Timo Lanki

Fine Particles In Urban Air
Exposure and Cardiovascular Health Effects

Department of Environmental Health,
National Public Health Institute Kuopio, Finland
and
Department of Environmental Sciences,
University of Kuopio, Finland

Kuopio 2006

Timo Lanki

FINE PARTICLES IN URBAN AIR

EXPOSURE AND CARDIOVASCULAR HEALTH EFFECTS

ACADEMIC DISSERTATION

To be presented with the permission of the Faculty of Natural and Environmental Sciences of the University of Kuopio for public examination in auditorium MET, Mediteknia, Yliopistonranta 1 B, on Saturday 25th of November 2006, at 12:00.

National Public Health Institute, Department of Environmental Health, Kuopio, Finland

and

University of Kuopio, Department of Environmental Sciences, Kuopio, Finland

Kuopio 2006

Publications of the National Public Health Institute
KTL A19 / 2006

S u p e r v i s e d   b y

Professor Juha Pekkanen, MD, PhD
National Public Health Institute (KTL)/
University of Kuopio
Kuopio, Finland

Professor Juhani Ruuskanen, PhD
University of Kuopio
Kuopio, Finland

Sari Alm, PhD
City of Lahti
Lahti, Finland

R e v i e w e d   b y

Professor Kari Lehtinen, PhD
University of Kuopio
Kuopio, Finland

Research professor Veikko Salomaa, MD, PhD
National Public Health Institute (KTL)
Helsinki, Finland

O p p o n e n t

ICREA Research professor Nino Künzli, MD, PhD
Institut Municipal d'Investigació Mèdica (IMIM)
Barcelona, Spain

To Sari, Hilla and Bennu…and Mom

ABSTRACT

Air pollution has been estimated to cause annually 370 000 premature deaths within the European Union alone which makes it by far the most important environmental health problem in Western countries. The adverse effects of ambient fine particulate matter ($PM_{2.5}$; <2.5 µm in aerodynamic diameter) on cardiovascular health seem to be responsible for the major part of the deaths. Evidence on the effects of $PM_{2.5}$ comes mainly from epidemiological time-series studies that link day-to-day changes in $PM_{2.5}$ at a central outdoor measurement site with day-to-day variations in health. However, it is unclear how well central outdoor measurements of $PM_{2.5}$ and its components reflect actual exposures in these studies. Also, it is not known which sources produce particles that are most harmful to health. Finally, the importance of brief exposures to high levels of $PM_{2.5}$, typical in traffic, is not known. This information is needed to most cost-effectively reduce the health effects associated with exposure to ambient $PM_{2.5}$.

The present thesis study aims to partly fill in these gaps in knowledge. The study was conducted within the ULTRA study in three cities: Amsterdam, the Netherlands, Erfurt, Germany, and Helsinki, Finland. Panels of non-smoking elderly persons (N=131; 50-84 years of age) with coronary heart disease were followed up biweekly with clinic visits for six to eight months. During the visits, electrocardiograms were recorded to evalute the occurence of ST segment depressions during light exercise test, an indicator for myocardial ischemia, and heart rate variability, indicator of autonomic control of heart. Concurrently with the clinic visits, outdoor levels of $PM_{2.5}$ were monitored at a fixed outdoor site. In Amsterdam and Helsinki, also personal and indoor measurements of $PM_{2.5}$ were conducted during the 24-hrs before clinic visit. In Helsinki, continuous personal $PM_{2.5}$ concentrations were measured with a new, portable photometer. The $PM_{2.5}$ samples were analysed for elemental composition, and the absorbance of $PM_{2.5}$ filters was measured as a marker for elemental carbon (originates from combustion processes). Information on housing characteristics and behavioural factors possibly

affecting personal exposure to $PM_{2.5}$ and elemental carbon was collected with questionnaires.

We observed high longitudinal correlations between outdoor, indoor and personal concentrations of $PM_{2.5}$, absorbance and sulphur in Amsterdam and Helsinki. The correlations were lower for Cu, Ca, and Cl. Besides outdoor concentrations, time spent in traffic and closeness of a major street increased exposure to elemental carbon as indicated by absorbance. Photometric $PM_{2.5}$ concentrations correlated highly with gravimetric concentrations (standard method). In Helsinki, personal and outdoor $PM_{2.5}$ concentrations during the four hours before clinic visits were associated with increased risk of ST segment depression. $PM_{2.5}$ both from local traffic and long-range transport was associated with the occurrence of ST segment depressions (Helsinki) and heart rate variability (pooled results of the three cities). The effect of source-specific $PM_{2.5}$ on heart rate variability was modified by beta-blocker use.

Measurements at a central outdoor site appear to sufficiently well estimate daily variation in personal exposures to $PM_{2.5}$, especially from combustion sources, in Amsterdam and Helsinki. Personal measurements are recommended for studies on the effects of soil-originating particles. Present results suggest that even very short-term exposures to high levels of $PM_{2.5}$ are associated with increased risk of myocardial ischemia among persons with coronary heart disease. It seems that particulate air pollution has both a rapid (within hours) and a more delayed (within days) effect on cardiovascular health. Local traffic was found to be a major determinant of both short-term and long-term personal exposure to (combustion related) $PM_{2.5}$. Traffic emissions also contribute to long-range transported particles. Thus, better control of traffic emissions is needed to decrease exposure to harmful $PM_{2.5}$ components.

TIIVISTELMÄ

Ilmansaasteiden on arvioitu aiheuttavan vuosittain jo pelkästään Euroopan unionin alueella 370 000 ennenaikaista kuolemaa, mikä tekee siitä ylivoimaisesti merkittävimmän ympäristöterveydellisen ongelman länsimaissa. Suurin osa kuolemista ilmeisesti selittyy ilman pienhiukkasten ($PM_{2.5}$; aerodynaaminen halkaisija <2,5 µm) haitallisilla vaikutuksilla sydämen ja verenkiertoelimistön terveyteen. Todisteita pienhiukkasten haittavaikutuksista on kertynyt ennen kaikkea epidemiologisista aikasarjatutkimuksista, jotka perustuvat kiinteällä ulkoilman mittausasemalla mitattujen päivittäisten pienhiukkaspitoisuuksien vaihtelun yhdistämiseen väestön terveydentilan päivittäiseen vaihteluun. On kuitenkin epäselvää, kuinka hyvin mitatut hiukkaspitoisuudet kuvastavat todellista altistumista pienhiukkasille ylipäänsä, ja toisaalta altistumista eri lähteistä peräisin oleville pienhiukkasille. Toistaiseksi ei kuitenkaan varmuudella tiedetä, mistä lähteistä ovat peräisin terveydelle kaikkein haitallisimmat hiukkaset. Hyvin lyhytaikaisen korkeille pienhiukkaspitoisuuksille altistumisen mahdollisia haittoja esim. liikenteessä ei myöskään tunneta. Uutta tutkimustietoa tarvitaan, jotta pienhiukkasille altistumiseen yhdistettyjä haittavaikutuksia voitaisiin kustannustehokkaasti vähentää.

Tämä väitöskirjatutkimus pyrkii osaltaan vastaamaan edellä mainittuihin tutkimuskysymyksiin. Tutkimus suoritettiin osana ULTRA-tutkimusta, johon osallistui kolme kaupunkia: Amsterdan (Alankomaat), Erfurt (Saksa) ja Helsinki. Tutkimuspaneelit koostuivat tupakoimattomista, sepelvaltimotautia sairastavista henkilöistä (yhteensä 131 henkilöä, iältään 50-84 vuotta), joiden terveydentilaa arvioitiin joka toinen viikko klinikkakäyntien avulla 6-8 kuukauden ajan. Näillä käynneillä tallennettiin sydänsähkökäyrät, joista sitten arvioitiin ST-segmentin laskujen esiintymistä (merkki sydänlihaksen hapenpuutteesta) sekä sydämen syketaajuuden vaihtelua (sydämen autonomisen hermotuksen mitta). Tutkimuksessa mitattiin ulkoilman pienhiukkaspitoisuuksia kiinteillä mittausasemilla. Amsterdamissa ja Helsingissä mitattiin lisäksi klinikkakäyntia edeltäneen vuorokauden ajan sisäilman pienhiukkaspitoisuutta, sekä kannettavan

hiukkaskeräimen avulla henkilökohtaista altistumista pienhiukkasille. Helsingissä oli käytössä myös uudentyyppinen kannettava fotometri, jolla pystyttiin mittaamaan hyvin lyhytaikaista vaihtelua pienhiukkasille altistumisessa. Kerätyistä pienhiukkasnäytteistä määritettiin alkuainekoostumus. Lisäksi näytteiden absorbanssi mitattiin; näin saatiin arvio polttoprosesseissa syntyvän alkuainehiilen pitoisuudesta. Kyselykaavakkeilla kerättiin tietoa sellaisista asunnon ominaisuuksista ja henkilökohtaisen käyttäytymisen piirteistä, joilla saattoi olla vaikutusta pienhiukkasille tai alkuainehiilelle altistumiseen.

Pienhiukkasten, absorbanssin ja rikin ulko- ja sisäpitoisuudet sekä henkilökohtainen altistuminen korreloivat vahvasti keskenään Amsterdamissa ja Helsingissä. Korrelaatiot olivat matalampia kuparille, kalsiumille ja kloorille. Alkuainehiilelle (absorbanssi) altistuminen oli sitä suurempaa, mitä enemmän liikenteessä vietettiin aikaa ja mitä lähempänä olivat vilkkaat liikenneväylät. Fotometriset pienhiukkaspitoisuudet korreloivat vahvasti gravimetristen (standardimenetelmä) pitoisuuksien kanssa. Helsingissä altistuminen pienhiukkasille neljän klinikkakäyntiä edeltäneen tunnin aikana lisäsi ST-laskun vaaraa. Ennen kaikkea paikallisesta liikenteestä peräisin olevat sekä kaukokulkeutuneet pienhiukkaset lisäsivät ST-laskujen esiintymisen todennäköisyyttä Helsingissä. Kolmen kaupungin yhdistettyjen tulosten perusteella näistä lähteistä peräisin olevat hiukkaset vaikuttivat myös sydämen syketaajuuden vaihteluun; vaikutuksen voimakkuus riippui siitä, käyttikö tutkimushenkilö beta-salpaajia.

Ulkoilman pitoisuudet kiinteällä mittausasemalla vaikuttivat kuvastavan riittävän hyvin päivittäistä vaihtelua henkilökohtaisessa altistumisessa erityisesti polttoperäisille hiukkasille Amsterdamissa ja Helsingissä. Henkilökohtaisia altistumismittauksia suositellaan tehtäväksi tutkimuksissa, joissa arvioidaan maaperän hiukkasten mahdollisia terveysvaikutuksia. Tutkimuksen tulosten perusteella varsin lyhytaikainenkin altistuminen korkeille pienhiukkaspitoisuuksille on yhteydessä lisääntyneeseen ST-laskujen riskiin sepelvaltimotautia sairastavilla. Hiukkasmaisilla ilmansaasteilla vaikuttaa olevan sekä hyvin nopeita (havaitaan tuntien sisällä altistumisesta) että viivästyneitä (päivien kuluessa) vaikutuksia sydämen ja verenkiertoelimistön terveyteen. Paikallisen liikenteen päästöjen havaittiin lisäävän sekä päivittäistä että pidempiaikaista altistumista (polttoperäisille) pienhiukkasille. Myös kaukokulkeutuneet hiukkaset sisältävät runsaasti liikenneperäisiä pienhiukkasia. Liikenteen päästöjen tehokkaampaa kontrollointia tarvitaankin haitallisimmille pienhiukkasille altistumisen vähentämiseksi.

Avainsanat: pienhiukkaset, ilmansaasteet, sydän- ja verisuonitaudit, altistumisen arviointi, ajoneuvojen pakokaasut, sydänlihaksen iskemia, sydämen syketaajuuden vaihtelu, pitkittäistutkimukset

CONTENTS

ABBREVIATIONS

ABS   absorbance, i.e. absorption coefficient

BMI   body mass index

CABG   coronary artery bypass graft

CAPs   concentrated ambient particles

CI   confidence interval

COPD   chronic obstructive pulmonary disease

CV   coefficient of variation

CVD   cardiovascular disease

EC   elemental carbon

ECG   electrocardiography

ED-XRF   energy-dispersive X-ray fluorescence

ETS   environmental tobacco smoke

GAM   generalized additive models

FP   fine particulate matter, usually refers to particles <2.5 µm in aerodynamic diameter, i.e. $PM_{2.5}$

HF   high frequency power (0.15-0.4 Hz) of heart rate variability

HI   Harvard impactor

IQR   interquartile range, the range between 25th and 75th quartile

HRV   heart rate variability

MI   myocardial infarction

PC   personal cyclone

PCA   principal component analysis

PM   particulate matter

$PM_{2.5}$ (fine) particulate matter, aerodynamic diameter < 2.5µm

PM_{10} (thoracic) particulate matter, aerodynamic diameter < 10 µm

PTCA	percutaneous transluminal coronary angioplasty
SD	standard deviation
SDNN	the standard deviation of NN intervals in electrocardiography
TSP	total suspended particulate matter, aerodynamic diameter often <40 μm, but not strictly defined
UF	ultrafine particulate matter, aerodynamic diameter <100 nm

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles:

I   Janssen NA, de Hartog JJ, Hoek G, Brunekreef B, Lanki T, Timonen KL, Pekkanen J. Personal exposure to fine particulate matter in elderly subjects: relation between personal, indoor and outdoor concentrations. *Journal of Air & Waste Management Association* 2000; 50:1133-1143.

II   Janssen NAH, Lanki T, Hoek G, Vallius M, de Hartog JJ, Van Grieken R, Pekkanen J, Brunekreef B. Associations between ambient, personal, and indoor exposure to fine particulate matter constituents in Dutch and Finnish panels of cardiovascular patients. *Occupational and Environmental Medicine* 2005; 62:868-877.

III Lanki T, Ahokas A, Alm S, Janssen NAH, Hoek G, de Hartog JJ, Brunekreef B, Pekkanen J. Determinants of personal and indoor $PM_{2.5}$ and absorbance among elderly subjects with coronary heart disease. *Journal of Exposure Science and Environmental Epidemiology*, in press. (doi:10.1038/sj.jes.7500470)

IV   Lanki T, Alm S, Ruuskanen J, Janssen NAH, Jantunen M, Pekkanen J. Photometrically measured continuous personal $PM_{2.5}$ exposure: Levels and correlation to a gravimetric method. *Journal of Exposure Analysis and Environmental Epidemiology* 2002; 12:172-178.

V   Lanki T, Hoek G, Timonen KL, Peters A, Tiittanen P, Vanninen E, Pekkanen J. Hourly variation in fine particle exposure is associated with transiently increased risk of ST segment depression. Submitted.

VI   Lanki T, de Hartog JJ, Heinrich J, Hoek G, Janssen NAH, Peters A, Stölzel M, Timonen KL, Vallius M, Vanninen E, Pekkanen J. Can we identify sources of fine particles responsible for exercise-induced ischemia on days with elevated air pollution? The ULTRA study. *Environmental Health Perspectives* 2006; 114:655-660.

VII de Hartog JJ, Lanki T, Timonen KL, Hoek G, Janssen NAH, Ibald-Mulli A, Peters A, Heinrich J, Tarkiainen T, van Grieken R, van Wijnen J, Brunekreef B, Pekkanen J. Associations between source-specific $PM_{2.5}$ and heart rate variability are modified by beta-blocker use in patients with coronary heart disease. Submitted.

1 INTRODUCTION

For a long time it has been generally accepted that exposure to high air pollution levels has harmful effects on human health. However, by the late 1970's levels of sulphur dioxide and particulate air pollution had decreased to a fraction of previous levels, and the scientific community was mostly convinced that air pollution no longer posed a risk to health (Pope and Dockery 2006). The new era of air pollution research begun in 1990's when two US cohort studies suggested than life-shortening was associated with fine particle concentrations even at low levels (Dockery et al. 1993, Pope et al. 1995). At the moment, air pollution is the main environmental health problem judging by the number of people affected and the severity of the effects. It has been estimated that in the 25 EU member states over 370,000 persons (in Finland 1,300) die annually due to exposure to ambient air pollution (European Union 2005).

Currently, the focus of air pollution research is on the cardiovascular effects. Cardiovascular diseases are the most common causes of deaths in Western countries, and thus even small increases in risk due to exposure to air pollution have significant effects on public health. Particulate air pollution seems to be responsible for most of the effects, although the effects of gaseous pollutants cannot be ignored. Fine particles ($PM_{2.5}$, aerodynamic diameter <2.5μm) are capable of penetrating deep into the lungs, to the alveolar region, and seem to be more harmful than larger particles. However, fine particles originate mainly from combustion processes whereas larger particles are soil derived; thus composition may also explain the differences in the health effects. Although the exact mechanisms by which particles affect cardiovascular health are not known, systemic inflammation and/or changes in the autonomic nervous control of heart seem to be in the pathway from exposure to clinical effects (Brook et al. 2004).

There are still gaps in the current knowledge that make the abatement of the cardiovascular effects of fine particles more difficult. First of all, it is not known which constituents of $PM_{2.5}$ are responsible for the effects. Because the source of particles defines their composition, cost-effective reduction of the effects requires identification and emission control of the most harmful particle sources. Further, there are only few studies on the effects of very short-term $PM_{2.5}$ exposures on cardiovascular health. Yet it has been suggested that even one hour exposure to traffic exhausts may trigger myocardial infarction (Peters et al. 2004). And finally, the acute effects of air pollution have mainly been estimated in epidemiological time-series studies, where daily changes in outdoor $PM_{2.5}$ concentrations measured at a central site are linked to daily changes in indicators of cardiovascular health

(Bell et al. 2004). However, it is not known, how well fixed site measurements of $PM_{2.5}$ or its constituents reflect actul variations in exposure among persons with cardiovascular disease.

The present thesis study aims for its part to fill in these gaps. The study is part of the EU funded ULTRA study (Pekkanen et al. 2000), which aimed to improve exposure and risk assessment for ambient fine and ultrafine (<0.1 μm) particles. During the study, panels of patients with coronary heart disease were followed up with biweekly clinic visits in Amsterdam, the Netherlands, Erfurt, Germany, and Helsinki, Finland for six to eight months in 1998 to 1999. Concurrently with the visits, outdoor concentrations of $PM_{2.5}$ and other air pollutants were measured at central measurement sites. With additional funding from the Health Effects Institute (U.S.), indoor and personal measurements of $PM_{2.5}$ were conducted in Amsterdam and Helsinki.

ULTRA study has already considerably increased the knowledge on the cardiovascular effects of particulate air pollution. Cardiorespiratory symptoms were shown to be associated more strongly with $PM_{2.5}$ than with ultrafine particles (de Hartog et al. 2003). Blood pressure and heart rate decreased in association with $PM_{2.5}$ (Ibald-Mulli et al. 2004). Again, there was less evidence on the effects of ultrafine particles. Occurrence of ST segment depression in electrocardiography during stress test is an indicator of myocardial infarction (ACC/AHA 1997). There were enough ST events for analyses only in Helsinki, where both ultrafine and fine particles were associated with increased risk of the ST segment depressions (Pekkanen et al. 2002). Effects of particulate air pollution on the autonomic control of heart were evaluated by linking outdoor concentrations to heart rate variability (Timonen et al. 2006). The effect estimates for many of the common measures of heart rate variability were heterogeneous between the three study centres, but a change in high frequency to low frequency ratio was associated with ultrafine particles. The effects of gaseous pollutants were difficult to distinguish from the effects of particulate air pollution in the ULTRA study due to high correlation. Daily mass concentrations of $PM_{2.5}$ during the ULTRA study period have been apportioned between different sources by Vallius et al. (2005). The main source categories identified were: traffic, long-range transport (secondary particles), oil combustion, industry, sea salt and crustal (soil) source.

1.1 References

ACC/AHA. Guidelines for Exercise testing. A Report of the American College of Cardiology/American Heart Association Task Force of Practice Guidelines (Committee on Exercise Testing). J Am Coll Cardiol 1997; 30:260-315.

Bell ML, Samet JM, Dominici F. Time-series studies of particulate matter. Annu Rev Public Health 2004; 25:247-280.

Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, Luepker R, Mittleman M, Samet J, Smith SC Jr, Tager I; Expert Panel on Population and Prevention Science of the American Heart Association. Air pollution and cardiovascular disease: a statement for health care professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. Circulation 2004; 109:2655-2671.

de Hartog JJ, Hoek G, Peters A, Timonen KL, Ibald-Mulli A, Brunekreef B, Heinrich J, Tiittanen P, van Wijnen JH, Kreyling W, Kulmala M, Pekkanen J. Effects of fine and ultrafine particles on cardiorespiratory symptoms in elderly subjects with coronary heart disease: the ULTRA study. Am J Epidemiol 2003; 157:613-623.

Dockery DW, Pope CA 3rd, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG Jr, Speizer FE. An association between air pollution and mortality in six U.S. cities. N Engl J Med 1993; 329:1753-1759.

European Union, Clean Air for Europe (CAFÉ) Programme, 2005. (http://ec.europa.eu/ environment/air/ cafe/index.htm

Ibald-Mulli A, Timonen KL, Peters A, Heinrich J, Wolke G, Lanki T, Buzorius G, Kreyling WG, de Hartog J, Hoek G, ten Brink M, Pekkanen J. Effects of particulate air pollution on blood pressure and heart rate in subjects with cardiovascular disease: a multi-centre approach. Environ Health Perspect 2004; 112:369-377.

Pekkanen J, Timonen KL, Tiittanen P, Vallius M, Lanki T, Sinkko H, Ruuskanen J, Mirme A, Kulmala M, Vanninen E, Bernard A, Ibald-Mulli A, Wölke G, Staedeler M, Tuch Th, Kreyling W, Peters A, Heinrich J, de Hartog JJ, Oldenwening M, Kos G, ten Brink H, Khlystov A, van Wijnen J, Brunekreef B, Hoek G. ULTRA: Exposure and risk assessment for fine and ultrafine particles in ambient air. Study manual and data book. Publications of National Public Health Institute 2000. Available at http://www.ktl.fi/ultra.

Pekkanen J, Peters A, Hoek G, Tiittanen P, Brunekreef B, de Hartog J, Heinrich J, Ibald-Mulli A, Kreyling WG, Lanki T, Timonen KL, Vanninen E. Particulate air pollution and risk of ST segment depression during repeated submaximal exercise tests among subjects with coronary heart disease. The ULTRA study. Circulation 2002; 106:933-938.

Peters A, von Klot S, Heier M, Trentinaglia I, Hormann A, Wichmann HE, Lowel H; Cooperative Health Research in the Region of Augsburg Study Group. Exposure to traffic and the onset of myocardial infarction. N Engl J Med 2004; 351:1721-1730.

Pope CA 3rd, Dockery DW. Health effects of fine particulate air pollution: lines that connect. J Air Waste Manag Assoc 2006; 56:709-742.

Pope CA 3rd, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, Heath CW Jr. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am J Respir Crit Care Med 1995; 151:669-674.

Timonen KL, Vanninen E, de Hartog J, Ibald-Mulli A, Brunekreef B, Gold DR, Heinrich J, Hoek G, Lanki T, Peters A, Tarkiainen T, Kreyling W, Pekkanen J. Effects of ultrafine and fine particulate and gaseous air pollution on cardiac autonomic control in subjects with coronary artery disease. The ULTRA study. J Expo Sci Environ Epidemiol 2006; 16:332-341.

Vallius M, Janssen NAH, Heinrich J, Hoek G, Ruuskanen J, Cyrus J, van Grieken R, de Hartog JJ, Kreyling WG, Pekkanen J. Sources and elemental composition of ambient $PM_{2.5}$ in three European cities. Sci Tot Environ 2005; 337:147-162.

2 REVIEW OF THE LITERATURE

2.1 Urban fine particulate matter (PM$_{2.5}$)

2.1.1 Sources of PM$_{2.5}$ in urban air

The mass distribution of ambient particulate matter has typically three modes: nucleation, accumulation and coarse mode, in increasing order of particle size (Seinfeld and Pandis 1998). These modes differ in composition and sources. Nucleation mode particles are mainly formed from gases through nucleation and condensation processes, but are also emitted directly through combustion processes (primary particles). The accumulation mode particles are formed by coagulation of smaller particles, and coarse particles are mainly formed by mechanical abrasion of materials. The aim in the sampling of ambient particles is often to separate between these modes and at the same time between different sources of particulate air pollution. The sampling is usually based on aerodynamic properties of particles, and there are three rather standardized size fractions. Ultrafine particles have an aerodynamic 50% cut-off diameter at about 0.1 µm, and they originate mainly from combustion, e.g. traffic and energy production. Fine particles (PM$_{2.5}$; <2.5 µm) include both nucleation and accumulation mode, but also part of the coarse mode (Wilson and Suh 1997). Most of the mass of PM$_{2.5}$ consists of accumulation particles, especially of secondary nitrate and sulphate particles, whereas ultrafine particles contribute minimally to mass, but make up most of the number count. Thoracic particles (PM$_{10}$; <10 µm) include all modes, but only part of the coarse mode due to the upper size limit. Total suspended particulate matter (TSP; often <40 µm, but no strictly defined cut-off size) includes most of the coarse fraction, that mainly originates from abrasion and resuspension of soil.

There are some source categories of PM$_{2.5}$ which are commonly observed in urban environments: traffic, long-range transport and crustal (soil) source (Vallius et al. 2005). Other common sources are oil combustion, biomass combustion, sea-spray, and various industrial sources (Harrison and Yin 2000, Lazaridis et al. 2002). At a given location, the contribution of different sources to PM$_{2.5}$ depends on the distance and activity of sources, emission height and meteorology. Statistical multivariate methods can be used to apportion the measured mass concentration between sources based on the variation in composition from day to day. However, this requires knowledge on the typical composition of emissions at sources. Ideally, every source would emit at least one characteristic element that would rarely be found in the emissions of other sources. However, these kinds of indicator elements do not exist for every source.

Traffic is a major source of fine particles in urban environments. There is no single indicator element for vehicle exhausts after lead was no more added to gasoline. Several mechanisms are responsible for the generation of traffic-originating particles; as a consequence particles differ in composition and size. Tail-pipe emissions are indicated by elemental carbon from combustion of fuel, whereas abrasion of roads and resuspension of road dust are indicated by soil related elements Al, Ca and Si (Huang et al. 1994, Sternbeck et al. 2002). Finally, Cu and Fe originate from wearing of brakes. In Northern countries studded tyres and sanding of icy roads contributes to traffic emissions. There is often a strong gradient in the concentrations of traffic related particle constituents due to rapid dilution of emissions, and exposure can be much higher within 100 m from the road than further away (Roorda-Knape et al. 1998).

Long-range transported particles (defined often as being transported over 500 km) are mainly in the accumulation mode due to slow gravitation of that size fraction, and vary in composition depending on sources of particles. Majority of mass of long-range transported particles is often sulphates formed by nucleation and coagulation of SO_2 from combustion, but in agricultural areas nitrates can form the major fraction (Harrison et al. 2000). Prevailing wind directions determine which sources are most likely to contribute to long-range transported particles.

Crustal particles are created through mechanical wearing of soil and create mainly local air quality problems. However, in some parts of the world desert dust can travel hundreds of kilometres during specific wind conditions creating episodes of high concentrations. Oil combustion originating $PM_{2.5}$ particles are rather easily characterized by high concentrations of Ni and V, coal combustion by Se. Marine aerosols are characterised by high concentrations of Cl and Na (Cyrus et al. 2003b, Vallius et al. 2005). Biomass combustion can be identified by high concentrations of K, but there are also other sources of K. Not only elements can be used as markers for sources: for some sources there exist more specific markers, e.g. levoglukosan for wood combustion (Sillanpää et al. 2005). However, indicator compounds often have specific requirements for PM analyses or collection methods.

2.1.2   Measurement of ambient $PM_{2.5}$ and its constituents

The measurement of ambient particulate matter at central outdoor sites started with the measurement of TSP and only later, when evidence on the health relevance of finer particle fractions accumulated, begun the measurement of PM_{10} and finally in the 90's $PM_{2.5}$. To date, no limit values have been set to $PM_{2.5}$ in the European Union, and consequently the building of $PM_{2.5}$ monitoring network has been slower in Europe than in the U.S. The fixed measurement stations can be categorised into

urban, urban background, and background stations, the category depending on the distance to major urban particle sources, mainly traffic. Administrative monitoring of particulate air pollution is largely based on the urban background stations, and they should be representative of the exposure (outdoors) of the general urban population. Problematic "hot-spots" can be monitored using urban stations, or even kerb-site stations that locate next to major streets. The location of a measurement station with respect to both particle sources and population is crucial also in epidemiological studies (de Hartog et al. 2005), and heterogeneous estimates of air pollution effects between cities could be partly due to differences in the accuracy of exposure estimation.

The measurement methods of $PM_{2.5}$ concentrations can be divided into continuous methods that record concentrations in short intervals, e.g. every minute, and into integrating methods that provide data on daily or sometimes on hourly basis. The latter are usually based on the collection of particulate matter on filters, which are then weighed; therefore the methods are called gravimetric (Marple et al. 2001). Gravimetric methods are regarded as "the golden standard" for administrative purposes, and methods based on other measurement principles have to be compared against a standard gravimetric method before they are taken into wider use. The disadvantage of filter collection methods is the requirement of manual work, but on the other hand once the samples have been collected, they can later be used for analyses of particle composition.

The basic principle of gravimetric methods is simple: air is drawn with a pump through usually size selective inlet and the particulate matter is collected on a filter. Even so, there are possibilities for error. The steepness of the particle collection efficiency curve as a function of particle size is dependent on the type of inlet, but also on the accuracy of flow control (Marple et al. 2001). If the right conditions are not met, the collected particulate matter might not be representative of the aimed size fraction. The weighing of the collected material requires high-accuracy balances and controlled weighing conditions. Buoyancy correction reduces the effect of room conditions on the results (Hänninen et al. 2002). Static charge on particulate matter results in erroneous weights, but can be removed using either electric dischargers or ionising radiation. Meticulous conduction of sampling and weighing is required also to minimize contamination of collected material, which is especially important if further analyses on composition are planned.

The continuous measurement methods for $PM_{2.5}$ that are in routine use are based on near real-time weighing of particles e.g. with tapered element oscillating microbalance (TEOM), or measurement of volume concentration with indirect optical methods, transformed then to mass with limited accuracy, or indirect measurement of mass based on attenuation of beta-radiation (Baron and Willeke

2001). The methods have given results that are comparable to gravimetric ones (Chung et al. 2001), but it should be acknowledged that particle properties together with atmospheric conditions like humidity yet influence the agreement with gravimetric methods.

There would be a need for continuous measurement methods for particle composition as well, but currently most methods are not entirely quantitative (Allen et al. 2000). Thus, compositional analyses are still usually based on filter collection, which can be done mainly on a daily base. However, there are a few continuous methods to estimate specific components of $PM_{2.5}$. Aethalometers are most relevant concerning the evaluation of the health effects of particulate air pollution. They are used to estimate the amount of optically-absorbing material in air, which can be interpreted as the amount of elemental carbon (EC), the dominant light-absorbing material in the submicron range. Most of the EC in city environments originates from diesel engines (Gray and Cass 1998).

Direct measurement of EC requires quartz filters, not suitable for general use, and the method is destructive. However, on filter samples the amount of EC can be estimated straightforwardly by measuring the light-reflectance of the sample. This proxy of EC is called absorption coefficient or absorbance (ABS), which is transformable to black smoke, a more traditional measure of atmospheric carbon (ISO 1993). The method has proven useful in epidemiological studies evaluating the effects of traffic exhausts on health (Cyrus et al. 2003a, Jansen et al. 2005). There are both destructive (mass spectrometry) and conservative (roentgen-fluorescence) methods for the elemental analyses of filter samples. The minute concentrations of elements on filters require dedicated laboratories. Often the interest is also on ions: the most common analysis method is ion chromatography.

2.2 Personal exposure to $PM_{2.5}$

2.2.1 Measurement methods

Exposure to particles can be be defined as a contact with a pollutant during a specified time period. This exposure is different from body dose, which depends e.g. on breathing patterns, lung volume, and particle size and shape. The aim of the $PM_{2.5}$ exposure measurements is to measure the particle concentration in contact, in practice the concentration in the breathing zone. Typically, the inlet of an exposure monitor is close to mouth, and the actual measurement device is carried on a belt or in a bag. The main requirements for a portable exposure monitoring system to be feasible in a community study are light weight, low noise, and long-battery life. The

first two requirements ensure that study subjects really are able (and willing) to carry the monitoring system everywhere and that they keep the devices nearby even during sedentary activities like sleeping. Otherwise, biased estimates of exposure will obviously be obtained, and the bias is difficult to estimate afterwards.

The measurement of personal $PM_{2.5}$ exposure is based on the same principles as the measurement of outdoor $PM_{2.5}$, and the methods can again be categorised as continuous or integrating. The integrating methods are based on the collection of particulate matter on a filter and subsequent weighing. As size-selective inlets either impactors or cyclones, both based on inertial separation of particles (Marple et al. 2001), are used in personal measurement systems. The pumps (as well as the power sources) used for personal measurements have to be light, which means that flow rates are necessarily lower than in outdoor measurements. This leads to lower sampled particle mass and makes weighing of filters and possible elemental analyses more challenging.

Continuous personal measurement methods are usually based on the optical properties of particles, although methods based on near real-time weighing also exist. Photometers, called also nephelometers, are based on the measurement of light scattered from a cloud of particles passing the measurement chamber. The amount of light scattered gives approximation of total volume of particles. This can be used to calculate the mass concentration if the density of particles is known. This is rarely the case in community studies, where personal exposure consists of heterogeneous particles from multiple sources. Other factors than density influencing the measurement of mass concentration, like differences in refractive properties of particles, have observed to be less important (Richards et al. 1999).

The mean density of particles can be set separately for every photometric measurement period, if collocated gravimetric measurements have been conducted. However, an unavoidable problem is caused by the different time-scales of the two methods. During one personal measurement day, multiple particle sources affect personal exposure causing fluctuating particle density. Fotometers are used to collect data on short-term changes in exposure, but the density can be corrected hour by hour only with limited accuracy as the gravimetric methods are operated on a daily basis.

Another problem in the use of photometers is caused by high levels of outdoor humidity which increase absorption of water into particles increasing also the volume (whereas reference methods are based on weighing of dry particle mass). There are empirical equations which can be used to reduce the effect of relative humidity on results (Richards et al. 1999). However, because of heterogeneity of urban $PM_{2.5}$, hydroscopic and hydrophilic particles can be found in the same sample, which makes creation of universal correction equations difficult (Malm et al. 2000).

2.2.2 Estimation of exposure to $PM_{2.5}$ in time-series studies

Most current epidemiological studies on the short-term effects of air pollution rely on longitudinal study design and time-series analyses (Bell et al. 2004b). The approach requires that (typically daily) variation in PM levels measured at a fixed outdoor monitoring site reflects (day-to-day) variation in exposure for study subjects. This correspondence is best estimated by calculating the longitudinal correlation: the mean of correlation coefficients between outdoor PM and personal exposure calculated separately for every subject; this obviously requires repeated measurements of exposure. Before the introduction of time-series methodology, exposure studies generally evaluated cross-sectional correlation, i.e. correlation between outdoor PM and personal exposure in study subjects, whose exposure was measured usually only once or twice. Cross-sectional studies usually indicated low or non-existing correlations between fixed outdoor PM_{10} or $PM_{2.5}$ concentrations and personal exposure (Ozkaynak et al. 1996, Patterson et al. 2000). This even raised a concern that the observed associations between outdoor PM levels and health would not be causal (Vedal 1997). However, longitudinal exposure studies have found considerable correlations between outdoor and personal PM_{10} (Janssen et al. 1998), and even higher correlations for $PM_{2.5}$ (Janssen et al. 1999, Williams et al. 2000; Rojas-Bracho et al. 2000). The main reason for the higher correlation of $PM_{2.5}$ is the lower spatial variation over urban areas because of regional rather than local emission sources (Burton et al. 1996, Hoek et al. 2002b).

