0.588
Average July Temperature	0.172** (0.062)	0.040 to 0.304	0.178** (0.076)	0.016 to 0.341
$PM_{2.5}$	0.065 (0.042)	-0.025 to 0.155	-	-
Sulfur	-	-	0.652 (0.668)	-0.780 to 2.084
F	14.23		12.33	
Prob > F	0.0004		0.0008	
Adjusted R^2	0.6231		0.5862	

Note: Cell entries are unstandardized OLS regression coefficients, with standard errors in parentheses. Null hypothesis test of coefficient equal zero, **p<.05,*p<.10.

The purpose of bringing in temperature data is not to nullify the reasonable logic of the manuscript written by Jacquemin et al. In fact, we advocate the approach of linking objective measures of air pollution and subjective reports of annoyance, and commend the authors for undertaking such an extensive data collection effort. Our comments address the scientific adequacy of the phrasing of the question of annoyance, and how it may be estimating concepts other than the intended empirical target. To their credit, negative binomial regression results show that all symptoms of respiratory illness, from asthma to wheezing, are significantly associated with the air pollution annoyance. This fact gives their measure significant criteria validity.

Other issues arise from the inadequate phrasing of the annoyance question. With the distribution of air pollution annoyance skewed left, Jacquemin et al. decide on a cut-point of "high annoyance" inconsistent with convention. A respondent is classified as highly annoyed if they score a 6 or more (or a 5 or more as reported in the summary section of the manuscript) on the disturbance scale. The Swiss SAPALDIA and EXPOLIS studies (including Finland, Greece, and Czech Republic), appropriately cited in the manuscript, define high annoyance at 8 and 7 or more respectively. Jacquemin et al. provide no adequate theoretical or empirical justification for lowering this benchmark.

Overall, these limitations associated with measurement of outdoor air pollution annoyance weaken (but do not theoretically nullify) their conclusion that "Annoyance due to air pollution is frequent in Europe."

Measuring Air Pollution and the Problem of Scale

The next set of potential problems with the research design relate to measurement of air pollution at the city scale. Agencies of environmental protection in most highly developed countries measure and track six common air pollutants – particulate matter, ground-level ozone, carbon monoxide, sulfur oxides, nitrogen oxides, and lead. Jacquemin et al. restrict their analysis of pollutants to annual mean mass concentrations of fine particles ($PM_{2.5}$) and sulfur (S) content. They justify the use of $PM_{2.5}$ and S on the basis that concentrations of these pollutants reflect the air quality for a region such as a city. However, studies show that sulfur dioxide concentrations vary spatially, high concentration signatures generally found directly over large industrial activities (Tayanc 2000; Chaulya 2004; Martuzeviciusa et al. 2004). Thus, proximity to such activities may increase reported levels of annoyance.

Furthermore, the study estimates air pollution based on "monitoring sites" but the nature of these sites are never fully discussed in the methods section. The specific locations of these sites should have been disclosed as they may affect the degree to which a respondent feel annoyed. How readings from multiple monitoring sites were aggregated (if at all) should have also been discussed in the methods section. The location of monitoring stations in relation to the population being studied may condition the relationship between annoyance and recorded air pollution levels. Finally, using air pollution monitoring stations to estimate regional air quality, researchers often interpolate a surface to generate a distance decay function for air quality (rather than assigning every respondent the same reading regardless of their proximity to a station). This issue is never discussed in the article and it is not clear how sulfur dioxide was measured and the role the variable played in the results.

Finally, Jacquemin et al. examine perceptions of individuals living in cities within various countries. Since most air pollution perceptions studies have been conducted at finer spatial scales, a major methodological issue here could be the Modifiable Areal Unit Problem (MAUP). This problem occurs if relations between variables change with the selection of different areal units, causing the reliability of results to be called into question (Unwin 1996). In other words, the results may depend on the spatial scale at which respondents are examined. The MAUP is most prominent in the analysis of socio-economic and epidemiological data given the need to summarize these data in an often time arbitrary zonal format (Nakaya 2000). Because this statistical issue is so prominent in the field of epidemiology, the authors should have at minimum discussed the potential problem as it has significant implications for interpreting the results.