There are fewer studies where longitudinal correlations for different components of $PM_{2.5}$ have been estimated. However, this information would be crucial to be able to link either different sources of $PM_{2.5}$, represented by indicator elements, or potentially toxic elements to health end-points. Personal exposure to soil derived element calcium, found in particles near the upper size limit of $PM_{2.5}$ and related to local sources, has been less strongly associated with central outdoor concentrations than sulphur (or SO_4), found in long-range transported particles within the accumulation mode (Ebelt et al. 2000, Landis et al. 2001). In the case of sulphur, the correlation is improved not only because of the regional nature of sources, but also because of lack of major indoor sources. Ranking of the correlations (personal vs. home outdoor) for indicator elements of crustal and long-range transported $PM_{2.5}$ has been similar in a cross-sectional study by Oglesby et al. (2000).

From a regulatory perspective, information on the health effects of *PM of outdoor origin* is the most relevant. In epidemiological studies aiming to link outdoor originating PM to health, indoor sources are a nuisance factor. Fortunately, in time-series studies the variation of $PM_{2.5}$ measured outdoors does reflect exposure to outdoor $PM_{2.5}$ irrespective of indoor sources, as the activity of indoor sources is not

likely to be correlated with outdoor $PM_{2.5}$ (Ebelt et al. 2005). However, indoor sources make the linking of measured personal $PM_{2.5}$ levels to health problematic. Total exposure to $PM_{2.5}$ is a sum of outdoor $PM_{2.5}$ and $PM_{2.5}$ generated by indoor sources and personal activities. In this case, indoor sources might conceal the underlying relationship between outdoor $PM_{2.5}$ and health. The main rationale for using personal measurements of (total) $PM_{2.5}$ to evaluate the health effects of outdoor $PM_{2.5}$ is to avoid the problem of spatial variation outdoors and indoors in $PM_{2.5}$ of outdoor origin. If there are few indoor sources and personal activities (and large spatial variation), stronger associations can be observed between health and personal $PM_{2.5}$ than when using central outdoor measurements.

Most reliable estimates of the effects of outdoor particulate air pollution can be obtained by linking personal measurements of outdoor originating PM to health. For example, sulphate has few indoor sources and it can be used in time-series studies as an indicator for exposure to outdoor PM (within the same size fraction) (Ebelt et al. 2005). An obvious reason for not carrying out personal measurements in every epidemiological study is the cost of measurements, both the cost of field work and of compositional analyses. There are not yet portable monitors for PM composition, and at least in the evaluation of the effects of short-term (less than a day) changes in exposure, real-time monitors of (total) PM mass are the only option. However, especially in the studies evaluating the effects of traffic originating particles, also questionnaires and geographic information systems have been used to collect information on exposure, but mainly in cross-sectional study designs (Hoek et al. 2002a, Peters et al. 2004, Gauderman et al. 2005).

General population can be divided into subgroups which are likely to have unequal levels and variation in PM exposure. Working population spends a major part of the day at working place, where exposure might be either lower (e.g. in clean office environments) or higher (e.g many types of manual work) than at home. Working population also spends on average more time in traffic than non-working population, e.g. due to commuting, and consequently is more exposed to vehicle exhausts. On the other hand, most children spend major part of their time at day-care centres or at school, where exposures again depend on building characteristics and location and might differ from exposures at home. Working age persons and children often engage activies that may increase their personal exposure, and spend also much of their time elsewhere than at home or at work/school. The more active the population group the more difficult it often is to study personal exposures without interfering with the normal activities.

Elderly persons and persons with compromised health have been observed to be especially susceptible to the effects of outdoor air pollution on cardiovascular health (Le Tertre et al. 2002, von Klot et al. 2005). These population groups (obviously

many belong to both groups at the same time), are typically less active and spend more time at home than the general population. It has been suggested that because of this, the linkage between outdoor PM levels and exposure would be tighter. However, among persons with chronic obstructive pulmonary disease, only low to moderate longitudinal correlations between outdoor and personal $PM_{2.5}$ have been found (Ebelt et al. 2000, Rojas-Bracho et al. 2000). In contrast, the longitudinal correlation of outdoor $PM_{2.5}$ and sulphate with personal exposure was high among elderly (Landis et al. 2001).

2.2.3 Determinants of $PM_{2.5}$ exposure

There are differences between persons in the average levels of exposure to $PM_{2.5}$ (between-subject variation), and between days in the exposure of a person (within-subject variation). Both between- and within-subject components contribute to total variation in exposures in a study population. In time-series studies the within-subject variation in PM exposure is the most interesting measure of variation. Factors other than outdoor concentrations that affect short-term PM exposure weaken the longitudinal correlation between outdoor concentrations and exposure. Within-subject variation is affected by personal behaviour that is not constant from day-to-day: activities conducted and time spent in various microenvironments. A single measurement of exposure is not predictive of the mean exposure of a person over a longer period of time large when large within-subject variation exists.

One of the determinants of exposure is the time spent in different microenvironments, because particle concentrations can differ greatly between microenvironments. Exposure outdoors is obviously determined by outdoor concentrations, but especially outdoors in traffic, the "local" outdoor concentration may be higher than the concentration at a fixed background measurement site. Daily changes in air exhange rates, in practice often the number of open windows on a given day, affects variation in exposure indoors to $PM_{2.5}$ of outdoor origin (Cyrus et al. 2004, Rojas-Bracho et al. 2000, Rodes et al. 2001,). Indoor $PM_{2.5}$ sources are a major determinant of total PM exposure, because most people spent more than 90% of their time indoors (Liu et al. 2003). Exposure to environmental tobacco smoke (ETS) indoors is such a major source of $PM_{2.5}$ that usually analyses on the determinants of exposure are done only after exclusion of days with ETS exposure (Williams et al. 2003). Other important indoor $PM_{2.5}$ sources are e.g. cooking, burning candles and cleaning (Özkaynak et al. 1996, Rojas-Bracho et al. 2004, Sørensen et al. 2005).

Information on the determinants of between-subject variation is needed for example in studies on the chronic effects of particulate air pollution. Determinants of

between-subject variation in PM exposures need to stay constant for most of the study period. Main determinants of long-term $PM_{2.5}$ exposure are apartment characteristics, including the location of an apartment, and constant person characteristics. Traffic density of the nearest street has been found to be a determinant of personal $PM_{2.5}$ exposure in the cross-sectional EXPOLIS study (Koistinen et al. 2001). The distance of a building from major streets determines exposure to traffic-originating $PM_{2.5}$ even more strongly than to (total) $PM_{2.5}$ (Janssen et al. 2001). Obviously, many of the factors determinining day-to-day changes in exposure also lead to differences between subjects in long-term $PM_{2.5}$ exposure. For example, the frequency that windows are kept open may differ between homes. However, smoking status of a spouse or parents is the major determinant of between-subject variability in $PM_{2.5}$ exposures (Gauvin et al. 2002). Another personal characteristic affecting long-term $PM_{2.5}$ exposure is occupation.

2.3   Effects of outdoor air pollution on health

The association between air pollution and human health became generally accepted after the research conducted on the effects of severe air pollution episodes, the most famous ones in Meuse Valley, Belgium, in 1930 and in London in 1952. By the 1970's, the associations of particulate air pollution and sulphur dioxide with cardiopulmonary health were established (Brunekreef and Holgate 2002). However, as a result of successful emission control efforts, the concentrations of these 'traditional' pollutants decreased to a level in the late 1970's, at which any health effects were considered unlikely. The new era of air pollution research begun when two US cohort studies published in 1993 and 1995 suggested that life-shortening was associated with fine particle concentrations even after the decline in the levels (Dockery et al. 1993; Pope et al. 1995). Although even the earlier studies reported associations of air pollution with cardiopulmonary health, research on the more specific effects on air pollution focused first on respiratory diseases (Dockery et al. 1994), and only in the late 90's the public health importance of the cardiovascular risks associated with air pollution caught more attention.

After more than a decade of intensive research, it is now widely acknowledged that outdoor air pollution represents one of the most important environmental health problems both in developed and developing countries because of ubiquity of exposure and severity of health effects associated with exposure. Cohort studies suggest that air pollution shortens life-expectancy in developed countries 1-2 years (Brunekreef et al. 1997). Epidemiological studies have demonstrated that the most harmful component in the current levels of outdoor air pollution mixture in Western countries is particulate matter. Gases as co-pollutans may enhance the effects of

particles, but ozone seems to have effects on health even withouth contribution from particulate air pollution (Bell et al. 2004a). Increases in daily particle levels have been associated with respiratory and cardiovascular hospitalisations and mortality (Samet et al. 2000, Atkinson et al. 2001, Le Tertre et al. 2002), but also with less severe end-points such as increased medication use and cardiorespiratory symptoms (de Hartog et al. 2003). In addition, long-term exposure to ambient particulate matter has been linked with the development of respiratory and cardiovascular diseases (Gauderman et al. 2004, Künzli et al. 2005).

Effect estimates from cohort studies have consistently been higher than estimates from time-series studies (Pope et al. 2004), in which short-term (typically daily) changes in air pollution levels have been linked to short-term (daily) changes in the rate of events. Effect estimates from cohort studies have been the basis for the regulation of air pollution levels. The importance of short-term effects observed in time-series studies have been sometimes disputed claiming that they represent merely a "harvesting effect", i.e. that the increase in deaths (or hospitalisations) associated with air pollution would be due to severely ill patients that would have died (or been hospitalised) within a few days even without air pollution exposure. However, this does not seem to be the case (Schwartz 2001a). Another debate has concerned the existence of a possible threshold PM concentration, below which health effects would not exist. It seems that no threshold exists (Samoli et al. 2005), which forces regulatory bodies to make the decision on the level of an acceptable risk themselves; the lower the target levels of particulate matter are set, the higher the costs of emission control will be.

Research on the health effects of particulate air pollution started by linking TSP concentrations to health, but later finer particles size fractions, first PM_{10} and then $PM_{2.5}$, have been found to be more strongly associated with health (Schwartz et al. 1999, McDonnell et al. 2000). There are several reasons for the stronger associations, the relative importance of which are not clear. The smaller the particle is, the deeper it will penetrate in the lungs and the longer is the retention time. Particle size is related to composition: finer size fractions originate mainly from combustion processes whereas coarse fraction, commonly defined as the fraction between PM_{10} and $PM_{2.5}$, is mainly soil derived. Finally, evidence on the health effects of particles comes mainly from epidemiological studies using central outdoor monitors to estimate exposure. However, outdoor levels are worse surrogates for exposure to coarse particles than for fine particles which may explain the higher effect estimates observed for finer size fractions. Coarse particles have been associated with respiratory diseases, but there are only few studies evaluating the effects of coarse particles on cardiovascular diseases (Burnett et al. 1997, Cifuentes

et al. 2000) It has recently been suggested that more attention should be paid to this size fraction (Brunekreef and Forsberg 2005).

There has been increasing research interest on the effects of ultrafine particles, which have been found to be harmful in toxicological studies, even irrespective of composition (Donaldson et al. 2001). Ultrafine particles in ambient air have some unique properties, which make them potentially more toxic than even fine particles: large number overwhelming the natural cleaning mechanisms of the lungs, high penetration in the lungs and ability to enter even circulation, high surface area per unit of mass, and finally large percentage of fresh, combustion originating material including polycyclic hydrocarbons (Delfino et al. 2005). However, in epidemiological studies the effects have not been as clear as in toxicological studies. One reason for this might be large misclassification of exposure, i.e. outdoor levels of ultrafine particles measured at fixed site may poorly reflect variation in personal exposure (Pekkanen and Kulmala 2004).

2.4   Health effects of ambient PM$_{2.5}$

2.4.1   Mechanisms of action of particulate matter on cardiovascular system

There is no more doubt about the biological plausibility of the associations observed between ambient particulate matter and cardiovascular health in epidemiological studies, because clear biological effects have been observed (Pope and Dockery 2006). However, none of the several proposed pathophysiological or mechanistic pathways have been directly linked to cardiopulmonary morbidity and mortality due to PM exposure. It is likely that there is no single pathway from exposure to effect, but that instead several mechanisms play a role.

Exposure to PM has been associated with pulmonary oxidative stress (Tao et al. 2003), which is able to induce local inflammation. It has been suggested that local inflammation starts a cascade of events that leads to systemic inflammation. Low-grade systemic inflammation has been linked to initiation and progression of atherosclerosis (Libby et al. 2002). Association has been observed between ambient PM$_{2.5}$ levels and carotid intima-media thickness indicating subclinical atherosclerosis (Künzli et al. 2005). Long-term exposure to PM$_{10}$ has been associated also with elevated levels of fibrinogen and platelet and white blood cell counts (Schwartz J 2001b).

Growing evidence indicates that systemic inflammation is associated with acute exacerbations of coronary heart disease (Libby et al. 2002). Plaque rupture is the most common type of plaque complication (Naghavi et al. 2003), and leads to

myocardial infarction or angina depending on how occlusive the thrombus is. Several epidemiological studies have demonstrated that daily outdoor PM levels are associated with increased circulatory levels of inflammatory proteins indicating systemic inflammation (Pekkanen et al. 2000, Peters et al. 2001b, Rückerl et al. 2006).

Another possible pathway from PM exposure to cardiovascular effects involves automic nervous system (Brook et al. 2004). Changes in autonomic control of heart are usually evaluated indirectly by measuring heart rate variability (HRV). Post-myocardial infarction patients with decreased HRV have increased risk of fatal coronary events (Task Force 1996). However, also increases in HRV may be harmful (De Bruyne et al. 1999). Most studies have linked long-term changes in HRV to increased cardiovascular risk; there is less evidence on the importance of short-term changes in HRV. However, decreased HRV has been observed minutes before ischemic events in ECG (Takusagawa et al. 1999, Kop et al. 2001).

There are plenty of studies where outdoor PM levels have been associated with decreased heart rate variability among healthy adults and elderly, as well as among persons with cardiovascular disease (e.g. Liao et al. 2004, Pope et al. 2004b, Timonen et al. 2006). In a few cases, increased HRV has been observed in association with increases in PM levels (Pope et al. 1999, Magari et al. 2001).

It should be noted that inflammation and the autonomic control of heart are not independent of each other: autonomic nervous system can be activated by cytokines, but it also controls the release of these inflammatory markers (Janszky et al. 2004). There is only one study, where $PM_{2.5}$ has been linked at the same time to reduced HRV and increased systemic inflammation (C-reactive protein) (Pope et al. 2004b). Direct effects of air pollution on the automic nervous system are expected to occur even within minutes of exposure, whereas the effects proceeding through inflammation could take even some days.

Convincing evidence on the involvement of a rather immediate component of action of $PM_{2.5}$ on HRV comes from the controlled human exposure study conducted by Devlin et al. among elderly persons (2003): only 2 hours of exposure to concentrated ambient pollution particles (CAPs) was enough to induce decreases in HF and SDNN observable immediately after the exposure. Two hours of exposure to fine CAPs (together with ozone) has been associated also with increased diastolic blood pressure (Urch et al. 2005).

Most of the epidemiological studies evaluating associations between very short-term changes (hours or minutes) in $PM_{2.5}$ and cardiovascular health have concerned HRV. Gold et al. (2000) found elevated levels of $PM_{2.5}$ over the hour of and the 3 hours before ECG recording to be most strongly associated with decreased r-MSSD and SDNN. Inverse associations between HRV and $PM_{2.5}$ measured during the 4 hours

before ECG recording have been observed also in other studies (Chuang et al. 2005, Wheeler et al. 2006). In some other studies prompt responses of automic nervous system have been observed in association with $PM_{2.5}$, but still the highest and most precice effect estimates have been observed with the mean $PM_{2.5}$ of the preceding 24 hours (Creason et al. 2001, Schwartz et al. 2005). This suggests that in addition to the rapid component in the mechanism of action of $PM_{2.5}$ on HRV, also a longer-term (daily) component is involved; alternatively a cumulative effect exists that begins shortly after the beginning of exposure (Magari et al. 2001).

In Boston, U.S., Peters et al. (2001a) have found evidence of an immediate and a delayed effect of $PM_{2.5}$, independent of each other, for myocardial infarction. The estimated odds ratio was 1.48 (95% CIs 1.09, 2.02) for an increase of 25 $\mu g/m^3$ in $PM_{2.5}$ during the 2-hour period before the onset of myocardial infarction, and 1.69 (95% CIs 1.13, 2.34) for an increase of 20 $\mu g/m^3$ in $PM_{2.5}$ during the 24-h period one day before the onset. However, Sullivan et al. (2005) could not replicate the results in King County, Washington, U.S.

2.4.2   Time-series studies on the effects of $PM_{2.5}$ and PM_{10} on cardiovascular health

Acute effects of particulate air pollution are analysed typically in longitudinal study designs using mostly time-series methodology (Bell et al. 2004b), but sometimes the case-crossover approach (Forastiere et al. 2005). The concept 'time-series studies' commonly refers to studies linking the short-term changes in outdoor PM measured at a central site to short-term changes in mortality or morbidity counts (typically hospitalisations) at a population level. However, the time-series methodology is in use also e.g. in panel studies, where short-term changes in PM are linked to changes in the study subjects' health.

The main advantage of time-series methodology is the fact that the individual serves as his/her own control: when day-to-day changes in PM are linked to health on a daily basis, relatively stable population characteristics like diet or smoking do not confound the results (because a confounder by definition should be associated both with the outcome and the predictor, in this case both should have similar temporal variation). However, there are other potential confounders, notably meteorology and gaseous co-pollutants.

In early studies, time-series data were analysed using linear regression models. Nowadays, sophisticated regression models are used to take into account also possible non-linear associations between confounders and health. The most common choices for the models are the generalised linear models (GLM) with parametric

splines and generalised additive models (GAM) with non-parametric splines (Bell et al. 2004b). Loess smoothing in S-Plus statistical software was de facto standard method in the analyses until a problem with the default convergence criteria in the software was found (Dominici et al. 2002). The observation led to comprehensive re-analyses of the major studies. Although decreased effect estimates for PM were often observed in the re-analyses, general conclusions about the effects of PM did not change (Dominici et al. 2005).

There is an abundance of time-series studies on the effects of PM_{10} and $PM_{2.5}$ on health, but the most influential of them have been large multi-city or multi-nation studies. Reasonably similar effect estimates for total mortality have been observed in European and US studies. The European APHEA 2 study included data from 29 cities and found a 0.6% increase in daily deaths per 10 $\mu g/m^3$ increase in PM_{10} levels (Katsouyanni et al. 2001). The US counterpart NMMAPS included 90 cities, and the recently revised analyses found a 0.27% increase in mortality per 10 $\mu g/m^3$ increase in PM_{10} (Dominici et al. 2005). However, total mortality is a fairly unspecific outcome, and later mortality has been divided into subcategories. The associations of PM with cardiovascular mortality have been similar or stronger than with total mortality (Samoli et al. 2005, Ostro et al. 2006). PM has also been associated with respiratory mortality (Dockery et al. 1994).

In some recent studies, cardiovascular mortality has been further divided into sub-categories: deaths due to ischemic heart disease (Ostro et al. 2006) and stroke (Hong et al. 2002) have been observed to increase in association with increased PM levels. Even more specific information on the effects of PM in different diagnostic groups has been obtained in studies linking PM concentrations to daily number of cardiovascular hospitalisations. Particulate matter concentrations have been associated with myocardial infarction (D'Ippoliti et al. 2003), congestive heart failure (Wellenius et al. 2006) and arrhythmia (Dominici et al. 2006).

Elderly persons seem to be especially vulnerable to the cardiovascular effects of particulate air pollution (Linn et al. 2000). However, time-series studies suggest that also some chronic diaseses increase sensitivity. These diseases include congestive heart failure (Mann et al. 2002), ischemic heart diasease (von Klot et al. 2005), and perhaps surprisingly also diabetes (Zanobetti and Schwartz 2001).

2.4.3 Effects of $PM_{2.5}$ from different sources on cardiovascular health

Emission controls focus on specific sources of particulate matter; therefore it would be crucial to know which sources emit the most harmful PM. PM originates from two broad source categories that differ by composition of produced PM: combustion

processes and mechanical processes. Combustion is the main source of $PM_{2.5}$. Combustion particles consist mainly of sulphates, nitrates and elemental and organic carbon. Wind and abrasion are examples of forces producing particles in the latter source category; typically the particles consist of crustal materials (Brunekreef and Forsberg 2005). Because coarse fraction (PM_{10}-$PM_{2.5}$) consists mainly of particles from this source category, by comparing the cardiovascular effects of coarse PM and $PM_{2.5}$, one can indirectly evaluate the effects of $PM_{2.5}$ from these source categories.

Both coarse and fine particles have been associated with cardiovascular mortality, but fine particles somewhat more strongly (Cifuentes et al. 2000; Mar et al. 2000). Coarse particles have been often at least as strongly as $PM_{2.5}$ associated with cardiovascular hospitalisations (Burnett et al. 1997; Ito 2003). Conflicting results have been obtained for HRV: in one study association was observed for $PM_{0.3-1.0}$, but not for $PM_{1.0-2.5}$ or coarse particles (Chuang et al. 2005), in another coarse fraction but not $PM_{2.5}$ was associated with HRV (Lipsett et al. 2006).

Cardiovascular effects of combustion particles can be evaluated also by linking elemental carbon to health end-points. Elemental carbon is associated with a variety of combustion processes, but urban concentrations are mostly affected by diesel particles from traffic (Gray and Cass 1998). Often a proxy is used for elemental carbon rather than actual chemical analyses; examples of proxies are black carbon measured with an aethalometer and absorbance, i.e. measurement of light reflectance of $PM_{2.5}$ filter samples. Usually EC proxies have been more strongly associated with indicators of cardiovascular health than (total) $PM_{2.5}$ (Gold et al. 2005, Schwartz et al. 2005).

Long-term exposure to traffic (related pollutants) has been associated with mortality in some recent studies (Hoek et al. 2002a, Finkelstein et al. 2004). In these studies, exposure to traffic was estimated by the distance of the residence from major roads. On the other hand, also short-term exposure to traffic has been associated with harmful effects on cardiac health: one hour exposure to traffic (time spent in cars, on public transportation, or on motorcycles or bicycles) was associated with the onset of myocardial infarction in a study by Peters et al. (2004). Evaluation of the effects of traffic originating particles is hampered by the fact that PM exposure correlates with exposure to noise, which also adversely affects the cardiovascular system (Franssen et al. 2004).

Detailed epidemiological information on the relative toxicities of various sources can be obtained by apportioning mass of $PM_{2.5}$ between major sources and then linking the obtained source-specific $PM_{2.5}$ concentrations to cardiovascular health. There are a few such time-series studies on mortality carried out in U.S. Most influential one has been a study by Laden et al. (2000) that included six U.S. cities. Fine particles both from traffic and coal combustion were associated with daily

mortality [3.4% (95% CIs 1.7, 5.2%) and 1.1% (0.3, 2.0%) increase in mortality for a 10 µg/m³ increase in source-specific $PM_{2.5}$, respectively]. In four of the six cities residual oil combustion was identied as a source of $PM_{2.5}$. The pooled effect estimate for oil combustion was positive, but not statistically significant [5.6% (-1.8-13.2%)]. Crustal $PM_{2.5}$ source was not associated with mortality. Ischemic heart disease mortality was only associated with traffic, and the association was relatively weak.

In a study conducted in Phoenix, U.S. (Mar et al. 2000), cardiovascular mortality was associated positively not only with traffic related $PM_{2.5}$, but also with $PM_{2.5}$ from biomass combustion and regional pollution (indicated by sulphate). Total mortality was weakly associated with regional pollution. At three sites in New Jersey (Tsai et al. 2000), cardiorespiratory mortality was associated with several sources of particles ($PM_{2.5}$ and PM_{15} were not separated in the model) including, site-dependently, traffic and oil combustion, industry, and sulphate aerosol.

It should be noted that differences in the effect estimates for various $PM_{2.5}$ sources in the above mentioned studies do not perfectly reflect true differences between sources in biological potential, because the validity of outdoor concentration as a proxy for personal exposure may depend on the source. In addition, different methods of source-apportionment may lead to somewhat different solutions. However, in a recent workshop report it was shown that soil-, sulphate, residual oil-, and salt-associated $PM_{2.5}$ were quite unambiguously identified by various methods (Thurston et al. 2005). The workshop recommended that more work should be done to characterise tracer profiles of the most problematic sources: vegetative burning and traffic.

2.5   References

Allen JO, Fergenson DP, Gard EE, Hughes LS, Morrical BD, Kleeman MJ, Gross DS, Gälli ME, Prather KA, Cass GR. Particle detection efficiencies of aerosol time of flight mass spectrometers under ambient sampling conditions. Environ Sci Technol 2000; 34:211-217.

Atkinson RW, Anderson HR, Sunyer J, Ayres J, Baccini M, Vonk JM, Boumghar A, Forastiere F, Forsberg B, Touloumi G, Schwartz J, Katsouyanni K. Acute effects of particulate air pollution on respiratory admissions: results from APHEA 2 project. Air Pollution and Health: a European Approach. Am J Respir Crit Care Med 2001;164:1860-1866.

Baron PA, Willeke K (Eds.) Aerosol measurement: principles, techniques and applications. 2001. New York: John Wiley and Sons.

Bell ML, McDermott A, Zeger SL, Samet JM, Dominici F. Ozone and short-term mortality in 95 US urban communities, 1987-2000. JAMA 2004a; 17:2372-2378.

Bell ML, Samet JM, Dominici F. Time-series studies of particulate matter. Annu Rev Public Health 2004b; 25:247-280.

Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, Luepker R, Mittleman M, Samet J, Smith SC Jr, Tager I; Expert Panel on Population and Prevention Science of the American Heart Association. Air pollution and cardiovascular disease: a statement for health care professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. Circulation 2004; 109:2655-2671.

Brunekreef B. Air pollution and life-expectancy: is there a relation? Occup Environ Med 1997; 54: 781-784.

Brunekreef B, Forsberg B. Epidemiological evidence of effects of coarse airborne particles on health. Eur Respir J 2005; 26:309-318.

Brunekreef B, Holgate ST. Air pollution and health. Lancet 2002; 360:1233-1242.

Burnett RT, Cakmak S, Brook JR, Krewski D. The role of particulate size and chemistry in the association between summertime ambient air pollution and hospitalization for cardiorespiratory diseases. Environ Health Perspect 1997; 105:614-620.

Burton RM, Suh HH, Koutrakis P. Spatial variation in particulate concentrations within Metropolitan Philadelphia. Environ Sci Technol 1996; 30:400-407.

Chuang K-J, Chan C-C, Chen N-T, Lin L-Y. Effects of particle size fractions on reducing heart rate variability in cardiac and hypertensive patients. Environ Health Perspect 2005; 113:1693-1697.

Chung A, Chang DPY, Kleeman MJ, Perry KD, Cahill TA, Dutcher D. McDougall EM, Stroud K. Comparison of real-time instruments used to monitor airborne particulate matter. J Air Waste Manage Assoc 2001; 51:109-120.

Cifuentes LA, Vega J, Kopfer K, Lave LB. Effect of fine fraction of particulate matter versus the coarse mass and other pollutants on daily mortality in Santiago, Chile. J Air Waste Manag Assoc 2000; 50:1287-1298.

Creason J, Neas L, Walsh D, Williams R, Sheldon L, Liao D, Shy C. Particulate matter and heart rate variability among elderly retirees: the Baltimore 1998 PM study. J Expo Anal Environ Epidemiol 2001;11:116-122.

Cyrys J, Heinrich J, Hoek G, Meliefste K, Lewne M, Gehring U, Bellander T, Fischer P, van Vliet P, Brauer M, Wichmann HE, Brunekreef B. Comparison between different traffic-related particle indicators: Elemental carbon (EC), PM(2.5) mass, and absorbance. J Expo Anal Environment Epidemiol 2003a; 13:134-143.

Cyrus J, Stölzel M, Heinrich J, Kreyling WG, Menzel N, Wittmaack K, Tuch T, H-E Wichmann. Elemental composition and sources of fine and ultrafine ambient particles in Erfurt, Germany. Sci Tot Environ 2003b; 305:143-156.

Cyrus J, Pitz M, Bischof W, Wichmann H-E, Heinrich J. Relationship between indoor and outdoor levels of fine particle mass, particle number concentrations and black smoke under different ventilation conditions. J Expo Anal Environ Epidemiol 2004; 14:275-283.

de Bruyne MC, Kors JA, Hoes AW, Klootwijk P, Dekker JM, Hofman A, van Bemmel JH, Grobbee DE. Both decreased and increased heart rate variability on the standard 10-second electrocardiogram predict cardiac mortality in the elderly: the Rotterdam Study. Am J Epidemiol 1999;150:1282-1288.

de Hartog JJ, Hoek G, Mirme A, Tuch T, Kos GPA, ten Brink H, Brunekreef B, Cyrus J, Heinrich J, Pitz M, Lanki T, Vallius M, Pekkanen J, Kreyling WG. Relationship between different size classes of particulate matter and meteorology in three European cities. J Environ Monit 2005; 7:302-310.

de Hartog JJ, Hoek G, Peters A, Timonen KL, Ibald-Mulli A, Brunekreef B, Heinrich J, Tiittanen P, van Wijnen JH, Kreyling W, Kulmala M, Pekkanen J. Effects of fine and ultrafine particles on cardiorespiratory symptoms in elderly subjects with coronary heart disease: the ULTRA study. Am J Epidemiol 2003; 157:613-623.

Delfino RJ, Sioutas C, Malik S. Potential role of ultrafine particles in associations between airborne particle mass and cardiovascular health. Environ Health Perspect 2005; 113:934-946.

D'Ippoliti D, Forastiere F, Ancona C, Agabiti N, Fusco D, Michelozzi P, Perucci CA. Air pollution and myocardial infarction in Rome; a case cross-over analysis. Epidemiology 2003;14:528-35.

Dockery DW, Pope CA 3rd. Acute respiratory effects of particulate air pollution. Annu Rev Public Health 1994; 15:107-132.

Dockery DW, Pope CA 3rd, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG Jr, Speizer FE. An association between air pollution and mortality in six U.S. cities. N Engl J Med 1993; 329:1753-1759.

Dominici F, McDermott A, Daniels M, Zeger SL, Samet JM. Revised analyses of the National Morbidity, Mortality, and Air Pollution Study: mortality among residents of 90 cities. J Toxicol Environ Health A 2005; 68:1071-1092.

Dominici F, McDermott A, Zeger SL, Samet JM. On Generalized Additive Models in Time Series of Air Pollution and Health. Am J Epidemiol. 2002; 156:193-203.

Dominici F, Peng RD, Bell ML, Pham L, McDermott A, Zeger SL, Samet JM. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. JAMA 2006; 295:1127-1134.

Donaldson K, Stone V, Clouter A, Renwick L, MacNee W. Ultrafine particles. Occup Environ Med 2001; 58:211-6.

Ebelt ST, Petkau AJ, Vedal S, Fisher T, Brauer M. Exposure of chronic obstructive pulmonary disease patients to particulate matter: relationships between personal and ambient air concentrations. J Air&Waste Manage Assoc 2000: 50: 1081-1094.

Ebelt ST, Wilson WE, Brauer M. Exposure to ambient and nonambient components of particulate matter. A comparison of health effects. Epidemiology 2005: 16: 396-405.

Forastiere F, Stafoggia M, Picciotto S, Bellander T, D'Ippoliti D, Lanki T, von Klot S, Nyberg F, Paatero P, Peters A, Pekkanen J, Sunyer J, Perucci CA. A case-crossover analysis of out-of-hospital coronary deaths and air pollution in Rome, Italy. Am J Resp Crit Care Med 2005; 172:1549-1555.

Franssen EA, van Wiechen CM, Nagelkerke NJ, Lebret E. Aircraft noise around a large international airport and its impact on general health and medication use. Occup Environ Med 2004;61:405-413.

Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, Berhane K, McConnell R, Künzli N, Lurmann F, Rappaport E, Margolis H, Bates D, Peters J. The effect of air pollution on lung development from 10 to 18 years of age. N Engl J Med 2004; 351:1057-1067.

Gauderman WJ, Avol E, Lurmann F, Künzli N, Gilliland F, Peters J, McConnell R. Childhood asthma and exposure to traffic and nitrogen dioxide. Epidemiology 2005; 16:737-743.

Gauvin S, Reungoat P, Cassadou S, Dechenaux J, Momas I, Just J, Zmirou D. Contribution of indoor and outdoor environments to PM2.5 personal exposure of children--VESTA study. Sci Total Environ 2002; 297:175-181.

Gold DR, Litonjua A, Schwartz J, Lovett E, Larson A, Nearing B, Allen G, Verrier M, Cherry R, Verrier R. Ambient pollution and heart rate variability. Circulation 2000; 101:1267-1273.

Gold DR, Litonjua AA, Zanobetti A, Coull BA, Schwartz J, MacCallum G, Verried RL, Nearing BD, Canner MJ, Suh H, Stone PH. Air pollution and ST-segment depression in elderly subjects. Environ Health Perspect 2005; 113:883-887.

Gray HA, Cass GR. Source contributios to atmospheric fine carbon particle concentrations. Atmos Environ 1998; 32:3805-3825.

Harrison RM, Deacon AR, Jones MR, Appleby RS. Sources and processes affecting concentrations of PM_{10} and $PM_{2.5}$ particulate matter in Birmingham (UK). Atmos Environ 2000; 31:4103-4117.

Harrison RM, Yin J. Particulate matter in the atmosphere: which particle properties are important for its effects on health? Sci Total Environ 2000; 249:85-101.

Hoek G, Brunekreef B, Goldbohm S, Fischer P, van den Brandt PA. Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. Lancet 2002a; 60:1203-1209.

Hoek G, Meliefste K, Cyrus J, Lewne M, Bellander T, Brauer M, Fischer P, Gehring U, Heinrich J, van Vliet P, Brunekreef B. Spatial variability of fine particle concentrations in three European areas. Atmos Environ 2002b; 36:4077-4088.

Hong Y-C, Lee J-T, Kim H, Ha E-H, Scwartz J, Christian DC. Effects of air pollutants on acute stroke mortality. Environ Health Perspect 2002; 110:187-191.

Huang X, Olmez I, Aras NK, Gordon GE. Emissions of trace elements from motor vehicles: potential marker elements and source composition profile. Atmos Environ 1994; 28:1385-1391.

Hänninen O, Koistinen KJ, Kousa A, Keski-Karhu J, Jantunen MJ. Quantitative analysis of environmental factors in differential weighing of blank Teflon filters. J Air Waste Manage Assoc 2002; 52:134-139.

ISO 9835. Ambient air - Determination of a black smoke index. 1993.

Ito K. Association of particulate matter components with daily mortality and morbidity in Detroit, Michigan. In: Health Effects Institute, Special Report. Revised analyses of time series studies of air pollution and health. 2003; pp. 143-156.

Jansen KL, Larson TV, Koenig JQ, Mar TF, Fields C, Stewart J, Lippmann M. Associations between health effects and particulate matter and black carbon in subjects with respiratory disease. Environ Health Perspect 2005; 113:1741-1746.

Janssen N.A.H., Hoek G., Brunekreef B., and Harssema H. Personal exposure to fine particles in children correlates closely with ambient fine particles. Arch Environ Health 1999: 54: 95-101.

Janssen N.A.H., Hoek G., Brunekreef B., Harssema H., Mensink I., and Zuidhof, A. Personal sampling of PM_{10} in adults: Relation among personal, indoor, and outdoor air concentrations. Am J Epidemiol 1998; 147: 537-547.

Janssen NAH, van Vliet PHN, Aarts F, Harssema H, Brunekreef B. Assessment of exposure to traffic related air pollution of children attending schools near motorways. Atmos Environ 2001; 35:3875-3884.

Janszky I, Ericson M, Lekander M, Blom M, Buhlin K, Georgiades A, Ahnve S. Inflammatory markers and heart rate variability in women with coronary heart disease. J Intern Med 2004; 256:421-428.

Katsouyanni K, Touloumi G, Samoli E, Gryparis A, Le Tertre A, Monopolis Y, Rossi G, Zmirou D, Ballester F, Boumghar A, Anderson HR, Wojtyniak B, et al. Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. Epidemiology 2001; 12:521-531.

Koistinen KJ, Hänninen O, Rotko T, Edwards RD, Moschandreas D, Jantunen MJ. Behavioral and environmental determinants of personal exposures to $PM_{2.5}$ in EXPOLIS - Helsinki, Finland. Atmos Environ 2001: 35: 2473-2481.

Kop WJ, Verdino RJ, Gottdiener JS, O'Leary ST, Bairey Merz CN, Krantz DS. Changes in heart rate and heart rate variability before ambulatory ischemic events. J Am Coll Cardiol 2001; 38:742-749.

Kunzli N, Jerrett M, Mack WJ, Beckerman B, LaBree L, Gilliland F, Thomas D, Peters J, Hodis HN. Ambient air pollution and atherosclerosis in Los Angeles. Environ Health Perspect 2005; 113:201-206.

Laden F, Neas LM, Dockery DW, Schwartz J. Association of fine particulate matter from different sources with daily mortality in six U.S. cities. Environ Health Perspect 2000; 108:941-947.

Landis MS, Norris GA, Williams RW, Weinstein JP. Personal exposures to $PM_{2.5}$ mass and trace elements in Baltimore, MD, USA. Atmospheric Environment 2001; 35:6511-6524.

Lazaridis M, Semb A, Larssen S, Hjellbrekke AG, Hov O, Hanssen JE, Schaug J, Torseth K. Measurements of particulate matter within the framework of the European Monitoring and Evaluation Programme (EMEP) I. First results. Sci Tot Environ 2002; 285:209-235.

Le Tertre A, Medina S, Samoli E, Forsberg B, Michelozzi P, Boumghar A, Vonk JM, Bellini A, Atkinson R, Ayres JG, Sunyer J, Schwartz J, et al. Short-term effects of particulate air pollution on cardiovascular diseases in eight European cities. J Epidemiol Community Health 2002; 56:773-779.

Liao D, Duan Y, Whitsel EA, Zheng ZJ, Heiss G, Chinchilli VM, Lin HM. Association of higher levels of ambient criteria pollutants with impaired cardiac autonomic control: A population-based study. Am J Epidemiol 2004; 159:768-777.

Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002; 105:1135-1143.

Linn WS, Szlachcic Y, Gong H Jr, Kinney PL, Berhane KT. Air pollution and daily hospital admissions in metropolitan Los Angeles. Environ Health Perspect 2000; 108:427-434.

Liu L-J S, Box M, Kalman D, Kaufman J, Koenig J, Larson T, Lumley T, Sheppard L, and Wallace L. Exposure assessment of particulate matter for susceptible populations in Seattle. Environ Health Persp 2003; 111: 909-918.

Lipsett MJ, Tsai FC, Roger L, Woo M, Ostro BD. Coarse particles and heart rate variability among older adults with coronary artery disease in the Coachella Valley, California. Environ Health Perspect 2006; 114:1215-1220.

Magari SR, Schwartz J, Williams PL, Hauser R, Smith TJ, Christiani DC. The association of particulate air metal concentrations with heart rate variability. Environ Health Perspect 2002; 110:875-880.

Magari SR, Hauser R, Schwartz J, Williams PL, Smith TJ, Christiani DC. Association of heart rate variability with occupational and environmental exposure to particulate air pollution. Circulation 2001; 104:986-991.

Malm WC, Day DE, Kreidenweis SM. Light scattering characteristics of aerosols at ambient and as a function of relative humidity: part II – a comparison of measured scattering and aerosol concentrations using statistical models. J Air Waste Manage 2000; 50:701-709.

Mann JK, Tager IB, Lurmann F, Segal M, Quesenberry CP Jr, Lugg MM, Shan J, Van Den Eeden SK. Air pollution and hospital admissions for ischemic heart disease in persons with congestive heart failure or arrhythmia. Environ Health Perspect 2002; 110:1247-1252.

Mar TF, Norris GA, Koenig JQ, Larson TV. Association between air pollution and mortality in Phoenix, 1995-1997. Environ Health Perspect 2000; 108:347-353.

Marple VA, Olson BA, Rubow KL. Inertial, gravitational, centrifugal, and thermal collection techniques. In: Baron PA, Willeke K, eds. Aerosol measurement: principles, techniques and applications. 2001. New York: John Wiley and Sons:229–260.

McDonnell WF, Ishikawa-Nishino N, Petersen FF, Chen LH, Abbey DE. Relationship of mortality with the fine and coarse fractions of long-term ambient PM_{10} concentrations in nonsmokers. J Expo Anal Environ Epidemiol 2000; 10:427-436.

Muller JE, Abela GS, Nesto RW, Tofler GH. Triggers, acute risk factors and vulnerable plaques: the lexicon of a new frontier. J Am Coll Cardiol 1994; 23:809-813.

Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, Badimon JJ, Stefanadis C, Moreno P, Pasterkamp G, Fayad Z, Stone PH, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part II. Circulation 2003; 108:1772-1778.

Oglesby L, Künzli N, Roosli M, Braun-Fahrlander C, Mathys P, Stern W, Jantunen M, Kousa A. Validity of ambient levels of fine particles as surrogate for personal exposure to outdoor air pollution--results of the European EXPOLIS-EAS Study (Swiss Center Basel). J Air Waste Manag Assoc 2000; 50:1251-1261.

Ostro B, Broadwin R, Green S, Feng WY, Lipsett M. Fine particulate air pollution and mortality in nine California counties: results from CALFINE. Environ Health Perspect 2006; 114:29-33.

Ozkaynak H, Xue J, Spengler J, Wallace L, Pellizzari E, Jenkins P. Personal exposure to airborne particles and metals: results from the Particle TEAM study in Riverside, California. J Expo Anal Environ Epidemiol 1996; 6:57-78.

Patterson E, Eatough D. Indoor/outdoor relationships for ambient $PM_{2.5}$ and associated pollutants: epidemiological implications in Lindon, Utah. J Air&Waste Manage Assoc 2000; 50:103-110.

Pekkanen J, Brunner EJ, Anderson HR, Tiittanen P, Atkinson RW. Daily concentrations of air pollution and plasma fibrinogen in London. Occup Environ Med 2000; 57:818-822.

Pekkanen J, Kulmala M. Exposure assessment of ultrafine particles in epidemiologic time-series studies. Scand J Work Environ Health 2004; 30 Suppl 2:9-18.

Pekkanen J, Peters A, Hoek G, Tiittanen P, Brunekreef B, de Hartog J, Heinrich J, Ibald-Mulli A, Kreyling WG, Lanki T, Timonen KL, Vanninen E. Particulate air pollution and risk of ST segment depression during repeated submaximal exercise tests among subjects with coronary heart disease. The ULTRA study. Circulation 2002; 106:933-938.

Peters A, Dockery W, Muller JE, Mittleman MA. Increased particulate air pollution and the triggering of myocardial infarction. Circulation 2001a; 103:2810-2815.

Peters A, Frohlich M, Doring A, Immervoll T, Wichmann HE, Hutchinson WL, Pepys MB, Koenig W. Particulate air pollution is associated with an acute phase response in men; results from the MONICA-Augsburg study. Eur Heart J 2001b; 22:1198-204.

Peters A, von Klot S, Heier M, Trentinaglia I, Hormann A, Wichmann HE, Lowel H; Cooperative Health Research in the Region of Augsburg Study Group. Exposure to traffic and the onset of myocardial infarction. N Engl J Med 2004; 351:1721-1730.

Pope CA 3rd, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. Circulation 2004a; 109:71-77.

Pope CA 3rd, Dockery DW. Health effects of fine particulate air pollution: lines that connect. J Air Waste Manag Assoc 2006; 56:709-42.

Pope CA 3rd, Hansen ML, Long RW, Nielsen KR, Eatough NL, Wilson WE, Eatough DJ. Ambient particulate air pollution, heart rate variability, and blood markers of inflammation in a panel of elderly subjects. Environ Health Perspect 2004b; 112:339-345.

Pope CA 3rd, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, Heath CW Jr. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am J Respir Crit Care Med 1995; 151:669-674.

Pope CA 3rd, Verrier RL, Lovett EG, Larson AC, Raizenne ME, Kanner RE, Schwartz J, Villegas GM, Gold DR, Dockery DW. Heart rate variability associated with particulate air pollution. Am Heart J 1999; 138:890-899.

Richards WL, Alcorn SH, McDade C, Couture T, Lowenthal D, Chow JC, Watson JG. Optical properties of the San Joaquin Valley aerosol collected during the 1995 integrated monitoring study. Atmos Environ 1999; 33: 4787-4795.

Rojas-Bracho L, Suh HH, Catalano PJ, Koutrakis P. Personal exposures to particles and their relationships with personal activities for chronic obstructive pulmonary disease patients living in Boston. J Air Waste Manag Assoc. 2004; 54:207-217.

Rojas-Bracho L, Suh HH, Koutrakis P. Relationships among personal, indoor, and outdoor fine and coarse particle concentrations for individuals with COPD. J Expos Anal Environ Epidemiol 2000; 10:294-306.

Rodes CE, Lawless PA, Evans GF, Sheldon LS, Williams RW, Vette AF, Creason JP, Walsh D. The relationships between personal PM exposures for elderly populations and indoor and outdoor concentrations for three retirement center scenarios. J Expo Anal Environ Epidemiol 2001; 11:103-115.

Roorda-Knape MC, Janssen NAH, de Hartog JJ, van Vliet PHN, Harssema H, Brunekreef B. Air pollution from traffic in city districts near major motorways. Atmos Environ 1998; 32:1921-1930.

Ruckerl R, Ibald-Mulli A, Koenig W, Schneider A, Woelke G, Cyrys J, Heinrich J, Marder V, Frampton M, Wichmann HE, Peters A. Air pollution and markers of inflammation and coagulation in patients with coronary heart disease. Am J Respir Crit Care Med 2006; 173:432-441.

Samet JM, Dominici F, Curriero FC, Coursac I, Zeger SL.. Fine particulate air pollution and mortality in 20 U.S. cities, 1987-1994. N Engl J Med 2000; 343:1742-1749.

Samoli E, Analitis A, Touloumi G, Schwartz J, Anderson HR, Sunyer J, Bisanti L, Zmirou D, Vonk JM, Pekkanen J, Goodman P, Paldy A, Schindler C, Katsouyanni K. Estimating the exposure-response relationships between particulate matter and mortality within the APHEA multicity project. Environ Health Perspect 2005; 113:88-95.

Schwartz J. Is there harvesting in the association of airborne particles with daily deaths and hospital admissions. Epidemiology 2001a; 12:55-61.

Schwartz J. Air pollution and blood markers of cardiovascular risk. Environ Health Perspect 2001b; 109 Suppl 3:405-9.

Schwartz J, Litonjua A, Suh H, Verrier M, Zanobetti A, Syring M, Nearing B, Verrier P, Stone P, MacCallum G, Speizer FE, Gold DR. Traffic related pollution and heart rate variability in a panel of elderly subjects. Thorax 2005; 60:455-461.

Schwartz J, Norris G, Larson T, Sheppard L, Claiborne C, Koenig J. Episodes of high coarse particle concentrations are not associated with increased mortality. Environ Health Perspect 1999; 107:339-342.

Seinfeld JH, Pandis SN. Atmospheric Chemistry and Physics: From Air Pollution to Climate Change. John Wiley & Sons, Inc., New York. 1998.

Sillanpaa M, Saarikoski S, Hillamo R, Pennanen A, Makkonen U, Spolnik Z, Van Grieke n R, Koskentalo T, Salonen RO. Chemical composition, mass size distribution and source analysis of long-range transported wildfire smokes in Helsinki. Sci Total Environ 2005; 350:119-135.

Sorensen M, Loft S, Andersen HV, Raaschou-Nielsen O, Skovgaard LT, Knudsen LE, Nielsen IV, Hertel O. Personal exposure to $PM_{2.5}$, black smoke and NO_2 in Copenhagen: relationship to bedroom and outdoor concentrations covering seasonal variation. J Expo Anal Environ Epidemiol 2005: 15:413-422.

Sternbeck J, Sjödin A, Andreasson K. Metal emissions from road traffic and the influence of resuspension-results from two tunnel studies. Atmos Environ 2002; 36:4735-4744.

Sullivan J, Sheppard L, Schreuder A, Ishikawa N, Siscovick D, Kaufman J. Relation between short-term fine-particulate matter exposure and onset of myocardial infarction. Epidemiology 2005; 16:41-48.

Takusagawa M, Komori S, Umetani K, Ishihara T, Sawanobori T, Kohno I, Sano S, Yin D, Ijiri H, Tamura K. Alterations of autonomic nervous activity in recurrence of variant angina. Heart 1999; 82:75-81.

Tao F, Gonzalez-Flecha B, Kobzik L. Reactive oxygen species in pulmonary inflammation by ambient particulates. Free Radic Biol Med 2003; 35:327-340.

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Eur Heart J 1996; 17:354-381.

Thurston GD, Ito K, Mar T, Christensen WF, Eatough DJ, Henry RC, Kim E, Laden F, Lall R, Larson TV, Liu H, Neas L, et al.. Workgroup report: workshop on source apportionment of particulate matter health effects--intercomparison of results and implications. Environ Health Perspect 2005; 113:1768-1774.

Timonen KL, Vanninen E, de Hartog J, Ibald-Mulli A, Brunekreef B, Gold DR, Heinrich J, Hoek G, Lanki T, Peters A, Tarkiainen T, Kreyling W, Pekkanen J. Effects of ultrafine and fine particulate and gaseous air pollution on cardiac autonomic control in subjects with coronary artery disease. The ULTRA study. J Expo Sci Environ Epidemiol 2006; 16:332-341.

Tsai FC, Apte MG, Daisey JM. An exploratory analysis of the relationship between mortality and the chemical composition of airborne particulate matter. Inhal Toxicol 2000; 12:121-135.

Urch B, Silverman F, Corey P, Brook JR, Lukic KZ, Rajagopalan S, Brook RD. Acute blood pressure responses in health adults during controlled air pollution exposures. Environ Health Perspect 2005; 113:1052-1055.

Vallius M, Janssen NAH, Heinrich J, Hoek G, Ruuskanen J, Cyrus J, van Grieken R, de Hartog JJ, Kreyling WG, Pekkanen J. Sources and elemental composition of ambient $PM_{2.5}$ in three European cities. Sci Tot Environ 2005; 337:147-162.

Vedal S. Ambient particles and health: lines that divide. J Air Waste Manag Assoc 1997; 47:551-581.

Wellenius GA, Scwartz J, Mittleman MA. Particulate air pollution and hospital admissions for congestive heart failure in seven United States Cities. Am J Cardiol 2006; 97:404-408.

Wheeler A, Zanobetti A, Gold DR, Schwartz J, Stone P, Suh HH. The relationship between ambient air pollution and heart rate variability differs for individuals with heart and pulmonary disease. Environ Health Perspect 2006; 114:560-566.

Williams R, Suggs J, Rea A, Leovic K, Vette A, Croghan C, Sheldon L, Rodes C, Thornburg J, Ejire A, Herbst M, Sanders W Jr. The Research Triangle Park particulate matter panel study: PM mass concentration relationships. Atmos Environ 2003; 37:5349-5363.

Williams R, Suggs J, Creason J, Rodes C, Lawless P, Kwok R, Zweidinger R, Sheldon L. The 1998 Baltimore Particulate Matter Epidemiology-Exposure Study: part 2. Personal exposure assessment associated with an elderly study population. J Expo Anal Environ Epidemiol 2000; 10:533-543.

Wilson WE, Suh HH. Fine particles and coarse particles: concentration relationships relevant to epidemiologic studies. J Air Waste Manage Assoc 1997; 47:1238-1249.

von Klot S, Peters A, Aalto P, Bellander T, Berglind N, D'Ippoliti D, Elosua R, Hörmann A, Kulmala M, Lanki T, Löwel H, Pekkanen J, Picciotto S, Sunyer J, Forastiere F for the HEAPSS Study Group. Ambient air pollution is associated with increased risk of hospital cardiac readmissions of myocardial infarction survivors in European cities. Circulation 2005; 112:3073-3079.

Zanobetti A, Schwartz J. Are diabetics more susceptible to the health effects of airborne particles? Am J Respir Crit Care Med 2001; 164:831-833.

3 AIMS OF THE STUDY

The present study, conducted among persons with coronary heart disease (the ULTRA study), has the following aims:

1   To evaluate how well daily variation in the levels of $PM_{2.5}$ and its components at a central outdoor measurement site reflects variation in personal exposures

2   To identify behavioural and environmental determinants of daily variation in personal $PM_{2.5}$ exposure and long-term average $PM_{2.5}$ exposure

3   To estimate the feasibility of using a new photometric measurement method for $PM_{2.5}$ in epidemiological studies

4   To evaluate whether hourly changes in $PM_{2.5}$ exposure are associated with the occurrence of ST segment depression, an indicator of myocardial ischemia

5   To compare the effects of $PM_{2.5}$ from different sources on the risk of myocardial ischemia and changes in autonomic nervous control of the heart

4 PERSONAL EXPOSURE TO FINE PARTICULATE MATTER IN ELDERLY SUBJECTS: RELATION BETWEEN PERSONAL, INDOOR, AND OUTDOOR CONCENTRATIONS

Janssen NAH, de Hartog JJ, Hoek G, Brunekreef B

Environmental and Occupational Health Group, Utrecht University, The Netherlands

Lanki T, Timonen KL, and Pekkanen J

Environmental Epidemiology Unit, National Public Health Institute (KTL), Kuopio, Finland

Abstract

The time-series correlation between ambient levels, indoor levels, and personal exposure to $PM_{2.5}$ was assessed in panels of elderly subjects with cardiovascular disease in Amsterdam, the Netherlands, and Helsinki, Finland. Subjects were followed for 6 months with biweekly clinical visits. Each subject's indoor and personal exposure to $PM_{2.5}$ was measured biweekly, during the 24-hr period preceding the clinical visits. Outdoor $PM_{2.5}$ concentrations were measured at fixed sites. The absorption coefficients of all $PM_{2.5}$ filters were measured as a marker for elemental carbon (EC). Regression analyses were conducted for each subject separately, and the distribution of the individual regression and correlation coefficients was investigated. Personal, indoor, and ambient concentrations were highly correlated within subjects over time. Median Pearson's R between personal and outdoor $PM_{2.5}$ was 0.79 in Amsterdam and 0.76 in Helsinki. For absorption, these values were 0.93 and 0.81 for Amsterdam and Helsinki, respectively. The findings of this study provide further support for using fixed-site measurements as a measure of exposure to $PM_{2.5}$ in epidemiological time-series studies.

Introduction

Numerous recent studies have demonstrated associations between day-to-day variations in ambient PM concentrations and day-to-day variations in health endpoints, such as mortality.[1-4] Most studies have used ambient concentrations of PM_{10} (or larger size fractions such as TSP), measured at central monitoring sites, as exposure variables. Few studies have incorporated measurements of fine particles (FP), usually defined as particles smaller than 2.5 μm ($PM_{2.5}$). A study on associations between PM and mortality has suggested that FP is more closely associated with day-to-day variations in mortality than is the coarse fraction of PM_{10}.[5] Two cohort studies have also suggested that ambient FP is closely associated with reduced survival.[6,7] Even fewer epidemiological studies have investigated the role of ultrafine particles (UFP, <100 nm in diameter) or particle transition metal content on health.[8-10] It has been suggested that UFP could be responsible for the effects of PM on the cardiovascular system.[11]

Studies on personal exposure to PM have suggested that the cross-sectional correlation between ambient and personal PM may be poor, and that personal exposure to PM_{10} may be higher than either ambient or indoor PM_{10} concentrations.[12,13] Since time-series studies relate day-today variations in outdoor concentrations to day-to-day variations in health endpoints, the correlation between the temporal variation of personal and outdoor concentrations within subjects is more relevant. A series of studies conducted in the Netherlands has recently shown that the time-series correlation between ambient and personal PM is reasonably high for PM_{10}, and that the time-series correlation between ambient and personal FP is even higher.[14-16] This suggests that ambient FP concentrations could be adequate proxies for estimating personal exposure to FP in time-series studies. The high time-series correlation between personal and outdoor FP concentrations, however, was found among a small group of primary school children. Only limited information is available about the correlation between personal and ambient FP for elderly subjects, who spend more time indoors. Even less information is available about the time-series correlation for components of PM from specific sources, such as traffic. The aim of the study, therefore, was to assess the time-series correlation between ambient levels, indoor levels, and personal exposure to $PM_{2.5}$ in panels of elderly subjects with cardiovascular disease living in the Netherlands and Finland. In addition to $PM_{2.5}$ mass concentrations, absorption of $PM_{2.5}$ filters was measured as a marker for elemental carbon (EC), a major component of diesel soot.[17]

Materials and Methods

Study Design

The study was conducted in the framework of an EU funded panel study on the effects of exposure to outdoor fine and ultrafine particles on cardiovascular and respiratory health of elderly subjects with cardiovascular disease (ULTRA study). The study was conducted in Amsterdam, the Netherlands, and Helsinki, Finland, in the winter/spring of 1998/1999. Subjects were 50- to 84-yr-old nonsmokers with doctor-diagnosed angina pectoris and/or coronary heart disease. Subjects were followed for 6 months with biweekly clinical visits. During these visits, ambulatory ECG was recorded during a fixed protocol including light exercise, and spirometric lung function was measured. During the entire study period, subjects kept diaries to record symptoms and medication use. Each subject's indoor and personal exposure to $PM_{2.5}$ was measured biweekly, during the 24-hr period preceding the intensive health status measurements.

Samplers were distributed and collected at the homes of the participants between 9:00 a.m. and 4:30 p.m. in Amsterdam and between 8:30 a.m. and 5:00 p.m. in Helsinki, with the exception of three cases for which the samplers were distributed between 5:00 p.m. and 7:00 p.m. For each subject, samplers were generally distributed on the same day of the week and at approximately the same time of day. Measurements were conducted from Monday to Friday in Amsterdam and from Sunday to Friday in Helsinki. One to six subjects were monitored on the same day. Outdoor concentrations of $PM_{2.5}$ were measured at a fixed site. In addition to the gravimetric analyses, reflectance of personal, indoor, and outdoor $PM_{2.5}$ filters was measured as a marker for EC. Measurements took place from November 2, 1998, to June 18, 1999, in Amsterdam, and from November 1, 1998, to April 30, 1999, in Helsinki. The longer observation period in the Netherlands was necessary because of low response rates and, therefore, slow recruitment of subjects.

Information on general characteristics, such as housing conditions, was assessed by questionnaire. In addition, participants were asked to fill out a more detailed questionnaire including questions on exposure to environmental tobacco smoke (ETS) both at home and elsewhere, time spent in several micro-environments, cleaning and cooking activities, and so forth, after each individual day of personal and indoor measurements.

Population

Non-smoking subjects between 50 and 84 years of age with doctor-diagnosed angina pectoris and/or current use of angina pectoris medication and/or coronary heart disease were selected for participation in the study. Before the start of the panel study, subjects were screened for several eligibility criteria, excluding subjects with a very severe disease status. Subjects with severe unstable angina pectoris or a fresh (<3 months ago) cardiac event or stroke, subjects unable to perform spirometry, and subjects at initial visit deemed by a physician too unfit to follow the study protocol properly were excluded from the study.

In Amsterdam, subjects were recruited by distribution of information letters and screening questionnaires in city areas that are, according to local authorities, mainly inhabited by the elderly. Furthermore, information about the study (including a call for participants) was published in a local newspaper. A total of 41 subjects started the study, 33 in 1998 and 8 in late February/early March, 1999. Four dropped out after the first measurement.

In Finland, the recruitment of subjects was conducted by using announcements in a patient organization journal and in a local newspaper, and by sending a personal letter to members of the Helsinki-area heart-disease patient organization. In addition, during weekly gymnastics sessions at the patient organization, information letters on the study were handed out. The study started with 50 subjects, of which two dropped out after the first measurement. One new subject started in early January 1999.

Sampling Methods

In both centers, the same sampling methods for personal, indoor, and outdoor PM$_{2.5}$ and the same standard operating procedures were used. In addition, quality control procedures included inter-laboratory comparisons of filter weights and reflectances of outdoor samples.

Personal PM$_{2.5}$ measurements were conducted using PM$_{2.5}$ GK2.05 cyclones (BGI Inc.; Waltham, MA) that were designed and constructed for the EXPOLIS (Air Pollution Exposure Distribution among Adult Urban Populations in Europe) study[18] and flow-controlled battery-operated pumps at a flow rate of 4 L/min. Two different pump systems were used. In the Netherlands, a Gillian pump (model Gil-Air 5) was used and placed in an acoustic shell to reduce pump noise levels.[19] Subjects could wear the sampler in a made-to-fit bag with a belt and shoulder strap. The bag with the monitor weighed approximately 1.5 kg. At night, the bag and monitor were placed near the bed in a wooden insulated box to further reduce pump noise levels. Furthermore, the box contained a wall plug converter, which subjects had to connect

to the pump before they went to sleep, to reduce battery usage overnight.[19] During the first 5 weeks of the sampling period, however, 14 out of 37 (38%) personal measurements were unsuccessful due to battery failure. To relieve the battery during the day, therefore, subjects were asked to also use the wall plug converter during long-lasting indoor sedentary activities (i.e., reading, watching TV). In Finland, a BGI AFC400S pump was used which ran on four ordinary 1.5 V D-size alkaline batteries. The personal exposure monitoring equipment was placed in a rigid aluminum briefcase filled with noise-absorbing material. The case weighed 4.1 kg and could be carried either on a shoulder strap or in backpack. A photometer (pDr-1200, MIE Inc.) was installed between the filter holder and the cyclone, which enabled the collection of continuous PM data in Finland.

Participants were instructed that the sampler should follow them as closely as possible, but they were allowed to place the sampler nearby during indoor sedentary activities (i.e., watching TV, reading) or activities during which wearing the sampler would be too inconvenient or impossible (i.e., sleeping, swimming). Subjects were instructed to record the kind and duration of those activities as well as the position of the sampler during these activities.

Measurements of $PM_{2.5}$ indoors were made with Harvard Impactors (HIs) operating at 10 L/min[20,21] using a flow-controlled pump (A.D.E. Inc., model SP-280E). Indoor samples were taken in the living room at about 1-m height.

Outdoor $PM_{2.5}$ concentrations were measured at fixed monitoring sites, which were operated for the panel studies mentioned earlier, using the same impactors that were used for indoor sampling. In Amsterdam, the site was located on the roof of a home for the elderly in the city district were the subjects lived, about 250 m away from the nearest busy road. Measurements were conducted at 7.7-m height (1.7 m above the roof). In Finland, the measurements were done on the roof of a measurement cabin at 4.5-m height (about 1.7 m above the roof). The cabin was situated in a small park. The nearest main road was about 60 m and the nearest building 15 m away from the cabin. In both cities, measurements were conducted on a continuous, daily basis (from 12:00 noon to 12:00 noon).

For all three types of measurements (personal, indoor, and outdoor), the same filters were used (Anderson 37-mm 2-μm-pore size Teflon filters). Field blanks were taken by loading an impactor or filter cassette with a filter and leaving it there for 24 hr (personal and indoor) or until the next site visit (outdoor). Mean field blank weight changes were subtracted from all sample weights. Flows were measured at the beginning and end of each 24-hr sampling period with calibrated rotameters (personal, indoor, outdoor measurements in Amsterdam and outdoor measurements in Helsinki) or a bubble flow meter (personal and indoor measurements in Helsinki), and elapsed time indicators were used to calculate the sampled volumes.

Gravimetric Analysis

Prior to weighing, filters were stored in a refrigerator at 4 or 10 °C. In both centers, filters were weighed using a Mettler MT5 micro-balance (Mettler-Toledo, Greifensee, Switzerland) with 1-µg reading. In the Netherlands, until the end of May, filters were weighed in a weighing room in which temperature and humidity were not completely controlled. On the days that filters were weighed, temperature and relative humidity (RH) in this room ranged from 19 to 26.5 °C (mean 21.7; s.d. 1.7), and from 32 to 51% (mean 38.1; s.d. 4.4), respectively. In this room, however, filters were equilibrated in a desiccator at 42% RH for 24 hr. From June 1999 on, filters were weighed in a temperature- and humidity-controlled room, after equilibrating for 24 hr. In this room, temperature ranged from 23 to 24 °C and relative humidity ranged from 37 to 40%. In Finland, filters were weighed after equilibrating at 19–24 °C and <40% RH for 24 hr. In the Netherlands, static electricity was controlled using a Simco (Hatfield, PA) Aerostat PC ionizing air blower. In Finland, a Po-210 deionizer was used.

Before each filter weighing session, at least one external mass piece with a weight close to the filter weight, two blank control filters, and two aged exposed control filters were weighed. Filter weighing was only continued if the weights of the mass pieces were within 5 µg of the target weight and the weights of the control filters were within 10 µg of the target weight, calculated as a moving average of the previous 10 weighing days. All filters were weighed twice. In the Netherlands, the second weighing was conducted after 10 filters were weighed, and a filter was re-weighted if the difference between the two weights exceeded 5 µg. In Finland, each filter was weighed two immediate consecutive times and the filter was reweighed if the difference between the two weights exceeded 1 µg. To document the stability of the weighing conditions, two blank and two exposed control filters were also weighed after each weighing session, so every weighing day a total of eight control filter weights were obtained. On 4 days in the Netherlands, filters were weighed despite the fact that the control filters were not within 10 µg of the target weight. On these days, however, filters had to be weighed in order to continue the fieldwork or to prevent the filters from being stored in the weighing room for too long. To correct for this, for each control filter, the difference between the weight on a specific day and the average weight of the 10 previous days was calculated. Next, the average difference of the eight control filters was subtracted from each filter that was weighed that day. This correction was done for all filter weights. Furthermore, the control filters showed an average increase of 10 µg in the new, as compared with the old, weighing room. This value was subtracted from filter weights of filters that were pre-weighed in the old weighing room and post-weighed in the new weighing room. In Finland, the weights of the control filters were always within 10 µg of the target weight, so no correction was applied.

All filter weights were corrected for the effects of air buoyancy according to the formulas given by Koistinen et al.[18]

Reflectance Measurements

Particle reflectance was measured using EEL 43 reflectometers. Each filter was measured 5 times on different locations (5-point method) and the average was used in the calculations. Reflectance of $PM_{2.5}$ filters was transformed into an absorption coefficient (a) according to ISO 9835[22]

$$a = (A/2V) \cdot \ln (R_0/R_s) \qquad (1)$$

where A = loaded filter area (m^2), V = sampled volume (m^3), R_0 = average reflectance of field blank filters, and R_s = reflectance of the sampled filter. Absorption coefficients are expressed in $m^{-1} \cdot 10^{-5}$.

Field Comparison

At the outdoor site and indoors, the personal cyclone was collocated with the HI. The relationship between the two methods was assessed using a method suggested by Cornbleet and Gochman.[23] This method simultaneously minimizes the squared distances from the observed data points to the regression line in the horizontal and vertical directions. One regression line is obtained regardless of which of the two methods is considered as the independent variable. This method was used instead of ordinary least squares regression because it is not obvious which variable should be selected as the independent variable. In addition, bias of the "true" regression slope to the null occurs in ordinary least squares regression when a considerable amount of measurement error is present.[23] Slope and intercept were calculated using the formulas given by Cornbleet and Gochman.[23] We assumed that the absolute error of the two compared methods was the same.

Measurements of Elemental Carbon

To establish the correlation between reflectance of $PM_{2.5}$ filters and direct EC measurements within our study, EC was measured in a subset of about 50 indoor samples in each of the two centers. For the EC measurements, duplicate sample collection was conducted using Harvard $PM_{2.5}$ Impactors and Schleicher and Schuell QF 20 quartz filters. Measurements of EC were conducted by the AMU TUV GMBH laboratory in Munchen, Germany, which is accredited to measure EC in the framework of a control program for the German EC ambient air quality standard. Measurements were conducted according to VDI 2465 standard.[24]

The limit of detection (DL) given by the German laboratory was 10 µg per filter. Values that were below the DL were set at 2/3 the detection limit. A total of five duplicate samples were taken in the homes of two of the researchers in the Netherlands in September 1999.

Analysis of the Correlation between Personal, Indoor, and Outdoor Concentrations

The correlation between personal, indoor, and outdoor $PM_{2.5}$ concentrations and between personal, indoor, and outdoor absorption coefficients was assessed by means of individual regression analysis, using the Statistical Analysis System (SAS) procedures "PROC REG" and "PROC CORR." The following models were used:

Model 1: $C_{personal, i\,t} = \alpha_{i\,1} + \beta_{i\,1} \cdot C_{outdoors, t}$ (2)

Model 2: $C_{personal, i\,t} = \alpha_{i\,2} + \beta_{i\,2} \cdot C_{indoors, i\,t}$ (3)

Model 3: $C_{indoors, i\,t} = \alpha_{i\,3} + \beta_{i\,3} \cdot C_{outdoors, t}$ (4)

where C = $PM_{2.5}$ concentration or absorption coefficient, i = subject i, t = day t, and 1, 2, and 3 = models 1, 2, and 3, respectively.

Only subjects with at least four valid observations were included in the analysis. The distribution of the individual regression results was investigated. Medians are presented because most correlation and regression coefficients were not normally distributed (Shapiro-Wilk Statistic, $p < 0.05$). Although all subjects were non-smokers, participants could still be exposed to ETS elsewhere, or at home in the case of a smoking spouse or visitor. To investigate the influence of occasional exposure to ETS on the relationship between personal, indoor, and outdoor $PM_{2.5}$, the same regression analyses were conducted after excluding days with exposure to ETS. Subjects with less than four remaining observations were excluded.

Results

Field Blanks and Duplicates

Limits of detection and coefficients of variation (CV) for personal, indoor, and outdoor samples are given in Table 1. Mean mass increases of field blanks varied between –1.5 and 3.0 µg for personal and outdoor measurements in Amsterdam, respectively. Limits of detection for $PM_{2.5}$ mass concentrations were higher in the Netherlands than in Finland, possibly due to a higher imprecision of the gravimetric analyses caused by the several corrections that were necessary or by the difference in the weighing procedures (see Gravimetric Analysis section). Limits of detection

for the absorption coefficients were similar for Amsterdam and Helsinki. Except for the personal measurements in the Netherlands, the median coefficient of variation was below 10% and the median absolute difference between the $PM_{2.5}$ duplicates was below 1 $\mu g/m^3$ for all types of measurements. In the Netherlands, all but one personal duplicate were taken some time after the study period (September 1999). In Finland, outdoor duplicates were collected from May 6 to May 12, 1999. All other duplicates were collected throughout the study period.

Table 1. Detection limits and precision of personal, indoor, and outdoor $PM_{2.5}$ and absorption measurements.

		Field blanks			Duplicates			
	n	Detection limit[a]		n	Median absolute difference		Median CV	
		$PM_{2.5}$	Absorption		$PM_{2.5}$	Absorption	$PM_{2.5}$	Absorption
		$(\mu g/m^3)$	$(m^{-1}\cdot 10^{-5})$		$(\mu g/m^3)$	$(m^{-1}\cdot 10^{-5})$	(%)	(%)
Amsterdam								
Personal	22	6.71	0.25	5	2.35	0.31	13.0	10.7
Indoor	28	3.15	0.12	20	0.94	0.06	4.5	2.9
Outdoor	19	2.13	0.15	21	0.58	0.05	1.9	2.9
Helsinki								
Personal	27	2.21	0.22	7	0.64	0.09	7.0	5.7
Indoor	26	0.85	0.10	35	0.72	0.08	6.6	4.1
Outdoor	24	0.77	0.08	7	0.69	0.05	7.8	4.7

Note: [a]Three times the standard deviation of field blanks divided by the samples volume.