Measuring Independent Variables

In this section we assess the right side of the air pollution annoyance equation. Specifically, we discuss three propositions in risk perception research that are not specifically addressed in Jacquemin et al. First, the *peak-end rule* in psychometric research suggests that people have a tendency to recall events by their highest point of intensity or how they end (Tversky and Kahneman 1974). That is, human memory is biased toward extremes not summations or central tendencies. Insofar as the peak-end rule is correct, future research may better predict air pollution annoyance with measures of *peak* air pollution, not annual mean estimates of fine particulate matter and sulfur concentrations as done by Jacquemin et al. Likewise, one can reasonably expect higher levels of air pollution annoyance among respondents exposed to visibly higher levels of pollution the day they are interviewed. In our own research, we find that perceptions of

air pollution risk in Texas are better predicted by the number extreme Air Quality Index (AQI) days (or days over the "unhealthy day" threshold) than by annual average AQI scores (Lubell, Vedlitz, Zahran, and Alston 2006).

The second cognitive rule in psychometric research applicable to Jacquemin et al. is the reference bias or framing effect (Samuelson and Zeckhauser 1988; Tversky and Kahneman1992). This concept of referencing is central to prospect theory in risk analysis. The main proposition of prospect theory is that people evaluate a risk outcome relative to a reference point, not a final status. Researchers find that people care less about gains or outcomes above a reference point than losses or outcomes below a reference point. In other words, people are loss averse. Jacquemin et al. hypothesize that annoyance scores in City X > City Y if, City X $PM_{2.5}$ > City Y $PM_{2.5.}$ A reformulation of Jacquemin et al. accounting for reference bias is that annoyance scores in City X > City Y if, City X value of time 2 $PM_{2.5}$ - time 1 $PM_{2.5}$ > City Y value of time 2 $PM_{2.5}$ - time 1 $PM_{2.5}$. That is, if residents in City X experience a noticeable decline in air quality from some known reference point, they are more likely to report higher levels of air pollution annoyance than residents in City Y (assuming residents in City Y experience no detectable change in air quality from some known reference point), even if persons in City Y reside in objectively worse air quality conditions. Of course, there are obvious limits to the proposition, but Jacquemin et al. have data for two time points in the European Community Respiratory Health Survey that would enable an adequate test of loss aversion in air pollution annoyance scores.

The third proposition in risk perception literature is the notion that affective and cognitive psychologies influence self-reports of risk, annoyance, concern and related notions. Scholars routinely estimate concepts like worldview, political philosophy, institutional trust, knowledge, and environmental beliefs to predict public perceptions of environmental risk (Dietz, Stern, and Guagnano 1998; Freudenberg 1988; Stern 2000; Brody, Peck, and Highfield 2004; Johnson and Tversky 1983; O'Connor, Bord, and Fisher 1999). These variables are correlated with, but are not perfectly reducible to the many demographic variables examined by Jacquemin et al.

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ANNEXE II

2 Response to the commentary: "Linking Particulate Matter and Sulfur Concentrations to Air Pollution Annoyance: Problems of Measurement, Scale, and Control"

Published in International Journal of Epidemiology, in press

Response: Linking Particulate Matter and Sulfur Concentrations to Air Pollution Annoyance: Problems of Measurement, Scale, and Control