Comparison between the Personal Cyclone and the Harvard Impactor

The results of the comparison between the personal cyclone (PC) and the HI are presented in Figure 1, Figure 2, and Table 2. In Finland, the outdoor comparison measurements were all conducted in 1 week (May 6–May 12, 1999) with very little variation in outdoor $PM_{2.5}$ concentrations. All other comparison measurements were conducted throughout the study period. Indoor comparison measurements were conducted in 20 different homes in Amsterdam on 25 different days and in 20 different homes in Helsinki on 19 different days. In the Netherlands, three indoor comparison measurements were conducted in homes with very high concentrations due to smoking and are not included in Figure 1. These three measurements showed the largest differences between the HI and the PC. The extremely large difference in $PM_{2.5}$ concentrations of 65 $\mu g/m^3$ (Table 2) was found at an average concentration level of 410 $\mu g/m^3$ (percent difference = 16%). In the Netherlands, the HI gave

significantly higher values than the cyclone, both indoors and outdoors and for both $PM_{2.5}$ mass concentrations and absorption coefficients. The average differences, however, were small. In Helsinki, only the difference for absorption in indoor air was significant, with a similar value as that found in Amsterdam (0.2 m^{-1} • 10^{-5}).
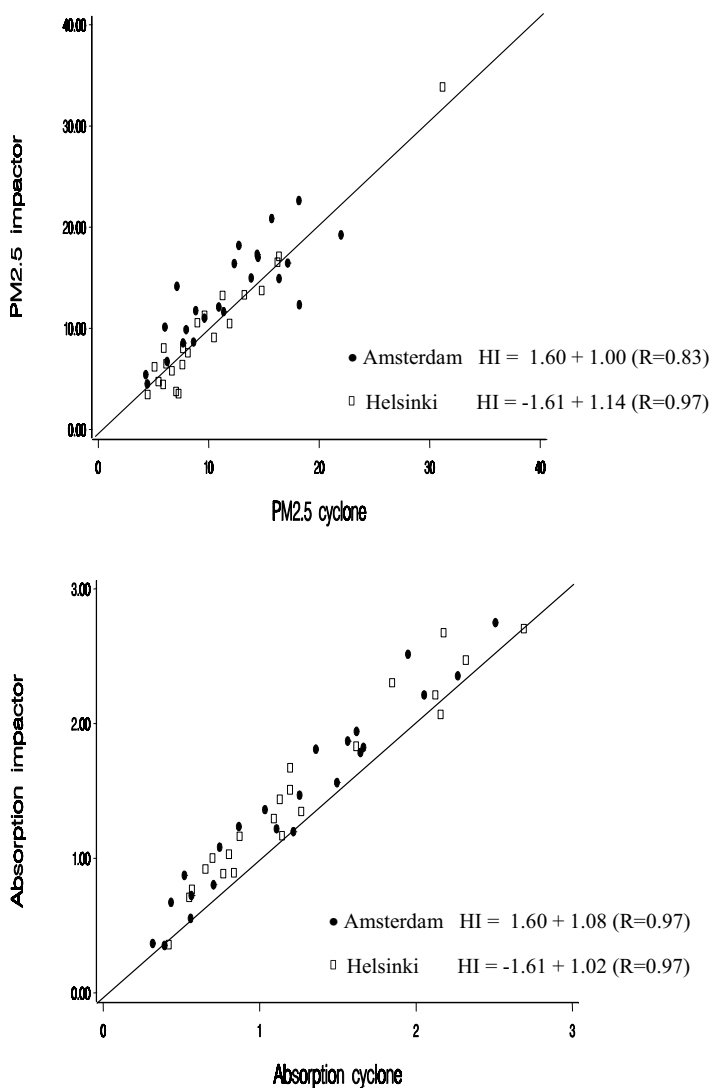
Figure 1. $PM_{2.5}$ concentrations (upper) and absorption coefficients (lower) in indoor air measured with a PC compared with an HI (line shown 1:1 line).
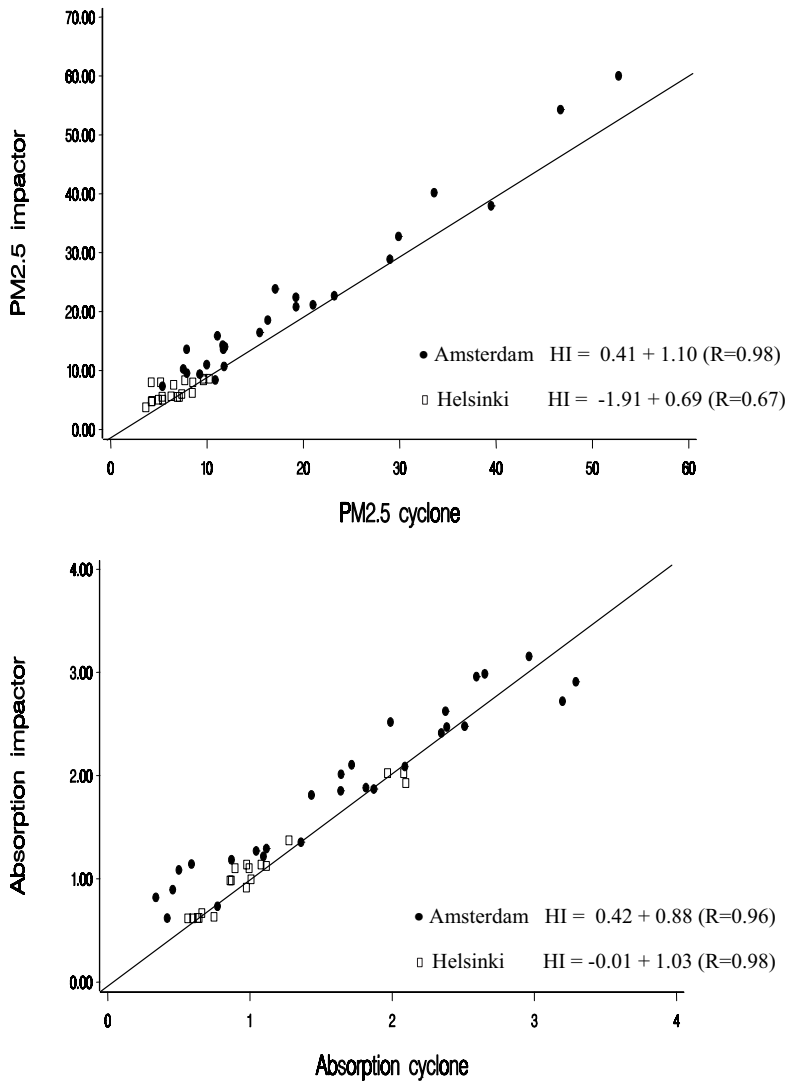
Figure 2. PM$_{2.5}$ concentrations (upper) and absorption coefficients (lower) in outdoor air measured with a PC compared with an HI (line shown 1:1 line).

Table 2. Distribution of the difference between collocated measurements with the Harvard impactor and the personal cyclone (impactor minus cyclone) in indoor and outdoor air.

	N	Median	Mean	SD	Rance	Median	Mean	SD	Range
		$PM_{2.5}$ (µg/m³)				**Absorption ($m^{-1} \cdot 10^{-5}$)**			
Amsterdam									
Indoor	26	1.30[a]	4.42	14.4	-16.7-65.4	0.16[a]	0.07	0.48	-1.83-0.57
Indoor-no ETS	23	1.20[a]	1.58[a]	2.86	-5.88-7.03	0.16[a]	0.20[a]	0.16	-0.04-0.57
Outdoor	25	1.96[a]	2.34[a]	2.80	-2.45-7.61	0.23[a]	0.21[a]	0.26	-0.48-0.59
Helsinki									
Indoor	22	-0.22	-0.16	1.67	-3.72-2.69	0.20[a]	0.20[a]	0.16	-0.09-0.50
Outdoor	19	-0.34	-0.12	1.53	-2.26-3.81	0.02	0.03	0.09	-0.17-0.21

Note: [a]$p<0.01$

Relationship between Absorption Coefficients and Elemental Carbon

The relation between absorption coefficients and measurements of EC is presented in Figure 3. Absorption coefficients were reasonably well correlated with EC concentrations. In Finland, 21 measurements were below the limit of detection (10 µg EC/filter). Without these measurements, the regression equation was Absorption $= 0.99 + 0.58 \cdot EC$ ($R = 0.61$). In Amsterdam, eight measurements were conducted in homes with exposure to ETS, whereas this was never the case in Helsinki. The regression equation for the measurements in homes with ETS exposure was different than the equation for measurements in homes with no ETS exposure. Using all data, both ETS and no ETS, the regression equation was Absorption $= 0.93 + 0.19 \cdot EC$ ($R = 0.85$). The slope of the regression line for measurements in homes with no ETS in Amsterdam (ß $= 0.30$; s.e. $= 0.07$) was lower than the slope for Helsinki (ß $= 0.73$; s.e. $= 0.09$ for all data, and ß $= 0.58$; s.e. $= 0.15$ for data above the DL). After excluding one outlier (EC $= 5.8$ µg/m³; Absorption $= 1.1$ $m^{-1} \cdot 10^{-5}$), the slope for homes with no ETS in Amsterdam increased to 0.43 (s.e. $= 0.07$; R $= 0.70$), which is more similar to the slopes found in Helsinki.

The average CV of five EC duplicates was 17% (s.d. 12; range 3–30%). The highest CV values (>25%) were found in two duplicates with the lowest amount of EC (about 30 µg EC/filter). In the Netherlands, only 28% of the filters collected in homes without smoking had levels of over 30 µg EC. For Finland, this percentage was only 14%.

Amsterdam

• No ETS: Absorption = 0.72 + 0.30 · EC (R=0.57)
ETS: Absorption = 1.49 + 0.15 · EC (R=0.85)

Helsinki

Absorption = 0.68 + 0.73 · EC (R=0.77)
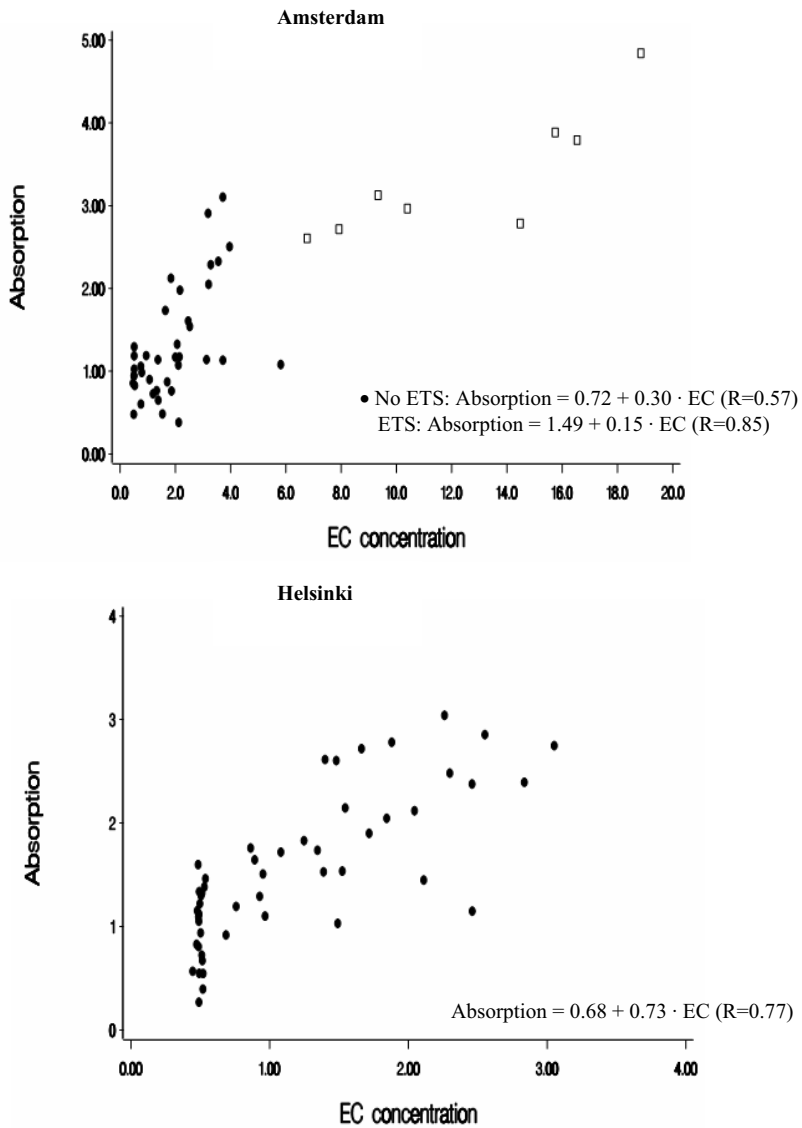
Figure 3.   Relationship between absorption coefficients and EC concentrations in indoor air in Amsterdam (upper) and Helsinki (lower).

Compliance and Population

In the Netherlands, during the first 5 weeks of the sampling period, 14 out of 37 (38%) personal measurements were unsuccessful due to battery failure. From the date that subjects were asked to use the wall plug converter during long-lasting indoor sedentary activities, 89% of personal sampling was successful. Failure occurred mainly because the subject forgot to use the wall plug converter. For indoor sampling, 98% of the measurements were successful. Valid outdoor concentrations were obtained for all days of personal/indoor sampling.

In Finland, a problem occurred with the suitcases used for personal exposure measurements at the beginning of the fieldwork. The difficulty was that the air that was pumped through the cyclone and filter could not escape well enough from the case. As a result, "cleaned air" was circulating in the system and the particle masses sampled were too low. The problem was noted and corrected in the second month of the fieldwork. One hundred seventy-two personal measurements were conducted with the poorly functioning suitcases and were excluded from the data analysis. Three hundred fifty-seven personal measurements were conducted with the repaired suitcases, of which 336 (94%) were successful. A total of 511 (98%) valid indoor samples were collected. On 13 days of personal and/or indoor measurements, outdoor measurements were unsuccessful for various reasons. As a result, 21 personal and 41 indoor measurements could not be used in the calculation of personal-outdoor or indoor-outdoor correlations.

In the Netherlands, three subjects dropped out during the course of the study. For all three, however, at least four successful personal and indoor measurements were obtained. For one other subject, who started in March 1999, only three of six personal samples were successful. For the other subjects, the number of valid measurements per subject ranged from 5 to 13 for personal and from 7 to 15 for indoor measurements.

In Finland, three subjects dropped out during the course of the study. Two of them dropped out after only three measurements and were not included in the data analysis. The third subject moved to another town in February, after seven valid indoor measurements and only two valid personal measurements. For the remaining 46 subjects, the number of valid measurements per subject ranged from 6 to 9 for personal and from 7 to 12 for indoor measurements.

Eventually, data from 37 adults (24 males and 13 females) in Amsterdam and 47 adults (24 males and 23 females) in Finland were included in the data analysis. In both cities, one married couple participated in the study; therefore, indoor measurements were available from 36 and 46 houses, respectively. Mean age was 72

years (s.d. 8; range 55–84) in Amsterdam and 68 years (s.d. 6; range 54–83) in Helsinki. In Amsterdam, 30 (81%) subjects lived in an apartment. The other seven (19%) lived in a single-family home. In Helsinki, all but one subject (98%) lived in an apartment. All homes had central heating in both Amsterdam and Finland. In Amsterdam, 28 (76%) subjects used gas for cooking, whereas this was only the case for five (11%) subjects in Helsinki. In Amsterdam, all subjects lived within 4 km of the outdoor monitoring site. In Helsinki, 43 (91%) subjects lived within 2 km of the outdoor monitoring site. The other four subjects lived within 5 km. On the days of valid personal measurements, subjects spent on average 1.2 hr outdoors and 21.5 hr at home in Amsterdam, and 1.1 hr outdoors and 21.3 hr at home in Helsinki. In Amsterdam, subjects either slept with the bedroom window open or had the window on the street side of the living room open on 82% of the days of personal and/or indoor measurements. In Helsinki, this percentage was only 32%.

Particle Concentrations

The distributions of the individual averages of personal, indoor, and outdoor $PM_{2.5}$ and absorption coefficients are presented in Table 3. In both centers, median outdoor concentrations exceeded both personal and indoor concentrations. Personal and indoor concentrations were similar. Since in Amsterdam the impactor used for indoor and outdoor sampling gave a significantly higher concentration than the PC (Table 2), the differences between personal and outdoor concentrations in Amsterdam are, in fact, somewhat smaller. In Amsterdam, some subjects had very high personal or indoor concentrations due to exposure to ETS. Exposure to ETS in the home occurred during 13% of the personal or indoor measurements. Exposure to ETS elsewhere occurred during 16% of the personal measurements. For Finland, these percentages were much lower: 1% for exposure to ETS in the home and 3% for exposure to ETS elsewhere. After excluding measurements with exposure to ETS, the mean individual average personal concentrations in Amsterdam decreased to 14.4 µg/m^3 (max 37.1) for $PM_{2.5}$ and to 1.41 m^{-1} • 10^{-5} (max 2.43) for absorption. For indoor concentrations these values were 16.0 µg/m^3 (max 43.7) and 1.61 m^{-1} • 10^{-5} (max 3.41) for $PM_{2.5}$ and absorption, respectively. In Finland, excluding the few measurements with exposure to ETS hardly affected the average concentrations.

The average range per subject in outdoor $PM_{2.5}$ concentrations (maximum minus minimum) on days of personal and/or indoor measurements was 43.2 µg/m^3 (s.d. 19.2; range 15.7–75.8 µg/m^3) in Amsterdam and 16 µg/m^3 (s.d. 4.8; range 8.6–27.2 µg/m^3) in Helsinki. For absorption, the average ranges were 2.9 m^{-1} • 10^{-5} (s.d. 1.0; range 0.9–4.7 m^{-1} • 10^{-5}) in Amsterdam and 2.2 m^{-1} • 10^{-5} (s.d. 0.5; range 1.1–3.3 m^{-1} • 10^{-5}) in Helsinki.

Table 3. Distribution of individual averages of personal, indoor, and outdoor PM$_{2.5}$ concentrations and absorption coefficients from elderly subjects in Amsterdam, the Netherlands, and Helsinki, Finland.

	n	(#)[a]	PM$_{2.5}$ concentrations (µg/m^3)				Absorption coefficients (m$^{-1}\cdot 10^{-5}$)			
			Median	Mean	(SD)	Range	Median	Mean	(SD)	Range
Amsterdam										
Personal	37	(338)	15.3	24.3	(25.7)	8.5-133.7	1.51	1.73	(0.78)	0.83-4.22
Indoor	36	(411)	14.9	28.6	(41.8)	9.1-238.8	1.67	1.84	(0.74)	1.03-4.15
Outdoor	37	(417)	21.0	20.6	(4.0)	12.8-31.1	1.85	1.79	(0.28)	1.06-2.49
Helsinki										
Personal	47	(336)	10.0	10.8	(4.4)	3.8-32.7	1.35	1.51	(0.67)	0.48-4.12
Indoor	46	(503)	10.2	11.0	(4.0)	3.2-26.6	1.49	1.57	(0.51)	0.49-2.94
Outdoor	47	(478)	12.0	12.6	(2.0)	10.4-18.0	2.10	2.05	(0.25)	1.59-2.50

Note: [a]Total number of observations

Correlation between Personal, Indoor, and Outdoor Concentrations

Results from the individual regression analyses are presented in Table 4 and Figure 4 for PM$_{2.5}$ concentrations and in Table 5 for absorption coefficients. In both centers, there was one subject with only 2–3 valid personal measurements and 6–7 valid indoor measurements. The measurements of these subjects were, therefore, only used in the calculation of the indoor-outdoor relationships. Excluding the days with exposure to ETS in Amsterdam from the analyses resulted in slightly higher correlations (median Pearson's R for PM$_{2.5}$ of 0.85, 0.94, and 0.85 for models 1, 2, and 3, respectively; median Pearson's R for absorption of 0.97 for all three models). After excluding days with exposure to ETS in Amsterdam, all individual correlation coefficients were positive. In Finland, one strongly negative correlation coefficient was found between personal/indoor and outdoor absorption coefficients. These negative values were caused by unexplained extremely high personal and indoor absorption coefficients of 24 m^{-1} • 10^{-5} and 11 m^{-1} • 10^{-5}, respectively, on a day with an outdoor absorption coefficient of 1 m^{-1} • 10^{-5}.

Table 4. Distribution of individual regression results of personal, indoor, and outdoor PM$_{2.5}$ concentrations.

	Model 1 $PM_{2.5personal} = PM_{2.5outdoors}$		Model 2 $PM_{2.5personal} = PM_{2.5indoors}$		Model 3 $PM_{2.5indoors} = PM_{2.5outdoors}$	
	Median	Range	Median	Range	Median	Range
Amsterdam	**N=36**		**N=36**		**N=36**	
Intercept ($\mu g/m^3$)	5.62	0.2-150.4	0.80	-9.9-101.8	5.98	0.6-206.2
Slope	0.43	-2.35-226	0.89	-0.27-1.68	0.47	-0.02-1.52
Pearson's R	0.79	-0.41-0.98	0.91	-0.28-1.00	0.84	-0.00-0.98
Helsinki	**N=46**		**N=46**		**N=46**	
Intercept ($\mu g/m^3$)	3.91	-12.1-35.9	1.57	-4.0-8.1	4.11	-10.3-15.0
Slope	0.45	-0.28-1.71	0.84	0.18-1.65	0.51	-0.31-2.73
Pearson's R	0.76	-0.12-0.97	0.89	0.14-1.00	0.70	-0.15-0.94

Table 5. Distribution of individual regression results of personal, indoor, and outdoor absorption coefficients.

	Model 1 $ABS_{personal} = ABS_{outdoors}$		Model 2 $ABS_{personal} = ABS_{indoors}$		Model 3 $ABS_{indoors} = ABS_{outdoors}$	
	Median	Range	Median	Range	Median	Range
Amsterdam	**N=36**		**N=36**		**N=36**	
Intercept (m^{-1})	-0.14	-1.34-4.29	-0.14	-2.41-0.46	0.05	-0.59-2.74
Slope	0.92	-0.30-2.51	1.06	0.51-1.94	0.84	0.16-1.66
Pearson's R	0.93	-0.16-1.00	0.97	0.66-1.00	0.96	0.24-0.99
Helsinki	**N=46**		**N=46**		**N=46**	
Intercept (m^{-1})	0.11	-0.84-15.57	-0.09	-2.27-1.64	0.36	-1.27-5.50
Slope	0.62	-6.45-1.37	1.01	0.07-2.41	0.49	-1.77-2.08
Pearson's R	0.81	-0.49-0.98	0.96	0.06-0.99	0.74	-0.34-0.98

Discussion

We found a high correlation between the temporal variation of personal and outdoor PM$_{2.5}$ concentrations within subjects. The median of the individual correlations between personal and outdoor PM$_{2.5}$ was 0.79 in Amsterdam and 0.76 in Helsinki. The correlations between personal and outdoor absorption coefficients were even
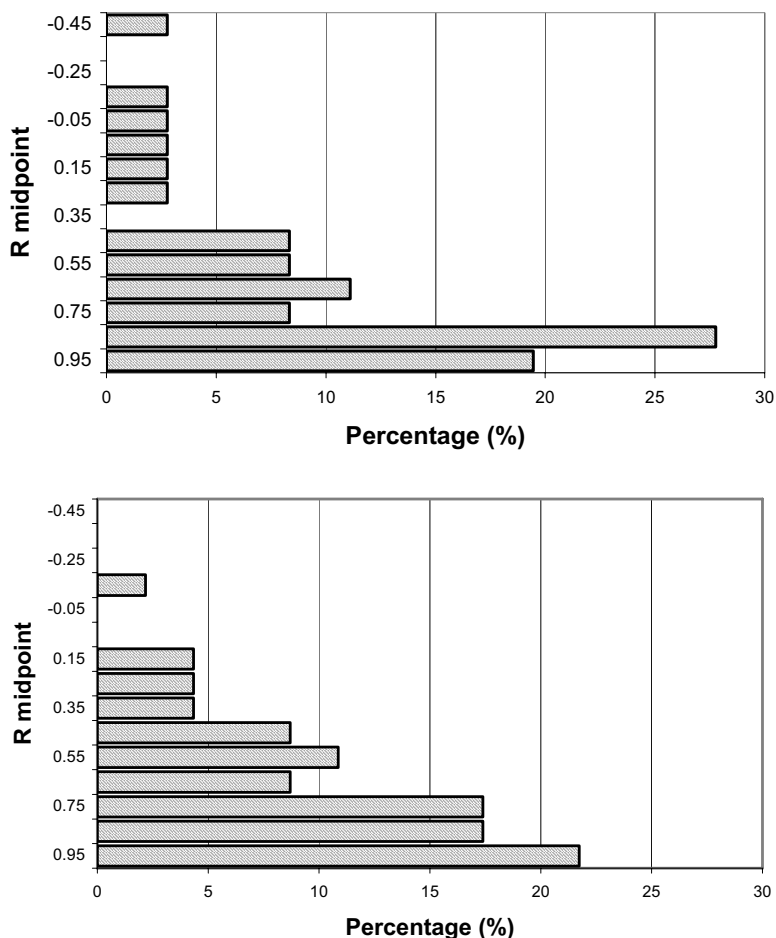
Figure 4. Distribution of individual correlation coefficients of the relation between personal and ambient PM$_{2.5}$ in Amsterdam (upper) and Helsinki (lower).

higher, especially in the Netherlands (median R = 0.93 in Amsterdam and 0.81 in Helsinki).

Few other studies have investigated the correlation between personal and outdoor PM$_{2.5}$ concentrations within subjects. In a study among 13 primary school children in Wageningen, the Netherlands, median Pearson's R between personal and outdoor FP concentrations was 0.86. After excluding measurements with exposure to ETS, the median correlation for the remaining nine children was 0.92.[16] The current study

documents that the correlation between personal and ambient $PM_{2.5}$ is also high for elderly subjects with cardiovascular disease who spend most of their time indoors. Several other studies have found a reasonably high correlation between personal and outdoor PM_{10}.[14,15,25] A study among 37 non-smoking, nonoccupationally exposed, 50- to 70-year-old adults living in Amsterdam showed a median Pearson's R between personal and ambient PM_{10} concentrations of 0.50 for all subjects and 0.71 after excluding days with exposure to ETS.[15] These correlations for PM_{10} are lower than those found for $PM_{2.5}$ in Amsterdam in this study (median Pearson's R = 0.79 for all subjects and 0.85 for non-ETS-exposed subjects). In a study of 18 adults with chronic obstructive pulmonary disease in Boston, MA, a median R of 0.55 for the within-subject correlation between personal and outdoor $PM_{2.5}$ concentrations was found. The within-subject correlation between personal and ambient PM_{10}, measured in the same subjects, was lower (median R = 0.35).[26] The lower correlations found in Boston compared with Amsterdam and Helsinki could be due to a more frequent use of air conditioning in Boston.

In Amsterdam, personal, indoor, and outdoor levels of $PM_{2.5}$ were all higher than in Helsinki. Personal and indoor levels of absorption, however, were only slightly higher, and outdoor levels were even lower in Amsterdam than in Helsinki. One explanation for the comparatively high outdoor absorption coefficients in Helsinki could be that the outdoor monitoring site in Helsinki was situated relatively close (60 m) to a busy road. Fischer et al.[27] found 1.8-fold higher absorption coefficients on the balconies of homes along busy streets in Amsterdam compared with those on quiet streets. For $PM_{2.5}$, the difference was only 20%. Another explanation could be that the $PM_{2.5}$ particles in Helsinki are mostly from traffic, including diesel engines, and contain less long-distance transport, sulfates, and nitrates. In the PEACE (Pollution Effects on Athsmatic Children in Europe) study, outdoor PM_{10} concentrations measured in the winter of 1993/1994 were also about 2- fold higher in Amsterdam than in Kuopio, Finland, whereas black smoke concentrations were similar.[28] In a study on wintertime particle concentrations in three European cities, $PM_{2.5}$ mass concentrations were almost 3 times higher in Alkmaar, the Netherlands, than in Helsinki, whereas absorption coefficients were only about 20% higher in Alkmaar.[29]

In Amsterdam, correlations and slopes were higher for absorption than for $PM_{2.5}$. Since EC or soot is generally associated with submicron particles,[17] this difference can be caused by a more efficient penetration and/or lower deposition of absorption-related particles compared with the larger-sized $PM_{2.5}$ particles. In Helsinki, however, correlations and slopes were similar for $PM_{2.5}$ and absorption. One explanation for this lack of difference between the slopes of $PM_{2.5}$ and absorption in Helsinki could be that the $PM_{2.5}$ particles in Helsinki are mostly due to traffic, so that the size distribution of outdoor particles in Helsinki compared with Amsterdam

is characterized by lower concentrations of coarse mode $PM_{2.5}$ particles, such as nitrates. In this case, the lower slopes for absorption in Helsinki compared to Amsterdam could possibly be caused by the fact that, due to the much colder climate, air exchange rates in Helsinki are probably lower than in Amsterdam. This is supported by the much lower percentage of open windows during the measurements in Helsinki (32%) compared with those in Amsterdam (82%). Another explanation for the lower correlation and slope for absorption in Helsinki could be that, due to the nearby busy road, the outdoor site did not represent urban background levels of absorption coefficients as well in Helsinki as in Amsterdam. The median slope between indoor and outdoor absorption, however, was 70% higher in Amsterdam than in Helsinki. It is unlikely that this difference can be completely attributed to the location of the outdoor monitoring site in Helsinki, since the 80% higher absorption coefficients along busy roads in Amsterdam found by Fischer[27] were observed at very short distances from the road whereas measurements in Helsinki were conducted at 60 m.

The subjects lived relatively close to the ambient monitoring site (within 4 km in Amsterdam and generally within 2 km in Helsinki). In epidemiologic time-series studies, one ambient site is generally used to assess exposures in larger areas. As a result, the correlations between personal, indoor, and outdoor concentrations in our study could overestimate the relevant associations. Since we only conducted single-site measurements of $PM_{2.5}$, we could not study the spatial variability of $PM_{2.5}$ for our study specifically. $PM_{2.5}$ concentrations, however, generally show little spatial variation across urban areas with no major industrial sources,[30] such as Amsterdam and Helsinki. The correlations between personal, indoor, and outdoor concentrations found in our study for subjects that lived relatively close to the outdoor monitoring site can, therefore, be considered representative for correlations in a larger area.

For $PM_{2.5}$ concentrations as well as for absorption, outdoor concentrations exceeded personal and indoor concentrations. Personal and indoor concentrations were similar. In recent studies of personal exposures to PM_{10}, personal concentrations were significantly higher than indoor or outdoor concentrations.[12-15] Resuspension of coarse particles has been suggested as one of the causes of this so-called "personal cloud."[13] The lack of this personal cloud for $PM_{2.5}$ and absorption in our study confirms the hypothesis that resuspension caused by personal activities mainly affects coarse particle concentrations.

The absorption coefficients of $PM_{2.5}$ filters were significantly correlated with EC concentrations. The correlation, however, was weaker than observed in some other recent studies. In a recent study conducted near highways in the Netherlands, absorption coefficients of $PM_{2.5}$ Teflon filters were highly correlated with EC concentrations, both in outdoor air ($R = 0.92$) and in classrooms ($R = 0.93$).[31] Kinney

et al.[32] also found a high correlation ($R = 0.95$) between absorption coefficients of $PM_{2.5}$ Teflon filters and EC concentrations, measured simultaneously on the sidewalk of three traffic-impacted sites and one background site for 5 days. In a study in Berlin, outdoor black smoke concentrations at a traffic-impacted site were also highly correlated with EC concentrations ($R = 0.98$).[33] Black smoke concentrations and absorption coefficients of PM_{10} Teflon filters were highly correlated in another study ($R = 0.97$).[34] These studies, however, were mostly conducted in outdoor air of traffic-impacted sites. The lower correlation found in our study could possibly be caused by an influence of indoor sources. The difference in the regression equation between homes with and without smoking illustrates that indoor sources can considerably influence the relationship between absorption of $PM_{2.5}$ filters and measurements of EC. Also, the relatively high imprecision of the EC measurement at the low levels that were collected in most samples could have reduced the correlation. Despite the lower correlation between absorption of indoor $PM_{2.5}$ filters and indoor EC in this study, the correlation between personal, indoor, and outdoor absorption was high in Amsterdam as well as in Helsinki. As outdoor absorption was shown to be highly correlated to EC in other studies, this suggests that outdoor absorption is a good proxy for personal exposure to EC of outdoor origin in time-series studies.

This study has shown that personal $PM_{2.5}$ concentrations and absorption coefficients are highly correlated with ambient concentrations within subjects over time. The results of this study confirm the results of previous studies, which also showed that short-term increases in outdoor air pollution are reflected in increased personal exposures for potentially susceptible subjects who spend most of their time indoors. The findings of this study provide further support for using fixed-site measurements as a measure of exposure to PM in time-series studies linking the day-to-day variation in PM to the day-to-day variation in health endpoints.

Implications

In time-series studies on acute health effects, exposure assessment is often based on ambient fixed-site measurements. It has been suggested that these ambient measurements correlate poorly with personal exposures, which raises questions about the plausibility of observed exposure-response relationships. Some recent studies, however, have shown that the time-series correlation between ambient and personal PM is reasonably high for PM_{10} and even higher for $PM_{2.5}$. This study shows that for elderly subjects with cardiovascular disease, both in Amsterdam and

in Helsinki, personal, indoor, and outdoor $PM_{2.5}$ concentrations are highly correlated. High correlations were also observed for a marker for EC, which is a major part of diesel soot. These findings provide further support for using fixed-site measurements as a measure of exposure to PM in time-series studies.

References

1. Dockery, D.W.; Pope, C.A., III. A Review of the Acute Respiratory Effects of Particulate Air Pollution; Annu. Rev. Pub. Health 1994, 15, 101–132.

2. Air Quality Criteria for Particulate Matter; EPA-600/P95/001cF; U.S. Environmental Protection Agency; ORD: Washington, 1996.

3. Schwartz, J. Air Pollution and Daily Mortality: A Review and Meta-Analysis; Environ. Res. 1994, 64, 36–52.

4. Brunekreef, B.; Dockery, D.W.; Krzyzanowski, M. Epidemiologic Studies of Health Effects of Low Levels of Major Ambient Air Pollution Components; Environ. Health Perspect. 1995, 103 (suppl. 2), 3–13.

5. Schwartz, J.; Dockery, D.W.; Neas, L.M. Is Daily Mortality Associated Specifically with Fine Particles? J. Air & Waste Manage. Assoc. 1996, 46, 927–939.

6. Dockery, D.W.; Pope, C.A., III; Xu, X.; Spengler, J.D.; Ware, J.H.; Fay, M.E.; Ferris, B.G.; Speizer, F.E. An Association between Air Pollution and Mortality in Six U.S. Cities; New Engl. J. Med. 1993, 329, 1753–1759.

7. Pope, C.A., III; Thun, M.J.; Namboodiri, M.M.; Dockery, D.W.; Evans, J.S.; Speizer, F.E.; Heath, C.W. Particulate Air Pollution as a Predictor of Mortality in a Prospective Study of U.S. Adults; Am. J. Respir. Crit. Care Med. 1995, 151, 669–674.

8. Peters, A.; Wichmann, H.E.; Tuch, T.; Heinrich, J.; Heyder, J. Respiratory Effects Are Associated with the Number of Ultrafine Particles; Am. J. Respir. Crit. Care Med. 1997, 155, 1376–1383.

9. Pekkanen, J.; Timonen, K.L.; Ruuskanen, J.; Reponen, A.; Mirme, A. Effects of Ultrafine and Fine Particles in Urban Air on Peak Expiratory Flow among Children with Asthmatic Symptoms; Environ. Res. 1997, 74, 24–33.

10. Dusseldorp, A.; Kruize, H.; Brunekreef, B.; Hofschreuder, P.; de Meer, G.; van Oudvorst, A.B. Acute Effects of PM10 and Airborne Iron on Respiratory Health: A Panel Study among Adults Living near a Steel Industry in the Netherlands; Am. J. Respir. Crit. Care Med. 1995, 152, 1932–1939.

11. Seaton, A.; MacNee, W.; Donaldson, K.; Godden, D. Particulate Air Pollution and Acute Health Effects; Lancet 1995, 345, 176–178.

12. Ozkaynak, H.; Xue, J.; Spengler, J.; Wallace, L.; Pellizzari, E.; Jenkins, P. Personal Exposure to Airborne Particles and Metals: Results from the Particle Team Study in Riverside, California; J. Exposure. Anal. Environ. Epidemiol. 1996, 6, 57–78.

13. Wallace, L. Indoor Particles: A Review; J. Air & Waste Manage. Assoc. 1996, 46, 98–126.

14. Janssen, N.A.H.; Hoek, G.; Harssema, H.; Brunekreef, B. Childhood Exposure to PM10: Relation between Personal, Classroom and Outdoor Concentrations; Occup. Environ. Med. 1997, 54, 888–894.

15. Janssen, N.A.H.; Hoek, G.; Brunekreef, B.; Harssema, H.; Mensink, I.; Zuidhof, A. Personal Sampling of PM10 among Adults: Relation between Personal, Indoor and Outdoor Concentrations; Am. J. Epidemiol. 1998, 147, 537–547.

16. Janssen, N.A.H.; Hoek, G.; Harssema, H.; Brunekreef, B. Personal Exposure to Fine Particles in Children Correlates Closely with Ambient Fine Particles; Arch. Environ. Health 1999, 54, 95–101.

17. Wolff, G.T. Characteristics and Consequences of Soot in the Atmosphere; Environ. Int. 1985, 11, 259–269.

18. Koistinen, K.J.; Kousa, A.; Tenhola, V.; Hänninen, O.; Jantunen, M.J.; Oglesby, L.; Kuenzli, N.; Georgoulis, L. Fine Particle (PM2.5) Measurement Methodology, Quality Assurance Procedures, and Pilot Results of the EXPOLIS Study; J. Air & Waste Manage. Assoc. 1999, 49, 1212–1220.

19. Janssen, N.A.H.; Hoek, G.; Harssema, H.; Brunekreef, B. Personal Sampling of Airborne Particles: Method Performance and Data Quality; J. Exposure Anal. Environ. Epidemiol. 1998, 1, 37–49.

20. Lioy, P.J.; Turner, W.; Marple, V.A. Intercomparison of the Indoor Air Sampling Impactor and the Dichotomous Sampler for a 10-µm Cut Size; J. Air Pollut. Control Assoc. 1988, 38, 668–670.

21. Marple, V.A.; Rubow, K.L.; Turner, W.; Spengler, J.D. Low Flow Rate Sharp Cut Impactors for Indoor Air Sampling: Design and Calibration; J. Air Pollut. Control. Assoc. 1987, 37, 1303–1307.

22. ISO 9835. Ambient Air–Determination of a Black Smoke Index. Geneva, Switzerland, 1993.

23. Cornbleet, P.J.; Gochman, N. Incorrect Least-Square Regression Coefficients in Method-Comparison Analysis; Clin. Chem. 1979, 25, 432–438.

24. VDI 2465. Measurement of Soot: Chemical-Analytical Determination of Elemental Carbon after Extraction and Thermodesorption of Organic Carbon (in German). Dusseldorf, Germany, 1995.

25. Buckley, T.J.; Waldman, J.M.; Freeman, N.C.G.; Lioy, P.D.; Marple, V.A.; Turner, W.A. Calibration, Intersampler Comparison, and Field Application of a New PM-10 Personal Air-Sampling Impactor; Aerosol Sci. Technol. 1991, 14, 380–387.

26. Rojas-Bracho, L.; Suh, H.H.; Koutrakis, P. Relationship Among Personal, Indoor, and Outdoor Fine and Coarse Particle Concentrations for Individuals with COPD; J. Expo. Anal. Environ. Epidemiol 2000; 10:294-306.

27. Fischer, P.H.; Hoek,G.; van Reeuwijk, H.; Briggs, D.J.; Lebret, E.; van Wijnen, J.H.; Kingham, S.; Elliot, P.E. Traffic-Related Differences in Outdoor and Indoor Concentrations of Particles and Volatile Organic Compounds in Amsterdam; Atmos. Environ., in press.

28. Hoek, G.; Forsberg, B.; Borowska, M.; Hlawiczka, S.; Vaskövi, E.; Welinder, H.; Branis, M.; Benes, I.; Kotesovec, F.; Hagen, L.O.; Cyrys, J.; Jantunen, M.; Roemer, W.; Brunekreef, B. Wintertime PM10 and Black Smoke Concentrations across Europe: Results from the PEACE Study; Atmos. Environ. 1997, 31, 3609–3622.

29. Ruuskanen, J.; Tuch, T.; ten Brink, H.; Peters, A.; Khlystov, A.; Mirme, A.; Kos, G.P.A.; Brunekreef, B.; Wichmann, H.E.; Buzorius, G.; Vallius, M.; Kreyling, W.G.; Pekkanen, J. Concentrations of Ultrafine, Fine and PM2.5 Particles in Three European Cities; Atmos. Environ. submitted for publication.

30. Burton, R.M.; Suh, H.H.; Koutrakis, P. Spatial Variation in Particulate Concentrations within Metropolitan Philadelphia; Environ. Sci. Technol. 1996, 30, 400–407.

31. Janssen, N.A.H.; van Vliet, P.H.N.; Aarts, F.J.H.; Harssema, H.; Brunekreef, B. Assessment of Exposure to Traffic Related Air Pollution of Children Attending Schools Near Motorways; Atmos. Environ. submitted for publication.

32. Kinney, P.L.; Aggarwal, M.; Northridge, M.E.; Janssen, N.A.H.; Shepard, P. Airborne Concentrations of PM2.5 and Diesel Exhaust Particles on Harlem Sidewalks: A Community-Based Pilot Study; Environ. Health Perspect. 2000, 108, 213–218.

33. Ulrich, E.; Israël, G.W. Diesel Soot Measurement under Traffic Conditions; J. Aerosol Sci. 1992, 23 (suppl. 1), S925–928.

34. Roorda-Knape, M.C.; Janssen, N.A.H.; de Hartog, J.J.; van Vliet, P.H.N.; Harssema, H.; Brunekreef, B. Air Pollution from Traffic in City Districts near Major Motorways; Atmos. Environ. 1998, 32, 1921–1929.

5 ASSOCIATIONS BETWEEN AMBIENT, PERSONAL, AND INDOOR EXPOSURE TO FINE PARTICULATE MATTER CONSTITUENTS IN DUTCH AND FINNISH PANELS OF CARDIOVASCULAR PATIENTS

Janssen NAH,[1,2] Lanki T,[3] Hoek G,[1] Vallius M,[3] de Hartog JJ,[1] Van Grieken R,[4] Pekkanen J,[3,5] and Brunekreef B[1]

[1] Division of Environmental and Occupational Health, Institute for Risk Assessment Sciences (IRAS), Utrecht University, The Netherlands

[2] National Institute for Public Health and the Environment (RIVM), Center for Environmental Health Research, Bilthoven, The Netherlands

[3] Environmental Epidemiology Unit, National Public Health Institute (KTL), Kuopio, Finland

[4] Department of Chemistry, University of Antwerp, Antwerp, Belgium

[5] Department of Public Health and General Practice, University of Kuopio, Finland

Abstract

Aims: To assess the relation between ambient, indoor, and personal levels of $PM_{2.5}$ and its elemental composition for elderly subjects with cardiovascular disease.

Methods: In the framework of a European Union funded study, panel studies were conducted in Amsterdam, the Netherlands and Helsinki, Finland. Outdoor $PM_{2.5}$ concentrations were measured at a fixed site. Each subject's indoor and personal $PM_{2.5}$ exposure was measured biweekly for six months, during the 24 hour period preceding intensive health measurements. The absorbance of $PM_{2.5}$ filters was measured as a marker for diesel exhaust. The elemental content of more than 50% of the personal and indoor samples and all corresponding outdoor samples was measured using energy dispersive *x* ray fluorescence.

Results: For Amsterdam and Helsinki respectively, a total of 225 and 238 personal, and 220 and 233 indoor measurements, were analysed from 36 and 46 subjects. For most elements, personal and indoor concentrations were lower than and highly

correlated with outdoor concentrations. The highest correlations (median r>0.9) were found for sulfur and particle absorbance, which both represent fine mode particles from outdoor origin. Low correlations were observed for elements that represent the coarser part of the $PM_{2.5}$ particles (Ca, Cu, Si, Cl).

Conclusions: The findings of this study provide support for using fixed site measurements as a measure of exposure to particulate matter in time series studies linking the day to day variation in particulate matter to the day to day variation in health endpoints, especially for components of particulate matter that are generally associated with fine particles and have few indoor sources. The high correlation for absorbance of $PM_{2.5}$ documents that this applies to particulate matter from combustion sources, such as diesel vehicles, as well.

Introduction

Numerous studies have demonstrated associations between day to day variations in ambient particulate matter concentrations and day to day variations in health endpoints such as mortality.[1–3] Most studies have used ambient particulate matter concentrations measured at central monitoring sites, as exposure variables. The plausibility of the epidemiological evidence has been challenged on the grounds that these ambient measurements may not properly reflect personal exposures. This criticism was supported by studies conducted in the 1980s to early 1990s that found that personal exposures to particulate matter were much higher than and poorly correlated with ambient concentrations.[4][5] A series of studies conducted in the Netherlands has shown that the correlation between ambient PM_{10} and personal exposure is much stronger if the analysis is conducted longitudinally (that is, within subjects over time), which is the relevant correlation for time series studies. The time series correlation between ambient and personal fine particles among a small group of primary school children, was even higher.[6–8] Several recent studies conducted in the US and Canada examined the longitudinal correlations for potentially sensitive subjects such as elderly and/or patients with chronic obstructive pulmonary disease (COPD).[9–13] These studies have shown variable results, with median individual correlation coefficients (r) ranging from 0.25 for 15 non-smoking elderly in Baltimore, MD in the winter of 1999[9] to 0.81 for 21 elderly also in Baltimore, MD in the summer of 1998.[11][12]

Personal particulate matter exposure includes particles both from ambient origin and indoor sources. To validate the use of central site monitoring as a proxy for personal exposure, we need to determine the correlation between personal exposure to particles from ambient origin and ambient concentrations.[14] One approach to achieve this is to use indicator elements that have little or no indoor sources. Several

studies have used sulfur (S) or sulfate for this purpose.[9–12] All of these studies reported higher correlations for sulfate than for $PM_{2.5}$ mass. This suggests that ambient fine particle concentrations could be adequate proxies for estimating personal exposure to fine particles from ambient origin in time series studies.

While the health effects of particulate matter are now generally accepted, the mechanism and the fraction of particulate matter responsible for the observed effects is less known. Some of the major current hypotheses for the responsible particle fraction are soluble transition metals, organic carbon compounds, strong aerosol acidity and ultrafine particles.[15] Other studies suggest that particles from specific sources, especially traffic related particles, are specifically associated with health effects. Laden et al[16] used data on outdoor elemental composition of $PM_{2.5}$ combined with factor analysis to assign measured $PM_{2.5}$ concentrations to particles from different sources. The approach uses indicator elements for sources (for example, Pb for traffic, Si for crustal sources). Little information is available on the time series correlation between personal exposure to particles from specific sources and ambient concentrations, or on the correlation between personal and ambient elemental (metal) concentrations.

We therefore studied the time series correlation between ambient, indoor, and personal $PM_{2.5}$ elemental concentrations in panels of elderly subjects with cardiovascular disease (CVD). Correlations for $PM_{2.5}$ mass concentrations in these same panels have been published previously.[17]

Methods

Study design

The study was conducted in the framework of a European Union funded panel study on the effects of exposure to outdoor fine and ultrafine particles on cardiovascular and respiratory health of elderly subjects with CVD (ULTRA study). The present personal exposure study was conducted in Amsterdam, the Netherlands, and in Helsinki, Finland, in the winter/spring of 1998/1999. A complete description of the study design and population characteristics has been published previously.[17] [18] Briefly, 24 hour average personal and indoor $PM_{2.5}$ exposures were measured biweekly for six months in 84 (37 in Amsterdam and 47 in Helsinki) nonsmoking elderly (age 50–84 years) with CVD. Outdoor concentrations were measured daily at a fixed site. In addition to gravimetric analyses, reflectance of all personal, indoor, and outdoor $PM_{2.5}$ filters was measured as a marker for elemental carbon, a major part of diesel soot.[19] Elemental composition of part of the personal and indoor samples and all outdoor samples was measured using energy dispersive *x* ray fluorescence (ED-XRF). Field measurements

took place from 2 November 1998 to 18 June 1999 in Amsterdam and from 1 November 1998 to 30 April 1999 in Helsinki.

Sampling methods

In both cities, the same sampling methods and standard operating procedures were used. Details about the sampling methods have been published elsewhere.[17] Briefly, personal, indoor, and outdoor $PM_{2.5}$ was measured using $PM_{2.5}$ GK2.05 cyclones (BGI Inc, Waltham, MA, USA) for personal sampling and the Harvard Impactor (ADE Inc, Naples, MA, USA) for indoor and outdoor sampling. Indoor samples were taken in the living room at about one metre height. Outdoor $PM_{2.5}$ concentrations were measured at fixed monitoring sites, representing urban background levels.

In both centres, filters were weighed using a Mettler MT5 micro-balance (Mettler-Toledo, Greifensee, Switzerland) with 1 mg reading. Particle reflectance was measured using EEL 43 reflectometers, and transformed into an absorption coefficient (ABS) according to ISO 9835.[20] This method is based on the old black smoke protocol,[21] with the exception of the particle cut size and filter material. Although the black smoke method involves a transformation from reflectance units into mass concentrations, these calculated mass concentrations are considered unreliable.[22] ABS is therefore expressed in $m^{-1} \times 10^{-5}$.

Measurements of elemental composition using ED-XRF

Elemental composition was measured using ED-XRF. Measurements were conducted by the Department of Chemistry of the University of Antwerp, Belgium, using an automated Tracor Spectrace 5000 ED-XRF system (Tracor *x* ray, Austin, TX, USA). Details have been published elsewhere.[23]

Only samples for which both the personal and indoor measurements, as well as the corresponding outdoor measurement, were successfully collected were considered eligible for *x* ray fluorescence analyses. This was the case for 337 pairs of personal and indoor samples in Amsterdam and 310 pairs in Helsinki. In both countries, one subject who had fewer than four valid pairs was excluded. For each subject, five (Helsinki) or six (Amsterdam) pairs of personal and indoor samples were randomly chosen. The difference between the two countries is caused by, on the one hand, the higher number of subjects in Helsinki (46 compared with 36 in Amsterdam) and, on the other hand, the longer observation period in Amsterdam (requiring a larger proportion of the available budget for analysis of outdoor samples). Out of the remaining, unselected, samples additional pairs of personal and indoor samples were

randomly chosen until the total number of budgeted analysis was reached. This resulted in 4–7 pairs per subject (for one subject only four pairs of samples were available). The total numbers of samples and duplicates analysed in both cities are included in table 1 and 2, respectively. In both cities, the difference between the number of personal and indoor samples is caused by the fact that one married couple participated, for which on five days the personal samples of both partners were selected, resulting in five fewer indoor samples that had to be analysed.

For each type of sample (personal, indoor, and outdoor), 10 field blanks per city were analysed. Median field blank values were subtracted from all sample values. Medians were used instead of means because field blank values were not normally distributed for all elements.

For each element the uncertainty per sample was calculated. This uncertainty is not only affected by analysis variables, such as calibration and system stability, but also by the concentration of the element in the sample. Uncertainty limits, calculated as three times the uncertainty, thus changed from sample to sample for each element, and increased with increasing concentrations. With the exception of the field blanks, measurements below the uncertainty limit were not reported by the Antwerp laboratory. We therefore set these measurements at two thirds of the uncertainty limit of the lower 25th percentile. We chose the 25th percentile instead of, for example, the average uncertainty limit of all reported values, because we expected the undetected values to be in the lower end of the distribution. Measurement that yielded negative concentrations after subtraction of the median field blank were set to zero. For elements that were used in the data analysis, this occurred only for Cu (five personal measurements in Amsterdam and one in Helsinki) and Ni (six indoor measurements in Amsterdam and one in Helsinki).

Statistical Methods and Data analysis

We assessed the correlation between personal, indoor, and outdoor concentrations by means of individual regression analysis, using the models published previously,[7] [17] and investigated the distribution of the individual regression results. Medians are presented because most correlation and regression coefficients were not normally distributed (Shapiro-Wilk Statistic, $p < 0.05$). Although all subjects were non-smokers, participants could still be exposed to ETS elsewhere, or at home in the case of a smoking spouse or visitor. To investigate the influence of ETS on the relation between personal, indoor, and outdoor $PM_{2.5}$, we conducted the same regression analyses after excluding days with ETS exposure. We excluded subjects with fewer than four remaining observations.

We performed additional analyses to estimate the (independent) contributions from outdoor and indoor air to personal exposure. This was achieved by including both indoor and outdoor concentrations as predictors of personal exposure in the same regression model:

$$C_{personal,\ it} = \alpha_i + \beta \times C_{outdoors,t} + \gamma \times C_{indoors,it}$$

where C= concentration, i=subject i, t=day.

Because of the small number of observations per subject and more than one explanatory variable in the model we did not specify individual multiple regression models, as in the previous analyses. The SAS procedure ''proc mixed'' was used to adjust regression results for correlations between repeated measurements. A random intercept model was used, as we did not expect any autocorrelation in the repeated measurements because measurements were conducted biweekly. We compared the results of individual regression analysis and the basic mixed model with models including an autoregressive covariance structure (AR(1)). We found that the model that specified an AR(1) yielded slopes and standard errors that were very similar to the results of the individual regression and random intercept model. Covariance parameter estimates for AR(1) were generally non-significant, consistent with the long approximately two week period in between successive measurements for the same individual. Addition of a random intercept for measurement date, to control for correlations between measurements that were conducted on the same day, also did not change the results (results not shown).

Results

Quality assurance and control

Percentages of samples that were above the uncertainty limit and remained positive after subtraction of the median field blank are given in table 1. Elements for which the percentages detected were lower than 50% for all three types of samples in one of the cities (Br, Cr, and Ti) were excluded in further analyses.

Median field blank values were generally similar for the two cities and different types of samples. Median field blanks were generally low (<10%) compared to the total amount measured for S, Zn, K, Ca, V, Si, and Cl. High field blank values (>500 ng/filter) were found for Pb and Al. Detailed information on field blanks is given elsewhere.[24]

Table 1. Percentages detected per sample type for Amsterdam and Helsinki (percentages <50 in bold)

	Amsterdam			Helsinki		
	Indoor (n=220)	Outdoor (n=228)	Personal (n=225)	Indoor (n=233)	Outdoor (n=168)	Personal (n=238)
S	100%	100%	100%	100%	100%	100%
Zn	100%	100%	100%	100%	100%	100%
Fe	100%	100%	100%	100%	100%	100%
K	100%	100%	100%	100%	100%	98%
Ca	100%	100%	100%	100%	99%	97%
Cu	100%	100%	98%	100%	98%	100%
Ni	97%	100%	83%	100%	99%	55%
Pb	89%	96%	75%	100%	83%	88%
Cl	80%	88%	58%	85%	71%	54%
Mn	93%	95%	66%	91%	95%	**45%**
Si	78%	**42%**	52%	89%	65%	89%
V	**40%**	63%	**8%**	62%	75%	52%
Al	52%	**41%**	52%	**24%**	64%	**20%**
Br	**47%**	71%	**9%**	**30%**	**42%**	**46%**
Cr	**18%**	**16%**	**3%**	**9%**	**8%**	**30%**
Ti	**16%**	**19%**	**2%**	**12%**	**15%**	**32%**

Table 2 presents coefficients of variation (CV) of duplicates, as a measure of precision, calculated as the median of the absolute percentage difference between co-located pairs divided by $\sqrt{2}$. Only duplicates for which at least one of the individual concentrations were detected are included.

Table 2. Precision (CV) of personal, indoor and outdoor XRF analysis by element in Amsterdam and Helsinki (median values > 25% are in bold)

	Amsterdam						Helsinki					
	Indoor n=10)		Outdoor (n=10)		Personal (n=5)		Indoor n=10)		Outdoor (n=10)		Personal (n=5)	
	n	Median	n	Median	n	Median	n	Median	n	Median	n	Median
PM$_{2.5}$	10	3.6	10	1.7	5	13.0	10	6.4	7	7.8	7	7.0
Abs	10	4.5	10	3.3	5	10.7	10	3.3	7	4.7	7	5.7
S	10	2.5	10	2.9	5	4.5	10	3.1	7	2.5	7	1.3
Zn	10	3.2	10	3.0	5	18.4	10	6.4	7	9.7	7	3.1
Fe	10	4.7	10	9.5	5	16.4	10	11.6	7	**35.4**	7	2.6
Ni	10	4.3	10	**33.6**	5	**70.8**	10	19.7	7	3.9	3	**35.7**
Mn	10	7.5	9	10.7	5	**39.0**	8	22.1	6	**41.2**	6	**141.4**
V	5	24.4	9	13.2	0		8	17.4	3	15.1	1	**32.5**
K	10	3.2	10	5.0	5	4.1	10	3.7	7	**30.0**	7	11.6
Ca	10	4.9	10	10.0	5	2.7	10	7.5	7	**46.2**	7	2.9
Cu	10	4.0	10	**43.8**	5	**34.0**	10	10.3	7	**64.3**	7	6.1
Si	8	11.7	3	12.1	4	22.3	10	13.6	7	**56.4**	6	23.9
Cl	8	9.3	8	23.0	3	14.5	8	5.1	1	**51.4**	5	6.9
Pb	9	**40.5**	10	**50.1**	4	20.3	10	14.2	7	**84.6**	6	**95.2**
Al	4	**89.7**	2	**26.0**	1	**141.4**	3	**141.4**	6	**30.4**	1	**141.4**

Coefficients of variation values were generally lowest for S (median CV <5% for all sample types). The poorest precision is found for outdoor duplicates in Helsinki, with median CV above 25% for nine out of the 13 elements. This low precision cannot readily be explained, especially since the precision of the personal duplicates appears to be better, despite the 2.5-fold lower sampled volume. All outdoor duplicates in Helsinki were conducted in the same one week period, which might not be representative for the full study period. In addition, despite the low precision of the outdoor duplicates of especially the soil related elements in Helsinki, the correlation among these elements was still relatively high, with Spearman r among Ca, Si, and Al ranging from 0.81 to 0.88 (data not shown). Only Pb and Al showed a consistent pattern of generally low precision and were therefore excluded from further analyses. In addition, personal concentrations of V, Mn, and Ni were excluded for combined reasons of poor detection and low precision.

Concentration levels and ratios

Concentration levels are generally fairly similar in Amsterdam compared with Helsinki (table 3). In outdoor air, the biggest difference is found for Si (median 14 ng/m^3 in Amsterdam compared to 94 ng/m^3 in Helsinki). Indoor Si levels were more similar, however. In Amsterdam, some subjects had very high personal or indoor concentrations as a result of exposure to ETS. ETS exposure in the living room and elsewhere occurred on 13% and 16% of the selected samples, respectively, whereas for Helsinki only one observation with ETS exposure occurred. For both PM$_{2.5}$ mass and most elements, excluding days with ETS exposure in Amsterdam resulted in a 5–15% reduction of median personal and indoor concentrations. The largest reduction was observed in personal Cl, for which the median concentration decreases from 40.8 to 16.5 ng/m3. Correlations among the different elements are published elsewhere.[24]

Figure 1 presents the distributions of individual median personal/indoor/outdoor ratios (n=36 in Amsterdam and n=46 in Helsinki). As a ratio based on replacement values only is highly unreliable, we excluded ratios for which both the denominator and the numerator were below the uncertainty limit. Personal/outdoor and indoor/outdoor ratios for PM$_{2.5}$ mass are below 1 and are similar for Amsterdam and Helsinki. For ABS, personal/outdoor and indoor/outdoor ratios are higher than those for PM$_{2.5}$ (but still <1) in Amsterdam, and similar to those for PM$_{2.5}$ in Helsinki. Personal/outdoor and indoor/outdoor ratios for S, Zn, Fe, Ni, Mn, and V are also below 1. In Amsterdam, personal/outdoor and indoor/outdoor ratios for these elements are similar to those for PM$_{2.5}$ mass, whereas in Helsinki these ratios are smaller to those observed for PM$_{2.5}$ mass. Personal/outdoor and indoor/outdoor ratios >1 are found for Ca, Cu (both cities), and Si (Amsterdam only). Personal/indoor ratios are generally similar to those for PM$_{2.5}$. Excluding days with ETS exposure in Amsterdam generally showed a small reduction in the overall median personal/outdoor and indoor/outdoor ratios. The variability in the individual median personal/outdoor and indoor/outdoor ratios (fig 1), however, decreased substantially for some elements, especially for K, for which the 75% percentile decreased from 3.3 to 1.2 for personal/outdoor ratios and from 4.4 to 1.6 for indoor/outdoor ratios.

Table 3. Distribution of personal, indoor, and outdoor concentrations in Amsterdam and Helsinki (PM$_{2.5}$ in µg/m^3; absorption in m^{-1}x10^{-5}; elements in ng/m^3)

	Amsterdam									Helsinki								
	Personal (n=225)			Indoor (n=220)			Outdoor (n=100)*			Personal (n=238)			Indoor (n=233)			Outdoor (n=70)*		
	Median	Min	Max	Median	Min	Max	Median	Min	Max	Median	Min	Max	Median	Min	Max	Median	Min	Max
PM$_{2.5}$	14.5	2.3	261.9	14.1	3.9	442.1	15.7	6.0	82.3	9.4	2.1	51.3	9.8	1.8	49.0	11.4	5.2	32.5
Abs	1.4	0.2	7.5	1.5	0.4	5.3	1.6	0.5	5.5	1.3	0.1	4.5	1.4	0.3	3.4	1.9	1.0	4.3
S	912.3	121.4	4,618.9	1100.6	42.6	4,965.4	1299.9	226.9	6,264.9	605.3	122.9	2097.4	811.6	165.7	2534.7	1435.7	303.8	3510.8
Zn	13.2	1.5	145.9	15.7	2.1	174.9	18.3	1.3	224.4	11.7	2.9	66.1	12.4	2.2	64.9	18.6	6.2	75.3
Fe	57.0	7.4	605.0	58.5	7.5	363.8	71.3	21.3	407.2	41.6	1.0	324.0	42.5	10.0	190.0	79.2	22.6	297.1
Ni	N.A.			1.4	0.0	9.2	1.7	0.1	13.1	N.A.			1.9	0.0	8.7	3.2	0.4	18.5
Mn	N.A.			2.7	0.4	28.2	3.1	0.3	36.9	N.A.			2.1	0.3	15.1	3.8	1.0	14.4
V	N.A.			2.7	2.0	14.2	4.1	2.4	21.3	N.A.			4.5	2.5	18.2	7.2	2.6	26.7
K	87.4	1.4	11,661.0	95.3	21.5	11,328.0	70.3	20.2	484.8	103.1	32.8	882.6	105.2	17.1	1667.2	93.9	26.8	431.9
Ca	72.9	18.6	1,603.0	65.9	13.5	812.4	40.2	14.6	119.1	68.5	21.6	316.3	45.3	10.8	380.4	36.4	11.6	154.6
Cu	5.4	0.0	78.2	8.1	0.9	98.4	2.5	0.3	17.8	4.3	0.0	85.3	5.5	1.2	54.1	1.8	0.1	22.6
Si	29.7	10.6	4,174.7	55.2	6.0	348.8	13.7	13.1	389.6	79.5	26.4	585.2	74.8	2.2	1030.2	93.9	16.1	662.4
Cl	40.8	13.0	13,997.7	59.2	6.2	14,388.6	72.7	8.8	1,789.4	9.8	7.9	410.6	31.9	4.6	1130.8	44.2	7.8	509.5

*Days that personal and indoor samples were selected for x ray fluorescence only.
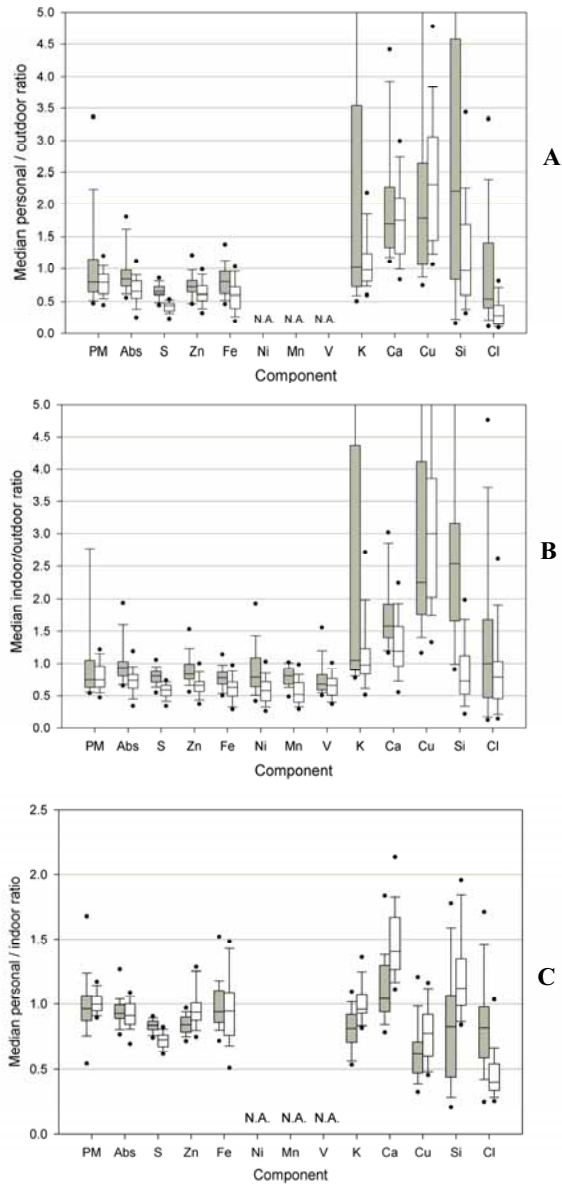
Figure 1. Distribution (5th, 10th, 25th, median, 75th, 90th, 95th percentiles) of individual median personal/outdoor ratios (A), indoor/outdoor ratios (B), and personal/indoor ratios (C) in Amsterdam (grey) and Helsinki (white).
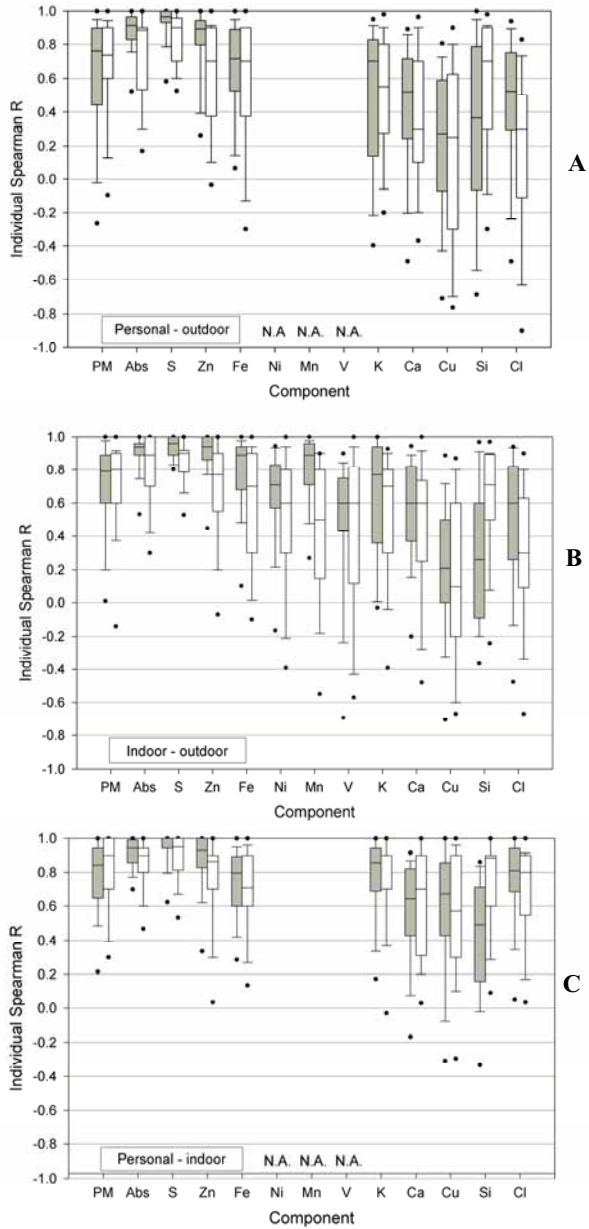
Relation between personal, indoor, and outdoor concentrations

Personal, indoor, and outdoor $PM_{2.5}$ concentrations were highly *correlated* (table 4; fig 2). Correlations between *personal and outdoor* ABS and S were higher and less variable than those for $PM_{2.5}$ in both cities (median Spearman r≥0.9). High correlations were also found for Zn and Fe, especially in Amsterdam. Correlations for the remaining elements are generally lower compared to $PM_{2.5}$ mass in both cities, with the poorest correlation observed for Cu. Excluding observations with ETS exposure resulted in slightly higher median correlations for some components. The correlations between *indoor and outdoor* elemental concentrations were generally similar or slightly higher than observed for personal-outdoor concentrations. Indoor-outdoor correlations for Ni, Mn, and V (not adequately available for personal samples) are in the same order of magnitude to the ones for $PM_{2.5}$ in Amsterdam, whereas they are somewhat lower in Helsinki. The correlations between *personal and indoor* elemental concentrations were in general high (r≥0.80), with the exception of Cu, Ca, Si (Amsterdam), and Fe (Helsinki).

For $PM_{2.5}$ mass, a median *slope* of the relation between personal/indoor and outdoor concentrations of about 0.5 is found in both cities (table 4). Personal-outdoor and indoor-outdoor slopes for ABS, S, and some of the transition metals (Zn, Fe, and Mn) are generally higher then those for $PM_{2.5}$ in Amsterdam, whereas slopes for these components are similar to those for $PM_{2.5}$ in Helsinki. For the mentioned elements with higher slopes in Amsterdam, the highest values are found for the relation between personal/ indoor and outdoor ABS and for the relation between indoor and outdoor S. Consistently lower personal-outdoor and indoor-outdoor slopes compared to the ones found for $PM_{2.5}$ mass are observed for Cu.

Independent contribution of indoor and outdoor air to personal exposure

The slopes in table 5 represent the independent contributions of indoor and outdoor air to personal exposure. For example, for non-ETS exposed subjects in Amsterdam a 10 µg/m^3 change in indoor or outdoor $PM_{2.5}$ will result in an 8.1 or 0.6 µg/m^3 change, respectively, in personal exposure. It should be noted, however, that the 0.6 µg/m^3 for outdoor air represents the *independent* contribution, that is the effect of outdoor air on personal exposure that is not through the impact of outdoor air on indoor air. Both in Helsinki and Amsterdam, slopes for outdoor air in the model with indoor air included were much smaller than in the model with only outdoor air included. Comparison of the standard errors of the two models showed that multicollinearity was not a major problem. Outdoor air remained a significant predictor for exposure for most elements including ABS, S, Zn, K,and Ca. For $PM_{2.5}$ only in Amsterdam a significant independent contribution of outdoor air was found.

Figure 2. Distribution (5th, 10th, 25th, median, 75th, 90th, 95th percentiles) of individual Spearman correlation coefficients between personal and outdoor concentrations (A), indoor and outdoor concentrations (B), and personal and indoor concentrations (C) for Amsterdam (grey) and Helsinki (white).

Table 4. Median Spearman R and regression slopes of the relation between personal, indoor and outdoor concentrations in Amsterdam and Helsinki.