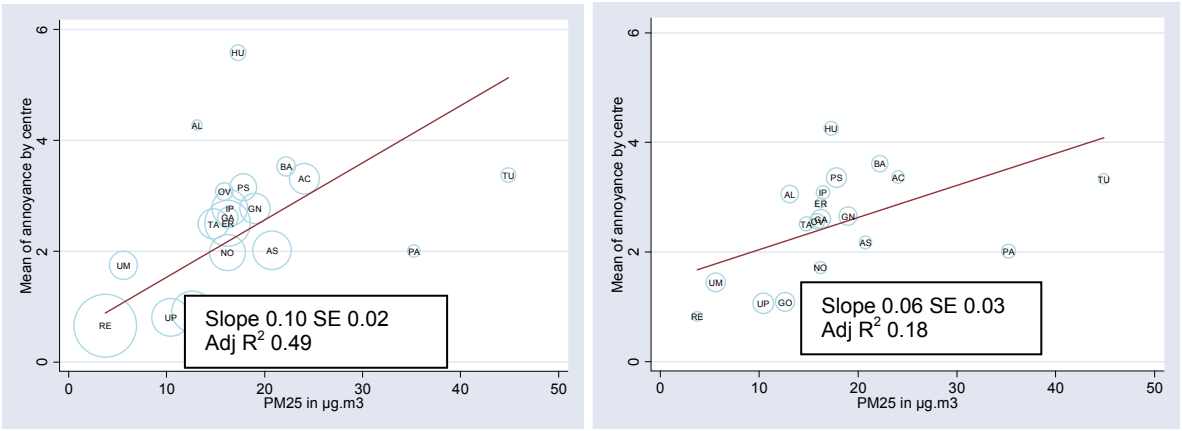
Bénédicte Jacquemin *, Jordi Sunyer, Nino Künzli

We thank doctors Brody and Zahran for their useful comments and we would like to respond to some of their points.

We agree that the phrasing of the question on annoyance could be misleading. The frequency with which subjects open the windows may indeed influence their perceptions. However, the decision to open windows may also be influenced by noise, which is a strong correlate of traffic-related pollution. The ECRHS included the following question: "Do you sleep with the window open at night during winter?", thus we decided to further investigate the issue. Answers to this question were not correlated with annoyance. In fact, the mean of annoyance was lower in subjects sleeping with the window open (1.76 vs. 2.35) which is in line with the notion that reported annoyance due to air pollution may be correlated with, if not driven by, the perception of traffic noise around the home.

We also tested whether the associations between the adjusted centre-specific means of annoyance and the air pollution measurements were different among subjects sleeping with or without open windows. Figure 1 shows that among subjects who sleep with open windows the association with air pollutants is indeed better compared with those who do not. However, the association shown in Figure 1a is mainly driven by the cleanest centre, namely Reykjavik, where most of the subjects (> 80%) sleep with open windows in winter; when data from Reykjavik are excluded, the two figures are more similar even if the association remains better – although poor – for the subjects sleeping with the window open in winter.

Figure 1: Plots of adjusted mean annoyance scores against $PM_{2.5}$ levels at each centre and estimated change in mean of annoyance per one µg m^{-3} increase in $PM_{2.5}$. The slope (standard error) and R^2 (adjusted for degrees of freedom) are shown. The size of circles indicates the weight of each centre in the regression analysis



a) Subjects sleeping with the window open b) Subjects sleeping with the window close

We also agree with the scale limitations raised by Brody and Zarhan. As we mentioned in the conclusion of our article, an analysis assessing the association between annoyance and home-based measurements would have avoided these limitations. We are currently estimating home outdoor air quality for all participants and re-analyzing the association with annoyance, as we do believe that subjects report environmental conditions around the residential location rather then the general background level of pollution, captured with our measurements of $PM_{2.5}$ or its sulphur content. Preliminary analyses indicate poor correlations between annoyance and estimates of home outdoor air quality with substantial heterogeneity across cities. This needs further evaluation.

Regarding the choice of the pollutants, as stated in the Methods, PM2.5 and S were chosen because they represent regional 'urban background' air quality. While S may vary spatially in places with industrial activities, it is important to note that none of our monitors were located in industrial hot spots. Most of the air pollution comes from traffic and the figures were shown non-adjusted and adjusted by traffic intensity, showing no difference between them.

Finally, we also agree that more socio-psychological variables, such as political affiliation, general beliefs and social connectivity, may be important determinants of perceived annoyance, and, more generally, the perception of risks. Because the ECRHS was primarily planned to investigate the distribution and aetiology of asthma, we lack more detailed psycho-social assessments that would allow us to further elaborate on the various issues raised by Brody and Zahran. However it is also important to note that even in social sciences, the predictability of environmental concern and or environmental willingness to act is still limited despite the adoption of elaborate methods and the inclusion of variables such as general beliefs or values.[1,2]

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