	Amsterdam			Helsinki		
	Personal–Outdoor (n=36)	Indoor-Outdoor (n=35)	Personal-Indoor (n=35)	Personal-Outdoor (n=46)	Indoor-Outdoor (n=45)	Personal-Indoor (n=45)
Spearman r						
PM$_{2.5}$	0.76	0.79	0.84	0.74	0.80	0.90
Abs	0.91	0.94	0.94	0.89	0.89	0.90
S	0.96	0.96	1.00	0.90	0.90	0.95
Zn	0.89	0.94	0.93	0.70	0.77	0.86
Fe	0.71	0.89	0.80	0.70	0.70	0.71
Ni	N.A.	0.71	N.A.	N.A.	0.60	N.A.
Mn	N.A.	0.89	N.A.	N.A.	0.50	N.A.
V	N.A.	0.60	N.A.	N.A.	0.60	N.A.
K	0.70	0.77	0.86	0.55	0.70	0.90
Ca	0.52	0.60	0.64	0.30	0.60	0.70
Cu	0.27	0.21	0.67	0.25	0.10	0.57
Si	0.36	0.26	0.49	0.70	0.71	0.89
Cl	0.52	0.60	0.81	0.30	0.30	0.80
Slope						
PM$_{2.5}$	0.46	0.46	0.95	0.48	0.53	0.93
Abs	0.95	0.83	1.08	0.61	0.60	1.02
S	0.65	0.79	0.82	0.40	0.52	0.78
Zn	0.55	0.64	0.80	0.37	0.42	0.88
Fe	0.65	0.68	0.89	0.47	0.44	0.94
Ni	N.A.	0.44	N.A.	N.A.	0.38	N.A.
Mn	N.A.	0.69	N.A.	N.A.	0.36	N.A.
V	N.A.	0.47	N.A.	N.A.	0.35	N.A.
K	0.60	0.79	0.69	0.55	0.51	0.79
Ca	0.73	0.55	0.81	0.64	0.50	1.05
Cu	0.16	0.32	0.59	0.20	0.01	0.80
Si	0.39	0.62	0.74	0.35	0.47	0.73
Cl	0.53	0.60	0.93	0.00	0.08	0.31

Table 5. Contribution of indoor and outdoor air concentrations to personal exposure. Regression model includes indoor and outdoor concentrations simultaneously (Model 4 Methods: PE= β*Outdoor + γ*Indoor). (PM$_{2.5}$ in µg/m^3; Absorption in m^{-1}x10^{-5}; elements in ng/m^3)

	Amsterdam, all observations				Amsterdam, no ETS				Helsinki, all observations			
	Outdoor		Indoor		Outdoor		Indoor		Outdoor		Indoor	
	β	SE	γ	SE	β	SE	γ	SE	β	SE	γ	SE
PM$_{2.5}$	0.13$^{\#}$	0.08	0.54**	0.03	0.06**	0.02	0.81**	0.01	-0.02	0.02	0.97**	0.03
ABS	0.07	0.05	1.04**	0.05	0.25**	0.07	0.77**	0.08	0.06*	0.03	0.98**	0.04
S	0.18**	0.04	0.59**	0.05	0.24**	0.04	0.51**	0.05	0.05*	0.02	0.66**	0.04
Zn	0.27**	0.03	0.39**	0.04	0.31**	0.03	0.35**	0.05	0.09**	0.03	0.81**	0.05
Fe	0.07	0.09	0.78*	0.13	0.04	0.10	0.81**	0.16	0.04	0.06	0.90**	0.10
K	-0.29	0.25	0.87**	0.02	0.15*	0.06	0.62**	0.02	0.17**	0.04	0.57**	0.02
Ca	0.23	0.46	0.78**	0.17	0.22	0.46	0.77*	0.30	0.23**	0.07	0.84**	0.05
Cu	0.06	0.12	0.56**	0.03	0.06	0.13	0.57**	0.03	-0.12	0.17	0.79**	0.07
Si	-0.22	0.35	1.17**	0.37	0.03	0.12	0.81**	0.13	0.15**	0.03	0.44**	0.03
Cl	-0.03	0.04	0.95**	0.01	0.01	0.03	0.97**	0.02	-0.01	0.02	0.37**	0.02

$^{\#}$ p<0.10; * p<0.05; ** p<0.01

(personal= β x outdoor + γ x indoor). (PM$_{2.5}$ in µg/m^3; absorption in m^{-1} x 10^{-5}; elements in ng/m^3)

Discussion

In this study we found that personal and indoor PM$_{2.5}$ mass and elemental concentrations are generally lower than and longitudinally highly correlated with ambient concentrations. In both cities, we found the highest correlations for S and ABS (median Spearman r ≥0.9). Low correlations were found for Si (Amsterdam), Ca, Cu, and Cl.

Correlation between personal, indoor, and outdoor concentrations

Several recent studies have investigated the longitudinal correlation between personal and outdoor PM$_{2.5}$ concentrations. Of these studies, two were conducted among older subjects with COPD,[10][13] two among elderly (>64 years of age) in Baltimore, MD, USA9 11 and one among children in the Netherlands.8 Correlations between personal, indoor, and outdoor PM$_{2.5}$ in our study were lower than, or similar

to those found in three of those studies[8 11 13] and higher than those found in the other two studies.[9 10] In all studies, considerable variability in individual correlations was observed, ranging from negative correlations to values close to 1.0 for individual subjects. This variability can partly be the result of low precision of the individual estimates, caused by the limited number of observations per person. Differences in correlation between subjects (and between different study populations) can be caused by differences in home air exchange rates, indoor sources, time activity patterns and the range in concentrations.

The higher correlations we observed for S are consistent with the results of some other studies that included measurements of sulfate, two of which also observed very high correlations (median r>0.9).[10 25] A cross sectional study among 21 cardiovascular patients in Saint John, New Brunswick, Canada also documented a very high correlation between daytime personal and outdoor sulfate (r=0.95).[26] The high correlations for S and ABS can be explained by fewer indoor sources for these components and (for S) smaller spatial variation of outdoor air pollution. The correlations for S document that the correlation between outdoor concentrations and personal exposure to particles of ambient origin is even higher than for $PM_{2.5}$. This conclusion is valid only for particles with the same size distribution as sulfate, since particle size determines penetration in the home. The high correlations for ABS document that this also applies for particulate matter from diesel vehicles, as other known outdoor sources of elemental carbon, such as wood smoke or coal fly ash,[27] are probably of minor importance in the urban areas studied in our study.

When comparing the median Spearman r for the different elements to the ones observed for $PM_{2.5}$ mass, three main groups of components can be seen: elements with higher correlations between personal/indoor and outdoor concentrations compared to $PM_{2.5}$ (S and ABS in both cities, Zn in Amsterdam only); elements with correlations similar to those observed for $PM_{2.5}$ (Fe, Ni, Mn, V in both cities, Zn and Si in Helsinki) and elements with lower correlations compared to $PM_{2.5}$ (Si in Amsterdam, K, Ca, Cu, and Cl in both cities). The first group represents fine mode particles of mainly outdoor origin, with few indoor sources; the second group consists primarily of transition metals with variable sources, and the last group includes the soil and marine related elements, which represent the coarser part of the $PM_{2.5}$ particles. With the exception of Cl, elements of the last group also showed increased personal and/or indoor concentrations compared with outdoor concentrations, suggesting that the lower correlations for these elements are due to the influence of indoor sources. Larger spatial variability in outdoor concentrations may play a role as well.

In contrast to the growing number of studies on the time series correlation between personal and outdoor particulate matter mass concentrations, few other studies have

investigated these correlations for elemental concentrations or ABS. In the study in a retirement facility in Baltimore, elemental concentrations were used to calculate two summary variables: a SOIL variable calculated as the sum of the oxides of crustal elements (Si, Ca, Fe, Ti), and a trace element oxides (TEO) variable calculated as the sum of other atmospheric metal oxides. The correlations between personal, indoor, and outdoor concentrations for these summary variables were lower (median Pearson r<0.5 for TEO and <0.1 for SOIL) than observed for most individual elements of the same groups in our study. For $PM_{2.5}$ mass and sulfate, correlations were similar to our results (median Pearson r=0.82 for $PM_{2.5}$ and 0.92–0.95 for sulfate),[25] indicating that the general pattern of high correlations for sulfate and low correlations for soil related elements is consistent. In the EXPOLIS study, a population based study on $PM_{2.5}$ exposures of the adult, urban population in six European countries, cross sectional correlations between personal and outdoor concentrations reported for Basel, Switzerland, were also high for S and weak for Ca (as an indicator for crustal particles).[28] In addition, indoor ABS, measured in four of the EXPOLIS cities (Athens, Basel, Helsinki, and Prague) were highly correlated with outdoor levels.[29]

Personal, indoor, and outdoor concentration levels

Some other studies on personal $PM_{2.5}$ concentrations have also found lower personal compared with outdoor concentrations, [9] [11] whereas others documented increased personal $PM_{2.5}$ exposures.[8] [10] [13] For most elements, personal and indoor concentrations were also lower than outdoor concentrations, with the exception of K, Cu, and Ca in both cities and Si in Amsterdam. Median indoor/outdoor ratios of $PM_{2.5}$ mass and elemental concentrations in Helsinki were generally similar to those observed in Helsinki in the EXPOLIS study.[30] For example, the median indoor/outdoor ratio in the EXPOLIS study in the winter season was 0.77 for $PM_{2.5}$ mass, 0.60 for S, and 0.65 for black smoke, compared with 0.79, 0.61, and 0.75, respectively, for $PM_{2.5}$, S, and ABS in Helsinki in our study. In the study in the retirement facility in Baltimore, personal (mean 13 $\mu g/m^3$) and indoor (mean 10 $\mu g/m^3$) were much lower than outdoor (mean 21 $\mu g/m^3$) $PM_{2.5}$ concentrations. For sulfate a similar pattern was found. Indoor and personal SOIL concentrations, however, were 10–20% higher than outdoor concentrations, whereas for TEO personal, indoor, and outdoor concentration were similar. When evaluating the slopes of the regression equations instead of the personal/indoor/outdoor ratios, slopes of the relation between personal and outdoor or between indoor and outdoor concentrations were similar for $PM_{2.5}$, sulfate and TEO concentrations, with median slopes ranging from 0.38 to 0.46 for the different components and models. For SOIL concentrations, however, median slopes were much lower (0.05–0.12).[25] These

results are in line with the finding of our study of comparable personal/indoor-outdoor slopes for S and the transition metals, and a higher influence of indoor generated particles for the soil related elements.

Median outdoor $PM_{2.5}$ mass concentrations were about 40% higher in Amsterdam compared with Helsinki. This difference was not reflected in higher elemental concentrations in Amsterdam, however. The small difference in ABS is consistent with the fact that "soot" in current day Western European cities is mostly related to traffic emissions, especially diesel engines. In the PEACE study, outdoor PM_{10} concentrations measured in the winter of 1993/1994 were also about twofold higher in Amsterdam than in Kuopio, Finland, whereas black smoke concentrations were similar.[31] Part of the higher PM levels in Amsterdam could possibly be due to higher nitrate concentrations, a result of the high ammonia levels in the Netherlands resulting from intensive livestock farming.

Independent contributions of indoor and outdoor air to personal exposure

When indoor and outdoor air concentrations were included simultaneously in one linear regression model to explain personal exposure, substantially higher slopes were found for indoor air. The slopes for outdoor air were much smaller compared with the slopes without indoor concentrations in the model. This should not be interpreted to imply that outdoor air has only very little effect on personal exposure, as indoor and outdoor concentrations were highly correlated which we interpret as a result of penetration of outdoor air in the home. The regression model with both indoor and outdoor concentrations in the model only shows the *independent* contribution of outdoor air to personal exposure, that is the effect of outdoor air on 24 hour average personal exposure that is not through the impact of outdoor air on indoor air. The results are thus consistent with the notion that most of the contribution of outdoor air to personal exposure is through its contribution to indoor air. Direct effects on personal exposure are much smaller. This is consistent with the short time spent outdoors for this population (about 1 hour/day). One implication of this finding is that factors that influence indoor/outdoor relations such as home air exchange rate can have a large effect on personal exposures. Another implication is that exposure assessment should include characterisation of home address (indoor and outdoor) concentrations.

Generalisability and limitations

Comparison of the correlation between personal and outdoor concentrations in our current study with those reported in the literature suggests that we cannot expect that the exact quantitative values we found can be transferred directly to other locations

and populations. We do expect that the major conclusions drawn from the correlation patterns hold in many other current day Western populations as well. This refers to the high longitudinal correlation between personal and outdoor $PM_{2.5}$ supporting the use of outdoor concentrations as an exposure estimate in time series studies; the very high correlation between personal and outdoor S; and the generally high correlation between personal and indoor elemental concentrations. The broadly similar patterns we observed in Amsterdam and Helsinki, in spite of the differences in climate, ETS exposure, and frequency of the use of gas for cooking, support this statement.

For the interpretation of our results, the following features are important. Firstly, the study population consisted of subjects with CVD who are probably at higher risk to respond to ambient air pollution. Secondly, subjects spent a large amount (88%) of their time in their own home. Thirdly, all subjects were non-smokers but especially in Amsterdam ETS exposure was relatively frequent. Fourthly, personal exposure monitoring was mostly conducted in the winter season, when air exchange rates are presumably low, especially in Finland. Low air exchange rates have been shown to result in lower correlations between outdoor and indoor air. Fifthly, subjects lived within a 2–4 km radius of the central monitoring site. We do not expect that this relatively small area has increased the personal-outdoor correlation substantially, especially for $PM_{2.5}$ and components that are mostly associated with the fine particle fraction and have little spatial variation. Finally, Amsterdam and Helsinki are both large cities with few large industrial sources within the built up area. In both cities altitude differences do not play a role. In more complex cities with large local sources, spatial variation of outdoor air pollution may be more substantial. In this case it can be expected that the correlation of outdoor air pollution measured at one central site with personal (and home outdoor) concentration is lower.

Conclusions

This study has shown that personal, indoor, and outdoor $PM_{2.5}$ concentrations are highly correlated in cardiovascular patients in two European cities. The correlation for specific components of $PM_{2.5}$ (S and ABS) were higher than for $PM_{2.5}$, indicating that personal exposure to ambient origin $PM_{2.5}$ is even more closely associated with outdoor $PM_{2.5}$. The results of this study together with the results of other recent studies have documented that short term increases in outdoor air pollution are reflected in increased personal exposures, also for potentially susceptible subjects who (because of their illness) spend most of their time indoors. The findings of this study provide further support for using fixed site measurements as a measure of exposure to particulate matter in time series studies linking the day to day variation in particulate matter to the day to day variation in health endpoints, especially for components of particulate matter that are generally associated with fine mode

particles and have few indoor sources. The high correlation for ABS documents that, for non-smoking elderly living in the urban areas included in our study, this applies to particulate matter from combustion sources such as diesel vehicles as well.

Main messages

Personal and indoor daily $PM_{2.5}$ mass concentrations for elderly with cardiovascular disease in two European cities (Amsterdam and Helsinki) were lower than and highly correlated with outdoor concentrations.

The correlations between personal and outdoor concentrations for S and ABS were higher than for $PM_{2.5}$, indicating that personal exposure to $PM_{2.5}$ of ambient origin is even more closely associated with outdoor $PM_{2.5}$.

Low correlations were observed for elements that represent the coarser part of the $PM_{2.5}$ particles and/or can have important indoor sources (Ca, Cu, Si).

Policy implications

The study shows that short term increases in outdoor fine particles are reflected in increased personal exposures, and also for potentially susceptible subjects who spend most of their time indoors.

Studies investigating the short term effects of outdoor fine particles (time series studies, panel studies) can therefore rely on outdoor concentrations as a measure of exposure.

The high correlation for ABS shows that, for the urban areas included in our study, this applies to particulate matter from combustion sources such as diesel vehicles as well.

Acknowledgements

References

1 Dockery DW, Pope CA III. A review of the acute respiratory effects of particulate air pollution. Annu Rev Public Health 1994;15:101–32.

2 Schwartz J. Air pollution and daily mortality: a review and meta-analysis. Environ Research 1994;64:36–52.

3 Brunekreef B, Dockery DW, Krzyzanowski M. Epidemiologic studies of health effects of low levels of major ambient air pollution components. Environ Health Perspect 1995;103(suppl 2):3–13.

4 Ozkaynak H, Xue J, Spengler J, et al. Personal exposure to airborne particles and metals: Results from the particle team study in Riverside, California, J Exp Anal Environ Epidemiol 1996;6:57–78.

5 Wallace L. Indoor particles: A review. J Air Waste Manage Assoc 1996;46:98–126.

6 Janssen NAH, Hoek G, Harssema H, et al. Childhood exposure to PM_{10}: relation between personal, classroom and outdoor concentrations. Occup Environ Med 1997;54:888–94.

7 Janssen NAH, Hoek G, Brunekreef B, et al. Personal sampling of PM_{10} among adults: relation between personal, indoor and outdoor concentrations. Am J Epidemiol 1998;147:537–47.

8 Janssen NAH, Hoek G, Harssema H, et al. Personal exposure to fine particles in children correlates closely with ambient fine particles. Arch Environ Health 1999;54:95–101.

9 Sarnat JA, Koutrakis P, Suh HH. Assessing the relationship between personal particulate and gaseous exposures of senior citizens living in Baltimore, MD. J Air Waste Manage Assoc 2000;50:1184–98.

10 Ebelt ST, Petkau AJ, Vedal S, et al. Exposure of chronic obstructive pulmonary disease patients to particulate matter: Relationship between personal and ambient air concentrations. J Air Waste Manage Assoc 2000;50:1081–94.

11 Williams R, Suggs J, Zweidinger R, et al. The 1998 Baltimore Particulate Matter Epidemiology-Exposure Study: Part I. Comparison of ambient, residential outdoor, indoor and apartment particulate matter monitoring. J Expo Anal Environ Epidemiol 2000;10:518–32.

12 Williams R, Suggs J, Creason J, et al. The 1998 Baltimore Particulate Matter Epidemiology-Exposure Study: Part 2. Personal exposure assessment associated with an elderly study population. J Expo Anal Environ Epidemiol 2000;10:533–43.

13 Rojas-Bracho L, Suh HH, Koutrakis P. Relationship among personal, indoor, and outdoor fine and coarse particle concentrations for individuals with COPD. J Expo Anal Environ Epidemiol 2000;3:294–306.

14 Wilson WE, Suh HH. Fine particles and coarse particles: concentration relationships relevant to epidemiologic studies. J Air Waste Manag Assoc 1997;47:1238–49.

15 US EPA. Air quality criteria for particulate matter (third external review draft). 2002 http://cfpub.epa.gov/ncea/cfm/partmatt.cfm?ActType = default (accessed 5 September 2005).

16 Laden F, Neas LM, Dockery DW, et al. Association of fine particulate matter from different sources with daily mortality in six U.S. cities. Environ Health Perspect 2000;108:941–7.

17 Janssen NAH, de Hartog JJ, Hoek G, et al. Personal exposure to fine particulate matter in elderly subjects: relation between personal, indoor, and outdoor concentrations. J Air Waste Manag Assoc 2000;50:1133–43.

18 Pekkanen J, Timonen KL, Tiittanen P, et al. ULTRA: Exposure and risk assessment for fine and ultrafine particles in ambient air. Study manual and data book. KTL Report B9/2000 (http://www.ktl.fi/ultra).

19 Janssen NAH, Vliet PHN van, Aarts FJH, et al. Assessment of exposure to traffic related air pollution of children attending schools near motorways. Atmos Environ 2001;35:3875–84.

20 ISO 9835. 1993. Ambient air—Determination of a black smoke index.

21 OECD. 1964. Methods of measuring air pollution. Organization for Economic Cooperation and Development, Paris.

22 Edwards JD, Ogren JA, Weiss RE, et al. A comparison of British smoke with optical absorption coefficient and elemental carbon concentrations. Atmos Environ 1983;17:2337–41.

23 Samek L, Injuk J, Van Espen P, et al. Performance of a new compact EDXRF spectrometer for aerosol analysis. X-Ray Spectrometry 2002;31:84–6.

24 Brunekreef B, Janssen NAH, de Hartog J. Personal, indoor and outdoor exposures to $PM_{2.5}$ and its components for groups of cardiovascular patients in Amsterdam and Helsinki, Research Report 127. Health Effects Institute, Boston, MA.

25 Landis MS, Norris GA, Williams RW, et al. Personal exposures to $PM_{2.5}$ mass and trace elements in Baltimore, MD, USA. Atmos Environ 2001;35:6511–24.

26 Stieb DM, Brook JR, Broder I, et al. Personal exposure of adults with cardiorespiratory disease to particulate acid and sulfate in Saint John, New Brunswick, Canada. Appl Occup Environ Hyg 1998;13:461–8.

27 Schauer JJ. Evaluation of elemental carbon as a marker for diesel particulate matter. J Expo Anal Environ Epidemiol 2003;13:443–53.

28 Oglesby L, Kunzli N, Roosli M, et al. Validity of ambient levels of fine particles as surrogate for personal exposure to outdoor air pollution—results of the European EXPOLIS-EAS study (Swiss Center Basel). J Air Waste Manage Assoc 2000;50:1251–61.

29 Gotschi T, Oglesby L, Mathys P, et al. Comparison of black smoke and $PM_{2.5}$ levels in indoor and outdoor environments of four European cities. Environ Sci Technol 2002;36:1191–7.

30 Koistinen KJ, Edwards RD, Mathys P, et al. Sources of $PM_{2.5}$ in personal exposures and residential indoor, outdoor and workplace microenvironments in EXPOLIS-Helsinki, Finland. Scand J Work Environ Health 2004;30(suppl 2):36–46.

31 Hoek G, Forsberg B, Borowska M, et al. Wintertime PM10 and black smoke concentrations across Europe: Results from the PEACE study. Atmos Environ 1997;31:3609–22.

6 DETERMINANTS OF PERSONAL AND INDOOR PM$_{2.5}$ AND ABSORBANCE AMONG ELDERLY SUBJECTS WITH CORONARY HEART DISEASE

Lanki T,[1] Ahokas A,[1] Alm S,[2] Janssen NAH,[3] Hoek G,[4] de Hartog JJ,[4] Brunekreef B,[4] and Pekkanen J[1,5]

[1] Environmental Epidemiology Unit, National Public Health Institute (KTL), Kuopio, Finland

[2] Technical and Environmental Affairs, City of Lahti, Finland

[3] Center for Environmental Health Research, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands

[4] Division of Environmental and Occupational Health, Institute for Risk Assessment Sciences (IRAS), Utrecht University, The Netherlands.

[5] Department of Public Health and General Practice, University of Kuopio, Finland

Abstract

Epidemiological studies have established an association between outdoor levels of fine particles (PM$_{2.5}$) and cardiovascular health. However, there is little information on the determinants of PM$_{2.5}$ exposure among persons with cardiovascular disease, a potentially susceptible population group. Daily outdoor, indoor, and personal PM$_{2.5}$ and absorbance (proxy for elemental carbon) concentrations were measured among elderly subjects with cardiovascular disease in Amsterdam, the Netherlands, and Helsinki, Finland, during the winter and spring of 1998-1999 within the framework of the ULTRA study. There were 37 non-smoking subjects in Amsterdam and 47 in Helsinki. In Amsterdam, where there were enough exposure events for analyses, exposure to environmental tobacco smoke (ETS) indoors was a major source of between-subject variation in PM$_{2.5}$ exposures, and a strong determinant of PM$_{2.5}$ and absorbance exposures. When the days with ETS exposure were excluded, within-subject variation accounted for 89% of the total variation in personal PM$_{2.5}$, and 97% in absorbance in Amsterdam. The respective figures were 66% and 61% in Helsinki. In both cities, outdoor levels of PM$_{2.5}$ and absorbance were determinants of personal and indoor levels. Traffic was also an important determinant of absorbance: living near a major street increased exposure by 22%, and every hour spent in a motor

vehicle by 13% in Amsterdam. The respective increases were 37% and 9% in Helsinki. Cooking was associated with increased levels of both absorbance and $PM_{2.5}$. Our results demonstrate that by using questionnaires in connection with outdoor measurements, exposure estimation of $PM_{2.5}$ and its combustion originating fraction can be improved among elderly persons with compromised health.

Introduction

Daily changes in the levels of ambient fine particles ($PM_{2.5}$; aerodynamic diameter < 2.5 μm) measured at fixed outdoor monitoring sites have been associated with cardiorespiratory health in epidemiological studies (Samet et al., 2000; Le Tertre et al., 2002). Recent studies suggest that particles originating from traffic are especially harmful (Hoek et al., 2002; Peters et al., 2004). Reflectance of $PM_{2.5}$ filters, transformed into absorbance (ABS), can be used as an indicator for diesel and other combustion particles (Cyrus et al., 2003).

Individuals spend most of their time indoors and conduct there particle generating activities. Consequently, the use of outdoor $PM_{2.5}$ concentrations to estimate personal exposure has been questioned. *Cross-sectional* correlation between outdoor and personal $PM_{2.5}$ has often been fairly low, although higher for ambient and combustion originating components of $PM_{2.5}$ (Patterson et al., 2000; Gotschi et al., 2002; Janssen et al., 2005). However, *longitudinal* correlation has often been higher (Janssen et al., 1998; Janssen et al., 1999). 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. The amount of within-subject variation also determines how many repeated measurements are needed to accurately estimate average individual exposure over a longer time period.

The fraction of within-subject variation in exposure unexplained by outdoor concentrations could be reduced by including in a study questions on time-varying factors possibly influencing exposure. Questionnaires can also be used to collect information on factors influencing between-subject variance, factors constant over the study period. By identifying and quantifying determinants of exposure, accuracy of exposure estimation could be improved in epidemiological studies. The information can also be used in the construction of exposure models. The determinants of $PM_{2.5}$ most often identified (besides outdoor concentrations) are exposure to environmental tobacco smoke (ETS) and cooking events (Özkaynak et al., 1996; Wallace et al., 2003; He et al., 2004).

Persons with cardiovascular disorders are proposed to be especially vulnerable to the effects of particles on health (von Klot et al., 2005). Due to their compromised health and high mean age, they usually spend more time at home and engage fewer

activities than general population, and thus have potentially lower and less variable exposures. There are only few studies evaluating the determinants of $PM_{2.5}$ exposures among elderly with compromised cardiovascular health (Liu et al., 2003), but more studies have been conducted among persons with chronic obstructive pulmonary disease, another susceptible population group (Ebelt et al., 2000; Rojas-Bracho et al., 2004). However, determinants of combustion originating $PM_{2.5}$ have not been evaluated in these studies.

Within the framework of the ULTRA study (Pekkanen et al., 2000), outdoor, indoor and personal $PM_{2.5}$ and absorbance were measured among persons with coronary heart disease in Amsterdam, the Netherlands, and Helsinki, Finland (Brunekreef et al. 2005). Within the study population, both $PM_{2.5}$ and absorbance exposures have been shown to correlate longitudinally reasonably well with outdoor concentrations (Janssen et al., 2000). The aim of the current study was to identify the factors determining the personal and indoor concentrations. In addition, the within- and between-subject components of variation in $PM_{2.5}$ and absorbance were evaluated.

Methods

The study was conducted in Amsterdam, the Netherlands, and Helsinki, Finland, during the winter and spring of 1998-1999. In both cities, participants of a larger epidemiological ULTRA study (Pekkanen et al., 2000), carried a personal measurement system for 24 hours preceding the biweekly clinic visits for determination of exposure to $PM_{2.5}$ and absorbance. At the same time, outdoor levels of the pollutants were monitored at a central site, and indoor levels in the participants' living rooms. Personal, indoor and outdoor measurements were conducted following the same standard operating procedures in both cities (Brunekreef et al., 2005).

All participants of the study were nonsmokers (although in Amsterdam 4 participants lived with someone who smoked regularly), 50-84 years of age, and had a doctor-diagnosed coronary artery disease according to self-report. Besides cardiac disease, 24% of patients in Amsterdam had COPD (0% in Helsinki). There were 2 persons in Amsterdam and 1 in Helsinki working part-time, all the others were retired. Details of the study panels have been reported elsewhere (Ibald-Mulli et al., 2003).

Personal measurements of $PM_{2.5}$ were conducted using GK2.05 cyclones (BGI, Inc. Waltham, MA, USA), and battery-operated pumps at flow rate of 4 l/min. Participants were instructed to carry the measurement system always with them, but were allowed to place the sampler nearby during indoor sedentary activities, or when carrying the sampler would have been impossible or too inconvenient; these occasions were recorded. Harvard Impactors and flow-controlled pumps (A.D.E.

Inc., model SP-280E) at flow rate of 10 l/min were used for indoor $PM_{2.5}$ sampling. The sampling height was 1 meter. The methods of personal, indoor and outdoor measurements are described in a paper by Janssen et al. (2000).

$PM_{2.5}$ filters were weighed using a Mettler MT5 micro-balance (Mettler-Toledo, Greifensee, Switzerland) with 1-µg reading. After weighing, reflectance of the filters was measured with a reflectometer (Model 43, Diffusion Systems Ltd., UK), and transformed into absorbance (absorption coefficient) according to ISO 9835 standard (1993):

absorbance = $((A/2)/V)) \cdot \ln (R_F / R_S)$, where

R_S is the reflectance of the sample filter as percentage of R_0

R_0 is the reflectance of the clean control filter (100.0 by definition)

R_F is the average reflectance of the field blank filters as percentage of R_0

V   is the volume sampled (in m^3)

A   is the area of the stain on the filter ($780 \times 10^{-6} m^2$)

The unit of absorbance in the current paper is $m^{-1} \cdot 10^{-5}$. The laboratory methods and quality control results have been reported elsewhere (Janssen et al., 2000; Brunekreef et al., 2005).

Information on patient and housing characteristics and behavior potentially determining exposure was collected with questionnaires. Baseline questionnaires filled in by researchers were used to collect information on variables that did not change during the study period (called permanent determinants in this study), such as gender, education, and the vicinity of a major street to residence. A self-administered questionnaire, filled in during each 24 h measurement, was used to obtain information on time-varying determinants, for example, exposure to environmental tobacco smoke (ETS), time spent (h) in different microenvironments, and cooking.

Distributions of indoor and personal $PM_{2.5}$ and absorbance were strongly skewed right with some very extreme values. To assure variance homogeneity and normal distribution of residuals in regression analyses, natural logarithms were taken from all exposure data. Even after logarithmic transformation, two indoor absorbance values in Amsterdam, and one value for personal $PM_{2.5}$ and absorbance in Helsinki, were more than 3 interquartile ranges away from the 75th percentile value. Multi-

determinant models were run also without the three values to evaluate the effect of the extremes on the results.

All statistical analyses were performed using mixed models (PROC MIXED procedure) in SAS statistical software version 8.02 (SAS Institute Inc., 1999-2001). To take into account that several, most likely correlating measurements were conducted on every subject, subject effects were included in the models as random-effects (random intercept). Because the repeated measurements were conducted in 2-week intervals, simple compound symmetry was considered a reasonable choice for the covariance structure.

Variance components in the data, i.e. within-subject and between-subject variation, were calculated using restricted maximum likelihood estimation. In the analyses, no-ETS indoor data included the measurements without ETS exposure at home, whereas in no-ETS exposure data, all measurements with ETS at home or elsewhere indoors were excluded.

Associations of questionnaire variables with $PM_{2.5}$ and absorbance were first evaluated in models including only one potential determinant at a time. To evaluate the effects of permanent determinants, subject-specific (individual) averages of $PM_{2.5}$ and absorbance were included in the models, in the case of time-variant factors subjects were again treated as random factors. To take into account that confounding factors might cause spurious associations in one-determinant models, multi-determinant models were also constructed. All the other determinants except the time spent in different microenvironments (outdoors, at home, indoors elsewhere, in a motor vehicle) were treated as binary variables, as there were no strong indications of linear relationships between the determinants and the pollutants in one-determinant models. The "final" model was constructed separately for all measures of exposure by starting from a model including all available determinants, and then dropping the variables one by one based on p-value, until p-values of all remaining determinants were below 0.1 (backward stepwise elimination). After the selection process, the variables that were found to fulfill the p-value criteria in one city were added in the model of the other one, if not otherwise included. The effect estimates for determinants are expressed as percentages: $(e^{estimate}-1) \times 100\%$.

Results

In Amsterdam, there were 3 to 13 personal measurements, and 6 to 15 indoor measurements per subject from 37 study participants. In Helsinki, there were 2 to 9 personal measurements and 7 to 12 indoor measurements per subject from 47 participants. In Amsterdam, study participants spent on average 22.5 hours per day indoors (21.1 hours at own home), in Helsinki 22.4 (21.3). In Amsterdam, 76% of

the participants used regularly gas stove for cooking, in Helsinki 11%. There was central heating in all residences in both cities.

Descriptive statistics for outdoor, indoor and personal $PM_{2.5}$ and absorbance are presented in Table 1. The statistics have been calculated using pooled data (n=260-503). In Amsterdam, mean levels of both $PM_{2.5}$ and absorbance decreased when the days with ETS exposure were excluded. In Helsinki, the effect of ETS could not be evaluated, because of the low number of ETS episodes (1.3-3.3% of measurements, depending on the pollutant). Mean levels of $PM_{2.5}$ were higher in Amsterdam than in Helsinki, even after exclusion of ETS exposures. In both cities, mean levels of indoor and personal $PM_{2.5}$ and absorbance were lower than outdoor levels.

In Table 2 are presented (total) variances of pollutants on log-scale, and the between- and within-subject components of variability. In Amsterdam, exposure to ETS accounted for much of the total variance and between-subject variation especially for $PM_{2.5}$. Even after exclusion of ETS, variability in the pollutant levels was higher in Amsterdam than in Helsinki. In both cities, within-subject variation was larger than between-subject variation with one exception: indoor $PM_{2.5}$ in Amsterdam when ETS exposures were included.

Median levels of $PM_{2.5}$ and absorbance in the categories of permanent determinants of exposure are presented in Table 3. Asterisks represent the significance levels of the differences between the categories tested using $\log_n$ -transformed data. The presence of a regular smoker at home was significantly associated with higher $PM_{2.5}$ and absorbance levels in Amsterdam. In Helsinki, there were no regular smokers. In both cities, living within 100 m from a major street was associated with higher absorbance levels, but only in Amsterdam significantly also with $PM_{2.5}$ levels. Living in the first two floors of a building was associated with lower $PM_{2.5}$ and absorbance levels in Helsinki. Keeping living room windows open was more common (22%) among those living in the upper floors than in the first two floors (9%) (data not shown). In Helsinki, also the age of the building seemed to have effect especially on absorbance. In Amsterdam, pollutants levels were higher in the older buildings, but no significant associations were observed. In Amsterdam, there was a suggestion that having a parking lot within 100 meters would increase especially absorbance, but the number of residents having parking lot in the vicinity was low (Table 3).

Table 1. Descriptive statistics for daily levels of outdoor, indoor and personal PM$_{2.5}$ and absorbance.

			n$_s$	n	AM	GM	GSD	50%	75%	95%
Amsterdam										
PM$_{2.5}$ ($\mu g/m^3$)	All	Personal	37	337	22.2	14.9	2.3	13.6	23.1	72.8
		Indoor	36	409	29.1	16.6	2.4	13.6	24.2	119.4
		Outdoor		409	20.8	17.2	1.8	16.5	28.9	47.1
	No ETS	Personal	32	260	14.5	11.7	2.0	11.7	16.9	29.8
		Indoor	34	353	15.8	13.0	1.8	12.3	18.5	33.7
ABS ($m^{-1}x10^{-5}$)	All	Personal	37	337	1.68	1.33	1.98	1.26	2.09	4.15
		Indoor	36	409	1.84	1.53	1.83	1.50	2.43	4.29
		Outdoor		409	1.82	1.61	1.65	1.63	2.29	3.52
	No ETS	Personal	32	260	1.41	1.15	1.86	1.14	1.69	3.14
		Indoor	34	353	1.61	1.38	1.74	1.35	2.02	3.42
Helsinki										
PM$_{2.5}$ ($\mu g/m^3$)	All	Personal	47	336	10.9	9.5	1.7	9.2	13.0	21.6
		Indoor	46	503	11.0	9.5	1.7	9.2	13.0	21.7
		Outdoor		463	12.7	11.6	1.5	11.1	15.8	23.6
	No ETS	Personal	47	325	10.8	9.4	1.7	9.1	12.8	20.9
		Indoor	46	495	10.9	9.4	1.7	9.1	12.8	21.5
ABS ($m^{-1}x10^{-5}$)	All	Personal	47	336	1.52	1.26	1.82	1.30	1.90	2.98
		Indoor	46	503	1.58	1.39	1.65	1.41	1.98	2.86
		Outdoor		463	2.05	1.93	1.41	1.91	2.47	3.56
	No ETS	Personal	47	325	1.52	1.28	1.83	1.30	1.90	2.98
		Indoor	46	495	1.58	1.39	1.65	1.41	1.97	2.90

No ETS = only measurements where no exposure to environmental tobacco smoke anywhere indoors (personal measurements) or at own living room (indoor measurements).

n$_s$ = number of subjects; n = number of measurements; AM = arithmetic mean; GM = geometric mean GSD = geometric standard deviation; 50%-95% = 50th-95th percentile.

Table 2. Total variances of indoor and personal PM$_{2.5}$ and absorbance, and the between- and within-subject components of variance.

			n_s	Total variance[1]	Between %	Within %
Amsterdam						
PM$_{2.5}$	All	Personal	37	0.76	47	53
		Indoor	36	0.77	63	37
	No ETS	Personal	32	0.47	11	89
		Indoor	34	0.33	20	80
ABS	All	Personal	37	0.47	22	78
		Indoor	36	0.37	27	72
	No ETS	Personal	32	0.39	3	97
		Indoor	34	0.31	7	93
Helsinki						
PM$_{2.5}$	All	Personal	47	0.26	34	66
		Indoor	46	0.26	28	72
	No ETS	Personal	47	0.26	34	66
		Indoor	46	0.26	29	71
ABS	All	Personal	47	0.36	39	61
		Indoor	46	0.25	40	60
	No ETS	Personal	47	0.36	39	61
		Indoor	46	0.25	40	60

n_s = number of subjects.

No ETS = only measurements where no exposure to environmental tobacco smoke anywhere indoors (personal measurements) or at own living room (indoor measurements) .

[1] The unit is $\log(\mu g/m^3)$ for PM$_{2.5}$ and $\log(m^{-1}x10^{-5})$ for absorbance.

Table 3. Daily median levels of PM$_{2.5}$ (μg/m^3) and absorbance (m^{-1}x10^{-5}) by permanent determinants of exposure. The significance levels of the differences between the categories of determinants have been indicated with asterisks.

| | AMSTERDAM | | | | | | HELSINKI | | | | | |
| | Personal | | | Indoor | | | Personal | | | Indoor | | |
	n$_s$	PM$_{2.5}$	ABS	n$_s$	PM$_{2.5}$	ABS	n$_s$	Pm$_{2.5}$	ABS	n$_s$	Pm$_{2.5}$	ABS
Gender												
Female	13	14.2	1.43	13	14.9	1.67	23	9.1	1.28	23	9.5	1.48
Male	24	16.3	1.62	23	14.9	1.71	24	10.4	1.39	23	11.3	1.50
Marital status												
Married	20	14.5	1.51	19	14.9	1.69	27	9.8	1.25*	26	10.7	1.41*
Open marriage, single or widow	17	17.7	1.58	17	14.9	1.67	20	10.4	1.57	20	9.7	1.66
Years of education												
≤9	12	13.6	1.40	12	14.6	1.55	27	9.4	1.22*	26	9.7	1.42
10-13	11	13.4	1.44	10	14.8	1.61	12	11.6	1.69	12	11.4	1.76
≥14	14	19.5	1.77	14	16.2	1.74	8	10.0	1.37	8	9.7	1.44
Floor subject lived												
1-2	23	15.7	1.58	22	14.9	1.70	10	7.4***	1.20***	9	8.2***	1.23***
3-4	8	12.0	1.32	8	13.6	1.41	18	12.0	1.88	18	11.7	1.74
≥5	6	16.8	1.61	6	16.4	2.02	19	9.6	1.27	19	9.5	1.41
Annoyance by traffic												
0-1	19	16.9	1.47	19	16.2	1.64	20	9.2	1.23*	19	9.0	1.25*
2-5	11	13.8	1.59	11	14.3	1.69	15	10.7	1.50	15	11.2	1.55
6-10	7	13.8	1.51	6	14.4	1.69	12	9.9	1.33	12	11.0	1.69
Annoyance by air pollution												
0-1	25	14.2	1.47	25	14.9	1.67	20	9.5	1.26	20	9.4	1.45
2-5	8	14.7	1.44	8	14.4	1.53	18	10.6	1.71	17	11.2	1.62
6-10	4	18.7	1.68	3	16.2	1.70	9	9.3	1.27	9	10.5	1.40
Building year of the house												
1980-	20	14.1	1.35	19	13.9	1.47	10	8.7	1.09**	9	8.0	1.21*
1970-1979	15	16.9	1.64	15	16.2	1.79	7	13.1	1.39	7	12.5	1.41
-1969	2	51.1	2.35	2	46.7	2.22	30	10.5	1.46	30	11.2	1.59
Apartment/more family house												
Yes	30	16.3	1.58	29	14.9	1.67	46	10.0	1.37	45	10.3	1.50
No	7	13.8	1.37	7	14.9	1.69	1	9.1	1.25	1	9.0	1.21
Regular smoker at home												
Yes	4	63.8***	3.18***	4	88.6***	3.21***	0					
No	33	13.8	1.47	32	14.7	1.65	47	10.0	1.35	46	10.2	1.49
Construction work within 100 m												
Yes	6	20.3	1.51	6	14.0	1.52	9	9.0	1.15*	8	8.7	1.44
No	28	15.5	1.55	27	15.3	1.69	38	10.2	1.41	38	10.4	1.52
Parking area/hall within 100 m												
Yes	5	17.7	1.61**	5	16.2	1.89*	22	11.0	1.25	21	11.2	1.40
No	29	15.3	1.47	28	14.9	1.65	25	9.6	1.42	25	9.7	1.62
Closest street												
Major street	0			0			23	10.5	1.42**	23	10.9	1.62***
Side street	37	15.3	1.51	36	14.9	1,67	24	9.3	1.26	23	9,0	1.41
Major street within 100 m												
Yes	9	29.4***	1.83***	9	16.2**	2.04***	38	10.2	1.39***	38	10.4	1.55***
No	28	13.6	1.43	27	14.6	1.66	9	9.1	0.99	8	9.4	1.22
Industrial plant within 500 m												
Yes	0			0			17	10.0	1.42	17	10.0	1.55
No	37	15.3	1.51	36	14.9	1.67	30	9.5	1.33	29	10.3	1.44

n$_s$ = number of subjects; * p<0.1, ** p<0.05, *** p<0.01.

Median levels of $PM_{2.5}$ and absorbance in the categories of time-varying determinants of exposure are presented in Table 4. Asterisks represent again the significance levels of the differences between the categories tested using log_n-transformed data. ETS exposure at home was a strong determinant of both $PM_{2.5}$ and absorbance in Amsterdam, and despite only few episodes occurred, the effect on indoor levels was evident also in Helsinki. ETS encountered elsewhere indoors was also strongly associated with exposure to $PM_{2.5}$ and absorbance in Amsterdam. Cooking was significantly associated with higher exposure to $PM_{2.5}$ in Helsinki, and there was a suggestion of an effect also for indoor levels. In Amsterdam, the levels of indoor and personal $PM_{2.5}$ were higher during days with cooking, but the differences between the levels were not significant. Only in Amsterdam, spending time indoors somewhere else than at home was associated with higher $PM_{2.5}$ and absorbance, but the exposures increased more clearly only after 4 hours. Only in Helsinki, spending time outdoors was associated with higher exposure to $PM_{2.5}$ and absorbance, but the increase became clear only after 3 hours. The more time was spent in a motor vehicle the higher the levels of $PM_{2.5}$ and absorbance seemed to be, but no significant associations were found.

Table 5 presents percentage increases in $PM_{2.5}$ and absorbance by permanent and time-varying determinants. In the multi-determinant models, all the variables remaining after stepwise regression in either of the cities have been included. In general, the same determinants turned out to be important in the multi-determinant models and in the models including one determinant at a time. However, there was no more evidence of an association between time spent indoors and the pollutants in Amsterdam, or building year and personal absorbance in Helsinki. The association between $PM_{2.5}$ and living near a major street also disappeared in Amsterdam. On the other hand, the time spent in a motor vehicle was now clearly associated with absorbance in both cities. Having a parking lot near residence seemed to decrease absorbance exposure in Helsinki. Forty percent of those having a parking lot near the residence did not spend time outdoors at all, compared to 22% among those having it within 100 m (data not shown). Looking at the time-variant determinant, it was now evident that not only was cooking associated with increased $PM_{2.5}$, but also with absorbance. In Helsinki, keeping either bedroom or living room window open seemed now to increase indoor levels of absorbance.

Table 4. Daily median levels of $PM_{2.5}$ (μg/m^3) and absorbance (m^{-1}x10^{-5}) by time-varying determinants of exposure. The significance levels of the differences between the categories of determinants have been indicated with asterisks.

	AMSTERDAM						HELSINKI					
	Personal			Indoor			Personal			Indoor		
	n[1]	$PM_{2.5}$	ABS	n	$PM_{2.5}$	ABS	n	$PM_{2.5}$	ABS	n	$PM_{2.5}$	ABS
Cleaning												
Yes	101	13.4	1.21	119	14.0	1.42	48	11.0*	1.62	80	8.7	1.44
No	230	13.8	1.37	281	13.6	1.52	285	8.9	1.29	412	9.2	1.41
Hot meal cooked												
Yes	246	14.2	1.28	295	14.2*	1.52	270	9.6***	1.30	418	9.3*	1.42
No	87	12.6	1.26	107	11.5	1.35	63	7.8	1.33	77	8.3	1.44
Living room window open												
Yes	163	13.3	1.22	194	13.7	1.50	61	8.9	1.38	73	9.0	1.32
No	154	14.4	1.38	190	13.9	1.52	266	9.3	1.26	296	9.5	1.42
Bed room window open at night												
Yes	222	12.9	1.20	266	12.6	1.40	53	11.0	1.37	59	11.1	1.64
No	105	17.0	1.44	127	15.8	1.59	280	9.1	1.29	315	9.0	1.39
ETS[2] at home												
Yes	39	62.7***	2.97***	51	91.4***	3.44***	2	14.2	1.2	5	23.6***	1.82*
No	295	12.6	1.17	353	12.3	1.35	334	9.2	1.3	495	9.1	1.41
ETS elsewhere indoors												
Yes	52	29.5***	2.06***				9	13.1	1.52			
No	280	12.7	1.17				327	9.2	1.30			
Time spent (hours)												
In a motor vehicle												
0	263	13.0*	1.21				221	9.0	1.19			
1	62	19.0	1.53				94	9.5	1.35			
≥2	12	17.0	1.61				21	10.0	1.56			
Indoors elsewhere												
0	251	13.0***	1.18***				187	9.1	1.19			
1-3	66	13.1	1.37				124	9.1	1.41			
≥4	20	24.8	2.89				25	10.0	1.39			
Outdoors												
0	156	12.9	1.16				109	9.8**	1.11**			
1-2	130	15.0	1.47				194	9.0	1.23			
≥3	51	13.2	1.21				33	12.1	1.95			

[1] n=total number of measurements; [2] ETS = environmental tobacco smoke.

Empy cells = determinants not relevant for indoor concentrations.

* p<0.1, ** p<0.05, *** p<0.01

Excluding the most extreme PM$_{2.5}$ value in Amsterdam and Helsinki did not change results of the multi-determinant models. However, excluding one extreme personal absorbance value in Helsinki resulted in some changes. As the value was known to be linked to burning candles, which was not one of the determinants studied, and it was 5 times higher than the second highest values (on normal scale), the results of the multi-determinant models have been given without this value.

Discussion

Besides outdoor concentrations, several other time-variant and permanent determinants of indoor concentrations of and exposures to PM$_{2.5}$ and absorbance were identified among persons with coronary heart disease in Amsterdam, the Netherlands, and Helsinki, Finland. The main determinants of PM$_{2.5}$ were ETS and cooking, which affected also the levels of absorbance. Other determinants of absorbance were the vicinity of a major street and time spent in traffic. In multi-determinant models some determinants were associated with exposure mainly in Helsinki, e.g. the time spent outdoors and opening of windows in the case of absorbance. In both cities, after exclusion of ETS the within-subject variation in PM$_{2.5}$ and absorbance exposures was larger than between-subject variation.

In the current study, within-subject variation in PM$_{2.5}$ and absorbance exposures accounted for over half of the total variance on days without ETS exposure, which increased between-subject variation. Without ETS, the contribution of within-subject variation to total variance was of the same magnitude for indoor and personal concentrations. In another population group susceptible for air pollution effects, asthmatic children, the within-subject variation was also found to account for over half of the total variation in indoor PM$_{2.5}$ (Wallace et al., 2003). Among adults, day-to-day variation in exposure has been observed to be higher than interpersonal variability also for the pollutants NO$_2$ and SO$_2$ (Lee et al., 2004).

Results of the current study indicate that repeated measurements of PM$_{2.5}$ and absorbance are needed to estimate long-term individual exposures.

In Amsterdam, ETS had a major effect on both personal and indoor PM$_{2.5}$. Despite the fact that all participating subjects were non-smokers, a substantial number of measurement days (19%) in Amsterdam included ETS exposure. In Helsinki, there were only few ETS exposure events, at least partly because nobody was living with a smoker unlike in Amsterdam, but the results suggest same kind of association. Previous studies have demonstrated that ETS is a major source of exposure to PM$_{2.5}$ among non-smokers in general population (Özkaynak et al., 1996) and among COPD patients (Rojas-Bracho et al., 2004). In Amsterdam, also absorbance was affected by ETS, but the percentage increase was lower than for PM$_{2.5}$. This is in line with the

results from Copenhagen, where among young adults the time exposed to ETS was associated with $PM_{2.5}$ exposure, but not with absorbance (Sørensen et al., 2005).

Table 5. Percentage changes in $PM_{2.5}$ and absorbance by permanent and time-varying determinants in multi-determinant models adjusted for outdoor levels.

	AMSTERDAM				HELSINKI			
	Personal		Indoor		Personal		Indoor	
	$PM_{2.5}$	ABS	$PM_{2.5}$	ABS	$Pm_{2.5}$	ABS	$Pm_{2.5}$	ABS
Married		-15 *				-9		
Floor subject lived (≥3)	-7	-12	1	-5	47 ***	34 **	40 ***	25 **
Parking area or hall within 100m		4				-21 **		
Annoyance by traffic (≥2)			-19				6	
Building year (before 1980)				13 *				20 *
Regular smoker at home	86 **	37 *	194 ***	57 ***	na	na	na	na
Major street within 100 m		22 ***		10		37 **		46 ***
Hot meal cooked	20 **	17 ***	17 **	13 ***	22 ***	14 ***	14 ***	1
Living window open				5				12 *
Bed room window open at night				7 *				17 **
ETS at home	139 ***	53 ***	124 ***	35 ***	NA	NA	131 ***	12
ETS elsewhere indoors	49 ***	22 ***	4)	4)	28 **	22 *	4)	4)
Time spent in a motor vehicle [1]	11 *	13 ***	4)	4)	-2	9 ***	4)	4)
Time spent indoors elsewhere [1]	3		4)	4)	-1		4)	4)
Time spent outdoors [1]		2	4)	4)		5 **	4)	4)
Outdoor $PM_{2.5}$ or absorbance [2]	27 ***	68 ***	28 ***	59 ***	50 ***	50 ***	58 ***	45 ***
Number of measurements	315	306	402	375	311	310	456	330
R-squared [3]	0.70	0.80	0.82	0.82	0.67	0.80	0.62	0.73

[1] continuous variable, estimate calculated for a change of 1 hour.
[2] continuous variable, estimate calculated for a change of 10 µg/m^3 in $PM^{2.5}$ and 1 m^{-1}x10^{-5} in absorbance.
[3] generalized linear models used to obtain the value.
[4] determinant not relevant for indoor concentrations.
NA=not enough exposure events for analyses.
* $p<0.1$, ** $p<0.05$, *** $p<0.01$.

In the current study, absorbance of $PM_{2.5}$ filters was used as a proxy for elemental carbon content of $PM_{2.5}$. Absorbance is associated with a variety of combustion processes, but ambient concentrations are mainly affected by diesel particles (Gray and Cass 1998). Absorbance might be closely associated with at least some health relevant fraction of particulate matter. Incomplete combustion produces elemental

carbon particles that adsorb transition metals and organic carbon compounds, which have been linked to cellular effects of particles (Obot et al., 2002).

Having a major street within 100 meters of the residence and spending time in traffic were major determinants of absorbance, demonstrating the effect of traffic on the exposure. In multi-determinant models, $PM_{2.5}$ was not associated with traffic, confirming the earlier reports that absorbance is a better marker for traffic than mass of particles (Cyrus et al., 2003). There are some earlier studies conducted in the two cities which have linked traffic to absorbance: in Amsterdam, both living along a main road and spending time in traffic were associated with increased exposure to absorbance (of PM_{10}) among 50-70-year-old adults (Wichmann et al., 2005). In the study, the time spent outdoors had less effect on absorbance than the time spent in transport, which is in line with the current results. In Helsinki among adult population, exposure to absorbance (of $PM_{2.5}$) has been associated with the traffic density of the nearest street, but the time in traffic had no effect on exposure (Koistinen et al., 2001).

Cooking was associated with increased daily $PM_{2.5}$ and absorbance exposures in both cities. In previous studies, cooking has often been associated with episodic peaks in $PM_{2.5}$ concentrations (Jones et al., 2000; Lanki et al., 2002). The contribution of indoor generated peaks to daily average concentration depends on the air exchange rate of the home (Rojas-Bracho et al. 2000). On the other hand, the type of cooking determines emission rates and size distribution of particles (He et al., 2004). Unfortunately, we could not add in the questionnaires more specific questions about the type of cooking, as the study participants also had to fill in a considerable number of questionnaires related to the epidemiological part of the study. It is unclear, how important are particles generated by indoor combustion sources like cooking in respect to health, but there's recent epidemiological evidence that indoor-generated particles in general might be less harmful than ambient particles (Ebelt et al., 2005; Koenig et al., 2005).

Keeping windows open is one of the factors affecting air exchange rate at home. In both cities open windows seemed to be associated with increased indoor levels of absorbance, but the association was stronger in Helsinki. The frequency of keeping windows open was much lower in Helsinki than in Amsterdam, obviously due to colder climate. Due to the climate, apartments are also tighter in Finland, and thus the occasional opening of windows probably alters the air exchange rate more than frequent opening in Amsterdam explaining the result. Interestingly, living in upper floors was associated with increased $PM_{2.5}$ in Helsinki. This is somewhat counterintuitive, but the reason for this might be the less frequent opening of windows in the two first floors, where traffic noise and coarse dust might make open windows a less attractive option. In Helsinki was observed another somewhat

surprising association: having a parking hall/lot near residence seemed to decrease absorbance exposure, not increase as expected. There is obviously some hidden confounding for which possibilities are many. For example, those having a parking place near them spent less time outdoors potentially decreasing their exposure.

During the measurement days, our study subjects spent an average of 88% of their time indoors. In other studies, COPD patients have been observed to spend around 90% of their time at home, while the fraction has been closer to 80% for persons without any cardiorespiratory disease (Ebelt et al., 2000; Liu et al., 2003). This is one indication that although our study was conducted among elderly with cardiovascular disease, the results are probably generalizable, to some degree, to elderly populations having health compromised in some other way that restricts their activities. However, generalization should be made cautiously beyond cold and moderate climates, as for example air exchange rates and indoor sources are likely to differ according to location.

One of the limitations of the study is the lack of year-round measurements. This is because the study was conducted within a larger epidemiological study, where intensive clinic visits could only be run for half a year. However, both warm and cold periods were included in the study period, thus the results are expected to represent reasonably well determinants of exposure during other seasons than perhaps mid-summer. Even when the available number of measurements was considerable, the data was considered too limited to construct extensive multi-determinant models separately for winter and spring. The correlations of outdoor $PM_{2.5}$ and absorbance with personal concentrations have been shown to be robust to seasonal effects in the current data (Brunekreef et al., 2005). However, in Helsinki $PM_{2.5}$ exposures have previously shown to be higher during summer than winter, at least partly because windows have been kept open longer times during summer (Koistinen et al., 2001).

In conclusion, although outdoor concentrations of $PM_{2.5}$ and absorbance were strongly associated with personal and indoor concentrations in two European cities, several additional determinants were identified and quantified. $PM_{2.5}$ and absorbance were observed to have partly different determinants. Our results demonstrate that by using relatively simple questionnaires in connection with outdoor measurements, exposure estimation of $PM_{2.5}$ and its combustion originating fraction can be improved among elderly with compromised cardiovascular health.

Acknowledgements

References

Brunekreef B., Janssen N.A.H., de Hartog J.J., Oldenwening M., Meliefste K., Hoek G., et al. Personal, indoor, and outdoor exposures to PM2.5 and its components for groups of cardiovascular patients in Amsterdam and Helsinki. *Res Rep Health Eff Inst* 2005: Jan (127): 1-70; discussion 71-79.

Cyrys J., Heinrich J., Hoek G., Meliefste K., Lewne M., Gehring U., et al. Comparison between different traffic-related particle indicators: Elemental carbon (EC), PM(2.5) mass, and absorbance. *J Expo Anal Environment Epidemiol* 2003:13:134-43.

Ibald-Mulli A., Timonen K.L., Peters A., Heinrich J., Wolke G., Lanki T., et al. Effects of particulate air pollution on blood pressure and heart rate in subjects with cardiovascular disease: a multi-centre approach. *Environ Health Perspect* 2004: 112: 369-377.

Ebelt S.T., Petkau A.J., Vedal S., Fisher T., and Brauer M. Exposure of chronic obstructive pulmonary disease patients to particulate matter: relationships between personal and ambient air concentrations. *J Air&Waste Manage Assoc* 2000: 50: 1081-1094.

Ebelt S.T., Wilson W.E., and Brauer M. Exposure to ambient and nonambient components of particulate matter. A comparison of health effects. *Epidemiology* 2005: 16(3): 396-405.

Gotschi T., Oglesby L., Mathys P., Monn C., Manalis N., Koistinen K., Jantunen M., Hänninen O., Polanska L., and Künzli N. Comparison of black smoke and $PM_{2.5}$ levels in indoor and outdoor environments of four European cities. *Environ Sci Technol* 2002: 36(6): 1191-1197.

He C., Morawska L., Hitchins J., and Gilbert D. Contribution from indoor sources to particle number and mass concentrations in residential houses. *Atmos Environ* 2004: 38(21): 3405-3415.

Hoek G., Brunekreef B., Goldbohm S., Fischer P., and van den Brandt P.A. Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. *Lancet* 2002: 360(9341): 1203-1209.

ISO 9835. 1993: Ambient air - Determination of a black smoke index.

Janssen N.A.H., Hoek G., Brunekreef B., and Harssema H. Personal exposure to fine particles in children correlates closely with ambient fine particles. Arch Environ Health 1999: 54: 95-101.

Janssen N.A.H., Hoek G., Brunekreef B., Harssema H., Mensink I., and Zuidhof, A. Personal sampling of particles in adults: Relation among personal, indoor, and outdoor air concentrations. *Am J Epidemiol* 1998: 147(6): 537-547.

Janssen N.A., de Hartog J.J., Hoek G., Brunekreef B., Lanki T., Timonen K.L., and Pekkanen J. Personal exposure to fine particulate matter in elderly subjects: relation between personal, indoor, and outdoor concentrations. *J Air Waste Manage* 2000: 50(7): 1133-1143.

Janssen N.A.H., Lanki T., Hoek G., Vallius M., de Hartog J.J., Van Grieken R., Pekkanen J., and Brunekreef B. Associations between ambient, personal, and indoor exposure to fine particulate matter constituents in Dutch and Finnish panels of cardiovascular patients. *Occup Environ Med* 2005; 62: 868-877.

Jones N.C., Thornton C.A., Mark D., and Harrison R.M. Indoor/outdoor relationships of particulate matter in domestic homes with roadside, urban and rural locations. *Atm Environ* 2000: 34: 2603-2612.

Koenig J.Q., Mar T.F., Allen R.W., Jansen K., Lumley T., Sullivan J.H., et al. Pulmonary effects of indoor- and outdoor-generated particles in children with asthma. *Environ Health Perspect* 2005: 113(4): 499-503.

Koistinen K.J., Hänninen O., Rotko T., Edwards R.D., Moschandreas D., and Jantunen, M.J. Behavioral and environmental determinants of personal exposures to $PM_{2.5}$ in EXPOLIS - Helsinki, Finland. *Atmos Environ* 2001: 35(14): 2473-2481.

Lanki T, Alm S, Ruuskanen J, Janssen NAH, Jantunen M, Pekkanen J. 2002. Photometrically measured continuous personal $PM_{2.5}$ exposure: Levels and correlation to a gravimetric method. *J Exposure Anal Environ Epidemiol* 2002: 12: 172-178.

Le Tertre A., Medina S., Samoli E., Forsberg B., Michelozzi P., Boumghar A., Vonk J.M., Bellini A., Atkinson R., Ayres J.G. Sunyer J., Schwartz J., and Katsoyanni K. Short-term effects of particulate air pollution on cardiovascular diseases in eight European cities. *J Epidemiol Community Health* 2002: 56(10):773-779.

Lee K., Bartell S.M., and Paek D. Interpersonal and daily variability of personal exposures to nitrogen dioxide and sulfur dioxide. *J Expos Anal Environ Epidemiol* 2004: 14(2): 137-143.

Liu L-J.S., Box M., Kalman D., Kaufman J., Koenig J., Larson T., Lumley T., Sheppard L., and Wallace L. Exposure assessment of particulate matter for susceptible populations in Seattle. *Environ Health Persp* 2003: 111(7): 909-918.

Obot C.J., Morandi M.T., Beebe T.P., Hamilton R.F., and Holian A. Surface components of airborne particulate matter induce macrophage apoptosis through scavenger receptors. Toxicol Appl Pharmacol 2002;184:98-106.

Patterson E., and Eatough D. Indoor/outdoor relationships for ambient $PM_{2.5}$ and associated pollutants: epidemiological implications in Lindon, Utah. *J Air&Waste Manage Assoc* 2000: 50: 103-110.

Peters A., von Klot S., Heier M., Trentinaglia I., Hormann A., Wichmann H.E., and Lowel H.; Cooperative Health Research in the Region of Augsburg Study Group. Exposure to traffic and the onset of myocardial infarction. *N Engl J Med* 2004: 351: 1721-1730.

Pekkanen J., Timonen K.L., Tiittanen P., Vallius M., Lanki T., Sinkko H., et al. ULTRA: Exposure and risk assessment for fine and ultrafine particles in ambient air. Study manual and data book. Publications of National Public Health Institute 2000. Available at http://www.ktl.fi/ultra.

Rojas-Bracho L., Suh H.H., Catalano P.J., and Koutrakis P. Personal exposures to particles and their relationships with personal activities for chronic obstructive pulmonary disease patients living in Boston. *J Air&Waste Manage Assoc* 2004: 54: 207-217.

Rojas-Bracho L., Suh H.H., and Koutrakis P. Relationships among personal, indoor, and outdoor fine and coarse particle concentrations for individuals with COPD. *J Expos Anal Environ Epidemiol* 2000: 10: 294-306.

Rotko T., Kousa A., Alm S., and Jantunen M. Exposures to nitrogen dioxide in EXPOLIS-Helsinki: microenvironmental, behavioral and sociodemographic factors. *J Expos Anal Environ Epidemiol* 2001: 11(3): 216-223.

Samet J.M., Dominici F., Curriero F.C., Coursac I., and Zeger S.L. Fine particulate air pollution and mortality in 20 US Cities, 1987-1994. *New Engl J Med* 2000: 343(24): 1742-1749.

Sørensen M., Loft S., Andersen H.V., Raaschou-Nielsen O., Skovgaard L.T., Knudsen L.E., Nielsen I.V., and Hertel O. Personal exposure to PM2.5, black smoke and NO2 in Copenhagen: relationship to bedroom and outdoor concentrations covering seasonal variation. *J Expos Anal Environ Epidemiol* 2005: 15: 413-422.

von Klot S., Peters A., Aalto P., Bellander T., Berglind N., D'Ippoliti D., Elosua R., Hörmann A., Kulmala M., Lanki T., Löwel H., Pekkanen J., Picciotto S., Sunyer J., and Forastiere F. for the HEAPSS Study Group. Ambient air pollution is associated with increased risk of hospital cardiac readmissions of myocardial infarction survivors in European cities. *Circulation* 2005: 112: 3073-3079.

Wallace L.A., Mitchell H., O'Connor G.T., Neas L., Lippmann M., Kattan M., Koenig J., Stout J.W., Vaughn B.J., Wallace D., Walter M., Adams K., Liu L-J.S. Particle concentrations in inner-city homes of children with asthma: The effect of smoking, cooking, and outdoor pollution. *Environ Health Persp* 2003: 111(9): 1265-1272.

Wichmann J., Janssen N.A.H., van der Zee S., and Brunekreef B. Traffic-related differences in indoor and personal absorption coefficient measurements in Amsterdam, the Netherlands. Atmos Environ 2005: 39: 7384-7392.

Özkaynak H., Xue J., Spengler J., Wallace L., Pellizzari E., and Jenkins P. Personal exposure to airborne particles and metals: Results from the particle team study in Riverside, California. *J Expos Anal Environ Epidemiol* 1996: 6(1): 57-78.

7   PHOTOMETRICALLY MEASURED CONTINUOUS PERSONAL PM$_{2.5}$ EXPOSURE: LEVELS AND CORRELATION TO A GRAVIMETRIC METHOD

Lanki T,[1] Alm S,[2] Ruuskanen J,[3] Janssen NAH,[4] Jantunen M,[2] and Pekkanen J[1]

[1] Unit of Environmental Epidemiology, National Public Health Institute, Kuopio, Finland

[2] Laboratory of Air Hygiene, National Public Health Institute, Kuopio, Finland

[3] Department of Environmental Sciences, University of Kuopio, Kuopio, Finland

[4] Institute for Risk Assessment Sciences (IRAS), Division of Environmental and Occupational Health (EOH), Utrecht University, Utrecht, The Netherlands

Abstract

There is evidence that hourly variations in exposure to airborne particulate matter (PM) may be associated with adverse health effects. Still there are only few published data on short-term levels of personal exposure to particulate matter in community settings. Objectives of the study were to assess hourly and shorter-term variations in personal PM$_{2.5}$ exposure in Helsinki, Finland, and to compare results from a portable photometer to simultaneously measured gravimetric concentrations. The effect of relative humidity on the photometric results was also evaluated. Personal PM$_{2.5}$ exposures of elderly persons were assessed for 24 hours every second week resulting in 308 successful measurements from 47 different subjects. Large changes in concentrations in minutes after cooking or changing microenvironment were seen. The median of daily 1-h maxima was over twice the median of 24-h averages. There was a strong significant association between the two means, which was not linear. Median (95th percentile) of the photometric 24-h concentrations was 12.1 (37.7) and of the 24-h gravimetric concentrations 9.2 (21.3) μg/m^3, respectively. The correlation between the photometric and the gravimetric method was quite good (R^2=0.86). Participants spent 94.1 % of their time indoors or in vehicle, where relative humidity is usually low and thus not likely to cause significant effects on photometric results. Even outdoors the relative humidity had

only modest effect on concentrations. Photometers are a promising method to explore the health effects of short-term variation in personal $PM_{2.5}$ exposure.

Introduction

Many epidemiological studies have shown that daily changes in the amount of ambient particulate matter are associated with morbidity and mortality (Vedal, 1997; Pope and Dockery, 1999). In most of the studies, exposures have been assessed as daily means. There is new evidence, that also shorter-term exposures can have health effects and that these effects can be quite immediate. Decreased heart rate variability has been observed within hours after exposure to $PM_{2.5}$ (Gold et al., 2000). Just one-hour exposure to diesel exhaust has been found to cause inflammatory reactions in 6 hours (Salvi et al., 1999). Maximum 1-h and 8-h PM_{10} concentrations have been reported to have larger effects on asthma symptoms than 24-h means (Delfino et al., 1998). These new observations indicate, that daily mean may not always be the most appropriate measure of exposure to particulate matter.

The evidence on the health effects of low levels of particulate matter (PM) comes from studies using mainly fixed outdoor monitoring site data. However, the relative importances of PM from different indoor and outdoor sources on health effects are mostly unknown. Daily total exposures to PM can be estimated more accurately using personal or indoor measurement systems, as people spend most of their time indoors. It is known that personal activities indoors (Abt et al., 2000), and local traffic outdoors (Alm et al., 1999) can cause short-term concentration peaks in personal exposures. Still there are only few studies estimating continuous personal exposure in community settings.

Epidemiological evidence on the health effects of PM, and thus also air quality standards, are mainly based on 24-h gravimetric measurements of PM. The time resolution of gravimetric techniques can not be much improved, because there has to be enough mass on the filter for weighing. In practice, the minimum measurement period is 12 hours for gravimetric personal measurements.

In contrast, photometers are capable of measuring PM concentrations in real time. Some of them are also lightweight, silent, and able to operate without external power supply for 24 hours making them ideal for personal measurements. For given PM in given environmental conditions, the photometers can be calibrated to correspond to gravimetric measurements. However, the correlation between photometric and gravimetric concentrations is weakened, when the particle size distribution or refractive index of aerosol material changes during or between measurements (Ruby et al., 1989, Sioutas et al., 2000). Increase in relative humidity of air also weakens the correlation by increasing the diameters and changing the

refractive properties of particles, thus increasing the photometric readings (McMurry et al. 1996; Day et al. 2000).

The objectives of the study were to produce information on short-term variation of personal PM2.5 exposure, and to compare photometric results to gravimetric results in field conditions. Effect of relative humidity on the photometric results was also evaluated.

Methods and feasibility

The continuous personal exposure measurements were done in Helsinki, Finland, between 1 November 1998 and 30 April 1999. Participants were elderly, non-smoking people taking part in a larger epidemiological study (Janssen et al., 2000).

Forty-nine participants carried the measurement case biweekly during the 24 hours preceding a clinical visit. Researchers delivered the cases to the participants' homes usually between 8:30 and 17:00 h. Measurements were conducted from Sunday to Friday, and one to six participants were monitored on the same day.

The personal sampling system used is shown in Figure 1. An aluminum case contained in series a $PM_{2.5}$ cyclone (Gk 2.05 KTL, BGI, Inc., Waltham, MA, USA), a datalogging photometer (pDR-1200 X, MIE, Inc., Bedford, MA, USA), a filter holder (M000037A0, Millipore, Corp., Bedford, MA, USA) with a 37 mm, 2-μm pore size, Teflon filter (SA240PR100, Andersen Instruments, Inc., Smyrna, GA, USA), and a pump (AFC400S, BGI, Inc., Waltham, MA, USA). The case weighted 4.6 kg. The sampler was thus at the same time able to record photometric PM concentrations and collect a gravimetric sample. The eight photometers used were set to record 1-min average concentrations. The gravimetric method gave 24-h average concentrations.

The filters were weighed using a Mettler MT5 microbalance (Mettler-Toledo, Inc., Greifensee, Switzerland) with 1 μg reading. Static electricity was controlled using a Po-210 deionizer. The gravimetric analysis method used in the study has been described in detail by Janssen et al. (2000), and the buoyancy correction method applied for the filter weights by Koistinen et al. (1999).

In MIE personalDataRAM (MIE, 1997) the light scattering sensing configuration has been optimized for the measurement of the respirable fraction of the PM. The particle size range of maximum response is from 0.1 to 10 μm. The photometer covers a measurement range from 1 $\mu g/m^3$ to 400 mg/m^3 (scattering coefficient range 1.5×10^{-6} m^{-1} to 0.6 m^{-1}). The instruments used were preproduction versions of the active sampling model pDR-1200. They were factory-calibrated with ISO Fine
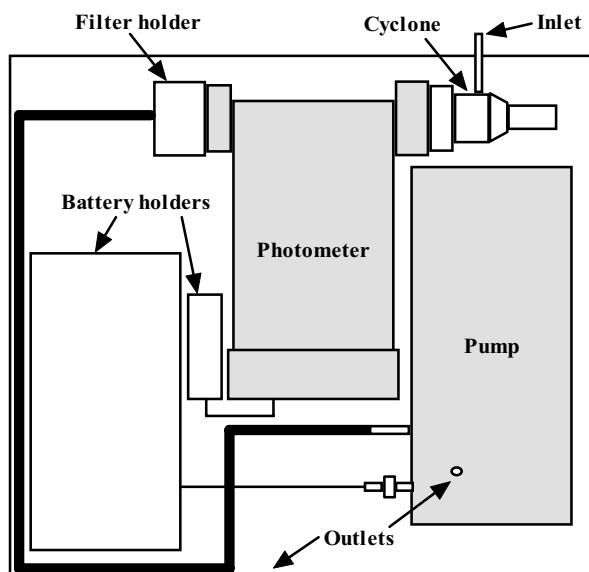
Figure 1.   Schematic picture of the personal PM$_{2.5}$ sampling system.

test dust (mass median diameter 2-3 µm, bulk density 2.6 g/cm^3, refractive index 1.54).

Sampling flow rate was 4 ($\pm$0.4) l/min. The flows were adjusted in the beginning of each measurement period using a bubble calibrator (M-30, Buck, Inc., Orlando, FL, USA), and checked again after each measurement. The photometers were zeroed using HEPA-filters provided by the manufacturer. This was done first once a month, but after zero drift was observed in one photometer in January, the zero levels were checked before every measurement and zeroing was done if necessary.

Fourteen duplicate measurements were done to evaluate the   precision of photometric and gravimetric methods. Six of those were measured indoors, four outdoors and four were personal measurements with both indoor and outdoor periods. Median (max) absolute difference between paired photometric measurements was 1.1 (3.9) µg/m^3, and between the corresponding paired gravimetric measurements 0.5 (1.7) µg/m^3. Median coefficient of variance was 6.7% for photometric duplicates and 3.8% for gravimetric duplicates.

Altogether 500 continuous personal exposure measurements were accomplished during the study. However, during the second month of the study a problem in the

technical design of the case was detected: it had been made too tight, and part of the exhaust air escaped near the inlet of the cyclone. Thus, some of the "cleaned air" returned to the measurement system and the collected masses were too low. The design failure was corrected and starting in the beginning of January, 357 measurements were done with fixed cases.

A power supply problem with the photometers was solved already before the design failure was noticed. The photometers run normally with one internal 9-V battery. However, the power of alkaline batteries used was not always sufficient to achieve a full 24-hour measurement. To solve the problem, participants were first instructed to connect the photometer to the mains voltage for nighttime. However, occasionally there was a momentary power breakdown at the moment the plug was connected, which led to stopping of the measurement. Therefore a separate battery holder for two 9-V batteries was added to the case. Even after the modification there were power supply problems, as the battery holders were easily broken. Only those photometric measurements lasting until the end of the corresponding gravimetric measurements were included in this analysis. There were altogether 308 valid measurements from 47 subjects.

Participants were instructed to carry the case wherever they were moving, but were allowed to place the case "at arm's length" during indoor sedentary activities, e.g. on a table or seat nearby. During the night, they were asked to keep the case next to their bed and if necessary, to put the case into a special sound insulated night-box. However, the measurement system was sufficiently quiet, and the night-boxes were not needed after the first visits.

There was a shoulder strap for carrying the case, but quite many participants felt the case was heavy to carry along. After a few visits, also backpacks were delivered to participants. After that only a few participants complained occasionally that the case was too heavy for them. The backpack also served another function: it hid the aluminum container, so that the measurement system did not draw attention from passers-by.

Time activity diaries with 15-min resolution were used to differentiate between the microenvironments (outdoors, indoors, in vehicle). In addition, the participants were asked to mark when someone was cooking or smoking in the same room. Thirty-five participants were willing to fill in the time activity diaries, but one was not able to do it correctly even after several visits. In the beginning of the study, also some other persons had difficulties in filling in the diaries. After excluding these diaries, 253 diaries were left for analysis.

Outdoor relative humidity data were obtained from the network of Helsinki Metropolitan Area Council. All participants lived within 5 km from the

measurement site.

One-hour averages were used to evaluate short-term variations in exposure. While calculating the 1-h averages, the 24-h measurements were first edited. To remove the effect of the researcher moving around, waiting for the flow of the pump to stabilize and calibrating them, 20 minutes were deleted from the beginning of the measurement. In the end of the measurement 10 min were deleted to remove the effect of checking the flow rate of the pump. To calculate a 1-h average, at least 54 min had to be available.

The effect of relative humidity on photometric results during the time spent outdoors was evaluated by estimating how strongly hourly photometric indoor/outdoor concentration ratios are associated with outdoor relative humidity. The ratios were calculated by dividing the average $PM_{2.5}$ concentration of any full hour that the participant spent indoors by the average concentration of the following (or, if there was missing data, preceding) full hour spent outdoors.

The approach is based on the fact that indoor relative humidity during winter/spring in Finland is usually below 50% (see e.g. Koponen et al., 2001), due to the large temperature difference between indoors and outdoors. As indoor relative humidity is thus too low to affect photometric reading indoors, any observed dependence of the indoor/outdoor $PM_{2.5}$ ratio on outdoor relative humidity would result from the effect of outdoor relative humidity on photometric reading outdoors. It is assumed that other factors influencing the differences between indoor and outdoor $PM_{2.5}$ levels are not correlated with outdoor relative humidity.

Results

A typical measurement consisted of long periods of even concentrations and a sudden rise of concentration level and its short-term variation after going outdoors (Figure 2). Cooking was often marked by a rapid rise and subsequent slower decay of concentration. Out of the 10 highest daily 1-h maxima (from persons using time activity diary) seven were linked to cooking, two going outdoors and one remained unexplained.

On average, the photometric concentrations were 4.7 $\mu g/m^3$ higher than the gravimetric concentrations (Table 1.). The average photometric/gravimetric concentration ratio was 1.37. During the study the ratio was observed to decrease linearly with day of study ($R^2=0.19$, $p<0.0001$). In January the average ratio was 1.68 and in April 1.10.
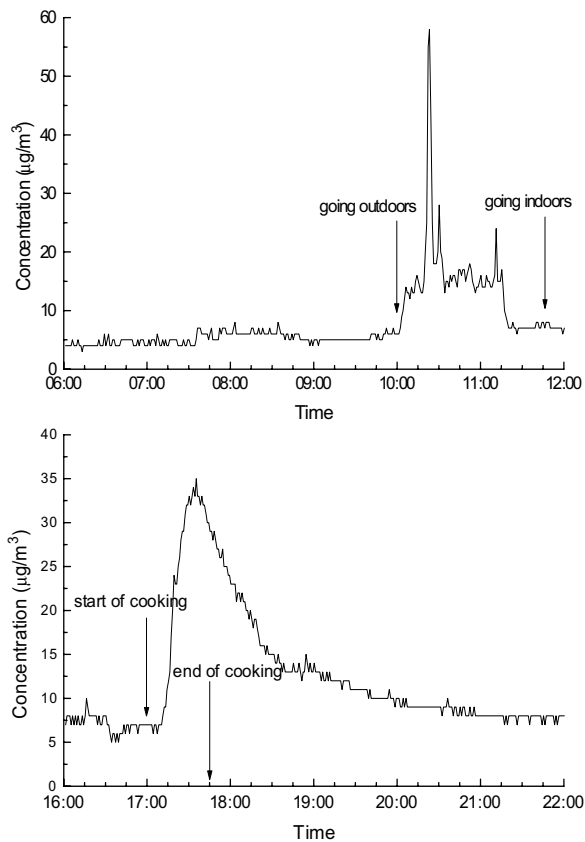
Figure 2. Examples of short-term PM$_{2.5}$ concentration changes during cooking and going outdoors. Two 6-h periods cut off from the 24-h measurements.

Median (95th percentile) of the photometric daily 1-h maxima was 26.7 (174) µg/m^3. The 1-h maxima are plotted against 24-h averages in Figure 3. A good fit was achieved with a quadratic model. Using the quadratic regression, 81.4% of the variation in daily 1-h maxima were explained with 24-h averages (p<0.0001). Both 1-h maxima and 24-h averages were logarithmically distributed.

Table 1. Descriptive statistics: photometric and gravimetric concentrations ($\mu g/m^3$).

	N	Mean	SD	Min	Max	25th percentile	50th percentile	75th percentile	95th percentile
24-h photometric average	308	15.5	12.5	1.07	112	7.80	12.1	19.1	37.7
24-h gravimetric average	308	10.8	6.28	2.07	51.4	6.91	9.23	13.0	21.3
24-h photometric / gravimetric ratio	308	1.37	0.46	0.31	4.12	1.07	1.34	1.63	2.06
1-h photometric average	6831	15.3	27.7	0	855	5.88	9.98	16.9	39.7
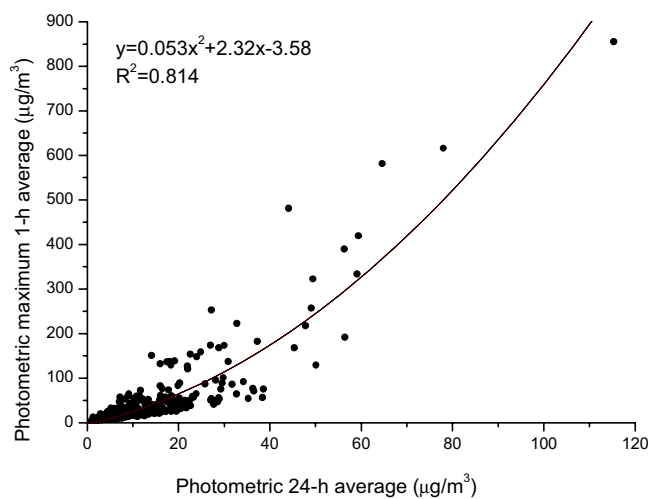
Figure 3. Association between photometric 24-h average concentration and the corresponding maximum 1-h average (N=308). The curve is a quadratic fit.

There was also a good correlation ($R^2=0.861$) between the 24-h photometric and gravimetric results (Figure 4). The linear regression equation was y= 1.85x (SE 0.04)– 4.52 (SE 0.53), with p-value <0.0001. As the photometric/gravimetric ratio changed during the study period, a trend variable was added into the regression model in an effort to improve the correlation. However, R^2 improved only slightly, to 0.89.
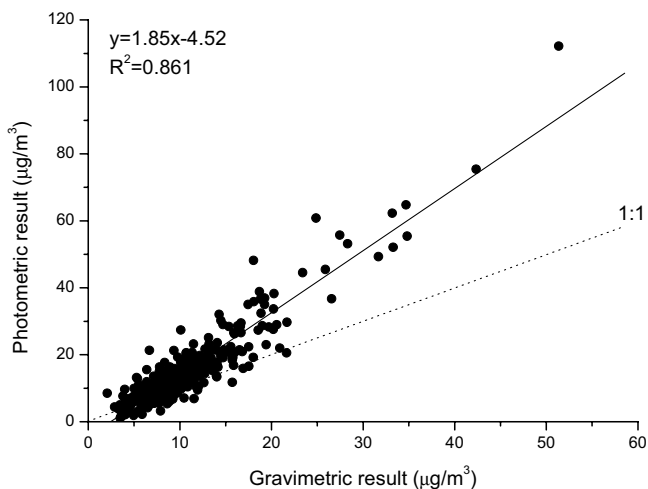
Figure 4. Relationship between gravimetric and photometric PM$_{2.5}$ results (N=308). 1:1 line shown for reference.

According to time activity diaries, the participants of the study spent 92.6% of their day indoors, and 1.5 % in a vehicle.

During the study the outdoor median (range) 1-h relative humidity was 89 (39-100) %. There seemed to be a linear relationship (p-value 0.019) between outdoor relative humidity and estimate of photometric indoor/outdoor ratio (Figure 5). The highest two values were excluded from this analysis, as the indoor concentrations were clearly higher than fixed site outdoor concentrations (obtained from local measurement network).

The average indoor/outdoor ratios for measurements done at relative humidity below 60% and above 90% were 0.93 (N=11) and 0.73 (N=28), respectively. Thus the artifact in outdoor concentrations caused by high relative humidity was 22%. Comparison of the two groups gave p-value of 0.029 (equal-variance T-test).
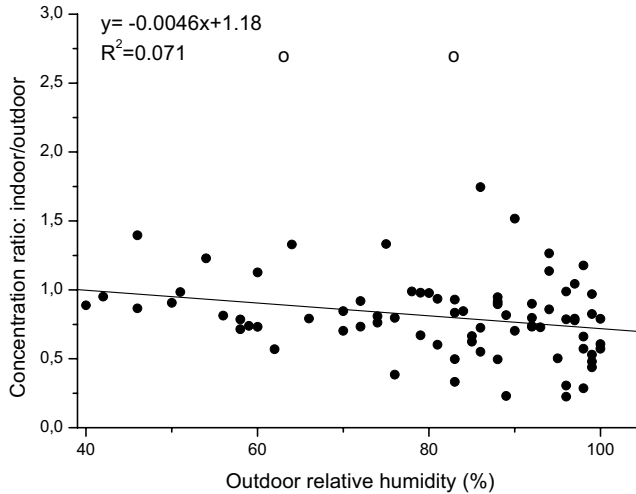
Figure 5. Ratio of photometric 1-h indoor concentration to the following 1-h outdoor concentration (N=79). Open circles not included in regression equation.

Discussion

The photometric-gravimetric personal $PM_{2.5}$ monitor proved to be feasible for measurements in community settings. It was quiet enough not to disturb the participants, and unnoticeable to others. It would have been desirable to make the sampler lighter, especially as the participants were elderly people.

The inlet and the cyclone of the sampler were attached to the wall of the case and were not taken to the breathing zone in order to make the measurements less disturbing to the participants. This might cause some bias in the estimation of exposure. However, the participants were instructed to use the backpack or the shoulder strap when carrying the case, and when sedentary, to place it on a table or seat nearby. In both cases the case was at arm's length and the inlet thus close to breathing zone. It is unlikely that there would have been large concentration gradients between breathing zone and the inlet, as $PM_{2.5}$ is quite homogeneously distributed because of its small size (Wigzell et al., 2000).

Change of microenvironment and cooking caused typical exposure patterns in 1-min photometric data. The observed cooking events manifest the ability of the

photometer to respond to rapid changes in concentrations, typical for indoor environments (Long et al., 2000). Using time activity diaries, the value of photometric results is greatly enhanced, as the contributions from different microenvironments and activities as PM sources can be evaluated. Seven out of ten highest daily 1-h maxima were linked to cooking, which is a known major indoor source of fine particles. If exposure monitoring had been done at fixed outdoor site, these peak concentrations would have remained undetected. It should be noted here that smoking did not significantly contribute to the exposure peaks, as the study subjects were non-smoking, and even passive exposure to smoking occurred only during 4% of the 24-h measurements (Janssen et., 2000).

The median of hourly values was 10 $\mu g/m^3$. As the participants were elderly, retired persons, the exposures were probably lower than for working age people (see Rotko et al., 2000; Koistinen et al., 2001). The median is the same as during wintertime in Baltimore in the study by Chang et al. (2000), where field technicians accomplished scripted activities for 12-h periods simulating activities typical of the elderly. The summertime median was higher - 19 $\mu g/m3$.

The median of the daily 1-h maxima was over twice the median of 24-h averages. The two exposure measures were highly associated (R^2=0.82), but the association was not linear. The strength of association was similar to what Chuersuwan et al. (2000) found in their fixed site outdoor measurements (R^2=0.62-0.85). They observed quite many high daily 1-h maxima occurring also during low 24-h average concentration days. Use of the 24-h average as exposure measure conceals part of the short-term variation in concentrations, which might be associated with adverse health effects.

The average photometric/gravimetric ratio (1.37) was almost the same as reported by Sioutas et al. (2000) for MIE DataRAM (diffusion drying tubes used for relative humidity control). There was a clear downward trend in the ratio from winter towards summer in our study. Seasonal dependency of the ratio of photometric concentration to gravimetric concentration has been reported also by Ramachandran et al. (2000). It would be possible to calibrate the photometric results against the 24-h filter samples, but on the other hand the photometric/gravimetric ratio may also depend on the microenvironment (Quintana et al., 2000) and thus vary within a day. The correlation between the two methods was also considered more interesting than absolute mass concentrations.

The correlation between the two methods was quite good (R^2=0.86). The use of a size selective inlet, and the use of the active model of personalDataRam instead of the passive one, has probably improved the correlation. In a number of other studies correlating mass concentrations to photometric concentrations, diverse study designs have been used. In the study by Howard-Reed et al. (2000), elderly persons carried

filter samplers and passive models of personalDataRAM at the same time. The correlation (R^2) between $PM_{2.5}$ and photometer was 0.66. Quintana et al. (2000) compared $PM_{2.5}$ in outdoor air with the results from active personalDataRAM (inlets heated for relative humidity control) and got correlation of 0.66 (R^2). In indoor air the passive model was used, and correlation was 0.42. Brauer (1995), also used passive personalDataRAM and found good correlations (R^2=0.81-0.96) in indoor air between the photometric and gravimetrical $PM_{2.5}$, but weaker correlations in outdoor air (0.50).

Part of the difference between the photometric and gravimetric results was probably due to nitrate, which evaporates before filter weighing but is measured with the photometer. Sioutas et al. (2000) found in ambient and concentrated air correlation of 0.88 (R^2) between MIE DataRAM and nitrate corrected gravimetric results. When nitrate uncorrected results were used the coefficient went down to 0.80.

According to time activity diaries the participants spent 92.6% of their time indoors. In Finland during winter the indoor relative humidity is low enough (below 50%) not to have detectable effect on the photometric results. Quintana et al. (2000) measured relative humidity values between 20-60% indoors and found no apparent effect of humidity on the indoor concentrations measured with passive personalDataRAM. Sioutas et al. (2000) found that for relative humidity lower than approximately 50%, the photometric method gave readings close to gravimetric method.

We were able to evaluate the effect of relative humidity on the photometric outdoor concentrations only indirectly. However, these results suggest that the concentrations measured during the short periods participants spent outdoors are fairly valid. The artefact caused by relative humidity when going outdoors on high relative humidity days was estimated to be in the order of 20 %. The study took place during the colder seasons, winter and spring. The effect of relative humidity was probably reduced because the warm measurement case heated the inlet air above the ambient temperature for some time after the participants had gone outdoors.

The effect of relative humidity could be reduced with various techniques like using a diffusion denuder or a preheated inlet, but their use for personal measurements is problematic. Typically the denuders cannot operate for 24 h without replacement of the absorbing material. The preheated inlet needs an additional power source gaining even more weight for the measurement system. Quintana et al. (2000) also found that even using a preheater provided by the manufacturer of pDR, some effect of relative humidity remained. Adding a datalogger for relative humidity would allow for correcting the results afterwards. Although the growth of particles with increasing relative humidity can depend strongly on particle material and size (McMurry and Stolzenburg, 1989), in some conditions the water uptake is a more simple function of relative humidity (Richards et al., 1999).

Conclusions

In this study, significant short-term variation in PM$_{2.5}$ concentrations was found in Helsinki, Finland. The median of daily 1-h maxima was twice the median of 24-h average concentrations. The daily 1-h maxima were strongly associated with the daily means, but the association was not linear. Use of 24-h averaging time conceals the short-term variation, which might have health relevance.

The photometer proved to be a useful tool for measuring the short-term variation in concentrations. On a 24-h level, the photometric method correlated well with the gravimetric method. The estimated effect of relative humidity on photometric concentrations was quite low even outdoors. If the photometers are used mainly outdoors, it is advisable to try to control the effect of relative humidity by measuring it continuously, or by using, for example, a preheated inlet.

Acknowledgements

References

Abt E, Suh HH, Allen G, Koutrakis P. Characterization of indoor particle sources: a study conducted in the metropolitan Boston area. Env Health Persp 2000; 108: 35-44.

Alm S, Jantunen MJ, Vartiainen M. Urban commuter exposure to particle matter and carbon monoxide inside an automobil. J Exposure Anal Environ Epidemiol 1999; 9: 237-244.

Brauer M. Assessment of indoor aerosols with an integrating nephelometer. J Exposure Anal Environ Epidemiol 1995; 45: 45-56.

Chang L-T, Koutrakis P, Catalano PJ, Suh HH. Hourly personal exposures to fine particles and gaseous pollutants – results from Baltimore, Maryland. J Air & Waste Manage Assoc 2000; 50: 1223-1235.

Chuersuwan N, Turpin BJ, Pietarinen C. Evaluation of time-resolved PM2.5 data in urban/suburban areas of New Jersey. J Air & Waste Manage Assoc 2000; 50: 1780-1789.

Day DE, Malm WC, Kreidenweis SM. Aerosol light scattering measurements as a function of relative humidity. J Air & Waste Manage Assoc 2000; 50: 710-716.

Delfino RJ, Zeiger RS, Seltzer JM, Street DH. Symptoms in pediatric asthmatics and air pollution: differences in effects by symptom severity, anti-inflammatory medication use and particulate averaging time. Environ Health Perspect 1998; 106: 751-761.

Gold DR., Litonjua A, Schwartz J, Lovett E, Larson A, Nearing B, Allen G, Verrier M, Cherry R, Verrier R. Ambient pollution and heart rate variability. Circulation 2000; 101: 1267-1273.

Howard-Reed C, Zufall MJ, Burke JM, Williams RW, Sugss JC, Sheldon LS, Walsh D, Kwok R. Use of continuous nephelometer to measure personal exposure to particulate matter during the U.S. Environmental Protection Agency Baltimore and Fresno panel studies. J Air & Waste Manage Assoc 2000; 50: 1125-1132.

Janssen NAH, de Hartog JJ, Hoek G, Brunekreef B, Lanki T, Timonen KL, Pekkanen J. Personal exposure to fine particulate matter in elderly subjects: relation between personal, indoor and outdoor concentrations. J Air & Waste Manage Assoc 2000; 50: 1133-1143.

Koistinen KJ, Kousa A, Tenhola V, Hänninen O, Jantunen MJ, Oglesby L, Kuenzli N, Georgoulis L. Fine particle (PM2.5) measurement methodology, quality assurance pro-cedures, and pilot results of the EXPOLIS study. J Air & Waste Manage Assoc 1999; 49: 1212-1220.

Koistinen KJ, Hänninen O, Rotko T, Edwards R, Moschandreas D, Jantunen MJ. Behavioral and environmental determinants of personal exposures to PM2.5 in EXPOLIS-Helsinki, Finland. Atmos Environ 2001; 35: 2473-2481.

Koponen IK, Asmi A, Keronen P, Puhto K, Kulmala M. Indoor air measurement campaign in Helsinki, Finland 1999 – the effect of outdoor air pollution on indoor air. Atmos Environ 2001;35:1465-1477.

Long CM, Suh HH, Koutrakis P. Characterization of indoor particle sources using continuous mass and size monitors. J Air & Waste Manage Assoc 2000; 50: 1236-1250.

McMurry PH, Stolzenburg MR. On the sensitivity of particle size to relative humidity for Los Angeles aerosols. Atmos Environ 1989; 23: 497-507.

McMurry PH., Zhang X., Lee QT. Issues in aerosol measurement for optical asses-ments. J Geophys Res 1996; 101: 188-197.

MIE. PersonalDataRam instruction manual. MIE Inc.: Bedford, Massachusetts 1997.

Pope CA III., Dockery DW. Epidemiology of particle effects. In: Holgate ST, Samet JM, Koren HS, Maynard RL, eds. Air pollution and Health, Academic Press: London, UK 1999.

Quintana PJE., Samimi BS, Kleinman MT, Liu L-J, Soto K, Warner GY, Bufalino C, Valencia J, Francis D, Hovell MH, Delfino R. Evaluation of a real-time passive per-sonal particle monitor in fixed site residential indoor and ambient measurements. J Exposure Anal Environ Epidemiol 2000; 10: 437-445.

Ramachandran G, Adgate JL, Hill N, Sexton K, Pratt GC, Bock D. Comparison of short-term variations (15-minute averages) in outdoor and indoor PM2.5 concentra-tions. J Air & Waste Manage Assoc 2000; 50:1157-1166.

Richards WL., Alcorn SH, McDade C, Couture T, Lowenthal D, Chow JC, Watson JG. Optical properties of the San Joaquin Valley aerosol collected during the 1995 integrated monitoring study. Atmos Environ 1999; 33: 4787-4795.

Rotko T, Koistinen K, Hänninen O, Jantunen M. Sociodemographic descriptors of personal exposure to fine particles (PM2.5) in EXPOLIS Helsinki. J Exposure Anal Environ Epidemiol 2000; 10: 385-393.

Ruby MG, Rood M.J, Waggoner AP, Robinson E, Blumenthal DL, Watson JG. Inte-grating nephelometer measurement of scattering coefficient and fine particle concen-trations. In: Lodge J.P., ed. Methods of Air Sampling and Analysis, 3rd ed. Lewis Pub-lishers: Chelsea, MI, 1989; 450-457.

Sioutas S, Kim S, Chang M, Terrel LL, Gong H Jr. Field evaluation of a modified Da-taRAM MIE scattering monitor for real-time PM2.5 mass concentration measurements. Atmos Environ 2000; 34: 4829-4838.

Salvi S, Blomberg A, Rudell B, Kelly F, Sandström T, Holgate ST, Frew A. Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers. Am J Respir Crit Care Med 1999; 159: 702-709.

Sundeep S, Blomberg A, Rudell B, Kelly F, Sandström T, Holgate S, Frew A. Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaus in healthy human volunteers. Am J Respir Crit Care Med 1999; 159: 702-709.

Vedal S. Ambient particles and health: Lines that divide. J Air & Waste Manage As-soc 1997; 47: 551-581.

Wigzell E, Kendall M, Nieuwenhuijsen MJ. The spatial and temporal variation of particulate matter within the home. J Exposure Anal Environ Epidemiol 2000; 10: 307-314.

8 HOURLY VARIATION IN FINE PARTICLE EXPOSURE IS ASSOCIATED WITH TRANSIENTLY INCREASED RISK OF ST SEGMENT DEPRESSION

Lanki T,[1] Hoek G,[2] Timonen KL,[3] Peters A,[4] Tiittanen P,[1] Vanninen E,[3] and Pekkanen J[1,5]

[1] Environmental Epidemiology Unit, National Public Health Institute (KTL), Kuopio, Finland

[2] Environmental and Occupational Health Division, Institute for Risk Assessment Sciences (IRAS), Utrecht University, the Netherlands

[3] Department of Clinical Physiology and Nuclear Medicine, Kuopio University and Kuopio University Hospital, Finland

[4] Institute of Epidemiology, GSF-National Research Center for Environment and Health, Neuherberg, Germany

[5] School of Public Health and Clinical Nutrition, University of Kuopio, Finland

Abstract

Rationale: We have previously observed an association between daily outdoor fine particle ($PM_{2.5}$; <2.5 µm) levels and the occurrence of exercise induced ST segment depressions, an indicator for myocardial ischemia. However, some epidemiological studies have observed cardiovascular system to be responsive even within hours of exposure.

Objective: To evaluate whether hourly changes in personal $PM_{2.5}$ exposure or outdoor particle concentrations are associated with a rapid ischemic response.

Methods: Forty-seven non-smoking elderly persons with coronary heart disease were followed up with biweekly exercise tests and measurements of personal and outdoor concentrations of particulate matter in Helsinki, Finland.

Measurements: The occurrence of ST segment depressions >0.1 mV was recorded during submaximal exercise test. Photometers were used to record hourly variation in personal $PM_{2.5}$ exposure during 24-hrs before the clinic visit. Outdoor levels of $PM_{2.5}$ and ultrafine particles (<0.1 µm) were measured at one fixed site. Associations between particulate air pollution and ST segment depressions were evaluated using logistic regression and generalized additive models.

Main results: Personal and outdoor $PM_{2.5}$ concentrations during 4 hours before exercise testing were associated with ST segment depressions (odds ratio for personal $PM_{2.5}$ 2.42 [per 10 $\mu g/m^3$], confidence interval, 0.75, 7.83; odds ratio for outdoor $PM_{2.5}$ 2.47, confidence interval, 1.05, 5.85). Outdoor concentrations of ultrafine particles were not associated with the end-point.

Conclusion: The results suggest that even very short-term elevations in fine particle exposure might increase the risk of myocardial ischemia. The mechanism is still open, but could involve changes in autonomic nervous control of heart.

Introduction

Increases in daily levels of particulate air pollution (PM) measured at fixed outdoor monitoring sites have been associated with increased risk for cardiovascular hospitalizations and mortality in numerous epidemiological studies.[1,2] The associations have been especially strong among persons with pre-existing cardiovascular disorder,[3,4] and stronger for fine particles ($PM_{2.5}$; particles <2.5 µm in aerodynamic diameter) than for larger size fractions.[5] Vehicular traffic and stationary combustion sources are responsible for a major part of fine particle emissions. There is increasing epidemiological evidence that particles from these sources are especially harmful.[6,7] Ultrafine particles (UF; <0.1 µm) represent fresh combustion particles, and have been found damaging especially in toxicological studies.[8,9]

Cardiovascular diseases can be considered in essence as inflammatory diseases, and correspondingly the hypothesized main pathway from particle exposure to clinically observable acute cardiovascular effects involves both local and systemic inflammation.[10] Particles originating from combustion sources contain transition metals, quinones and polycyclic aromatic hydrocarbons which have oxidative properties.[9,11] Oxidative stress caused by inhaled ambient particles has been associated in controlled human exposure studies with the induction of pulmonary inflammation.[12] This localized inflammation in turn may develop into systemic inflammation impairing coronary endothelial function.[10] Daily increases in particulate air pollution have been associated with increased circulating levels of inflammatory and coagulatory markers in epidemiological studies.[13,14] However, exposure to particles has also been observed to have an effect on heart rate variability (HRV), a measure of autonomic control of heart.[15,16] It is not clear, whether exposure to particles affects HRV via systemic inflammation or by direct activation of neural receptors in lungs.

Most epidemiological studies have examined the health effects of average PM levels during a few days before hospitalization or death. However, some studies have associated hourly changes in outdoor PM levels with changes in heart rate variability

and repolarization dynamics, suggesting involvement of an additional immediate physiological response.[17,18] Consistent with this, one hour exposure to traffic has been associated with the onset of myocardial infarction.[19] However, the effects of stress, noise and traffic-related air pollution could not be separated in the study. Exposure to particles has been hypothesized to trigger myocardial infarction by altering autonomic tone of heart, which would enhance the instability of a vascular plaque or initiate cardiac arrhythmias.[10]

We evaluated among persons with coronary heart disease, whether there is evidence of an immediate (within hours) effect of $PM_{2.5}$ and ultrafine particles on the occurrence of exercise induced ST segment depressions in electrocardiography, an indicator for myocardial ischemia. Personal measurements of $PM_{2.5}$ were conducted for 22 hrs before the clinic visit to decrease exposure misclassification. Although daily $PM_{2.5}$ exposures have been shown to correlate longitudinally reasonably well with central outdoor measurements,[20] on hourly level the correlations are expected to be worse. We have previously demonstrated that the levels of outdoor $PM_{2.5}$ and ultrafine particles two days before a clinic visit are associated with ST segment depression in the same study population.[21]

Methods

Forty-seven subjects with coronary artery disease were followed-up with biweekly clinic visits and personal and outdoor measurements of particulate air pollution for 4 months in Helsinki, Finland, as part of the European ULTRA study. The main inclusion criteria for the study were: a self report on a doctor-diagnosed coronary artery disease, being a non-smoker, and age > 50 years. All methods used in the study were conducted according to Standard Operating Procedures.[22]

The occurrence of ST depressions larger than 0.1 mV during a 6-min submaximal exercise test was used as the end-point in the current study. The ambulatory electrocardiograms were recorded with Oxford MR-63 tape recorders (Oxford Instruments, Abington, U.K.), and the recordings were analyzed with the Oxford Medilog Excel II system (V7.5, Oxford Instruments, Abington, U.K.) in one core laboratory.[22] The study protocol was approved by the ethical committee of the National Public Health Institute. A written consent was obtained from all study participants.

During winter/spring 1999 (7.1.-30.4.), exposure to fine particles was measured in 1-minute intervals during the 24 hours preceding a clinical visit. The personal sampling system, build into an aluminum case, contained in series a $PM_{2.5}$ cyclone, a data logging photometer (pDR-1200 X, MIE, Inc., Bedford, MA, USA), a filter holder with a Teflon filter for gravimetric analyses of particles on daily level, and a pump (AFC400S, BGI, Inc., Waltham, MA, USA).[23] After every measurement, the study

participants filled out a questionnaire characterizing exposure, and including questions on time spent in several microenvironments, cleaning and cooking activities.

Central outdoor hourly $PM_{2.5}$ concentrations were measured with beta-attenuation method (ESM Eberline, FH 62 I-R) and number concentration of ultrafine particles with the Electric Aerosol Spectrometer.[24] All participants lived within 5 km from the measurement site.

Hourly and daily outdoor and personal particle concentrations were used in the analyses. Hour 0 was defined as the hour of the clinic visit, and thus particle concentration at lag 1 represented the exposure (or outdoor concentration) during the hour preceding the clinic visit. Further, 4-hour personal $PM_{2.5}$ concentration was calculated as the average of hours 1-4, 8-h average took into account hours 1-8 and so on. The maximum averaging time used for personal measurements was 22 hours, which was the length of the shortest measurements. The longitudinal correlation between personal and outdoor $PM_{2.5}$ was calculated as the median of subject specific correlation coefficients.

Data were analyzed using logistic regression and the statistical software R. A basic confounder model was built first without including particulate matter.[22] The model included a dummy for each subject and linear terms for long-term time trend, 4-h average temperature and relative humidity, and difference in heart rate between a 5-min rest period in supine position and the exercise test. We used penalized thin plate regression splines and the mgcv-procedure (Ver. 1.3-12) in the generalized additive models framework to evaluate possible non-linear effects of confounders.[25] The estimated degree of freedom for the smooth terms was less than 1.5 for all covariates, and they were considered to be linear.

The effect of extreme PM concentrations was evaluated by calculating an outlier concentration corresponding to 3 times the interquartile range of each averaging time, excluding observations higher than the value, and then repeating the procedure once.

For the analyses we standardized the measured photometric $PM_{2.5}$ concentrations by multiplying hourly concentrations with the average photometric to gravimetric $PM_{2.5}$ ratio during the specific 24-h period.

Results

There were 179 clinic visits with successful recording of ST segment depressions during exercise test for which personal hourly $PM_{2.5}$ data was available. Thirteen persons had visits both with and without ST segment depressions, and they provided 64 observations with 31 ST segment depressions. There were 229 visits with outdoor $PM_{2.5}$ data, and during these visits there were 98 observations and 45 ST events from 17 persons having variation in the outcome. Typically the clinic visits started between 10 and 11 am (median time).

Only persons having variation in the outcome were included in further analyses. The mean age of the study panel was nearly 70 years (Table 1). Approximately half of the study participants had had myocardial infarction, and over 60% of them used daily β-receptor antagonists.

Table 1. Characteristics of the study participants with personal $PM_{2.5}$ measurements and all subjects during the same period (n [%] or mean [±stdev]).

	Personal $PM_{2.5}$ measurements	Outdoor $PM_{2.5}$ and UF measurements
N of subjects	13	17
Sex / female	8 (62)	12 (71)
Age (y)	68.4±6.7	69.5± 7
Body mass index (kg/m^3)	27.3±3.9	27.0±3.4
History of past myocardial infarction	7 (54)	8 (47)
Coronary bypass or PTCA	8 (62)	10 (59)
Hypertension	7 (54)	10 (59)
Diabetes	1 (8)	1 (6)
Regular, daily use of β-blockers	8 (61.5)	11 (65)
Heart rate at the end of exercise test	91.2±6.5	91.9±5.9

The 1-h personal $PM_{2.5}$ concentration before the clinic visit (lag 1) was approximately the same as outdoor $PM_{2.5}$, but lower at longer averaging times (Table 2). Exclusion of extreme personal $PM_{2.5}$ concentrations drastically decreased the maximum concentrations. Using the exposure questionnaires, the extremes were all linked to indoor PM sources: 4 out of 6 peaks (affecting multiple lags) were caused by cooking and 2 by environmental tobacco smoke. As we were interested mainly on the effects of outdoor air pollution, the results on the effects of air

pollution on ST segment depressions are given without the extremes. Considering outdoor particles, one extreme value was identified among 1-h UF concentrations.

Table 2. Descriptive statistics for personal and outdoor PM$_{2.5}$ (µg/m^3) and outdoor ultrafine particles (1/cm^3).

	N	Averaging time	25th percentile	Median	75th percentile	Max
Personal PM$_{2.5}$	64	1-h	8.9	13.6	20.0	746.3
	64	4-h	7.1	11.3	16.9	189.6
	64	8-h	5.9	10.1	14.9	117.8
	64	12-h	6.3	10.1	14.6	79.4
	64	22-h	7.4	10.0	14.0	52.9
Personal PM$_{2.5}$	59	1-h	8.5	13.1	17.3	41.5
without extreme values	59	4-h	6.6	11.1	16.0	35.3
	61	8-h	5.7	9.9	13.8	29.2
	61	12-h	6.2	10.0	12.6	25.9
	60	22-h	7.3	9.7	13.0	23.5
Outdoor PM$_{2.5}$	96	1-h	9.2	13.4	18.1	42.9
	97	4-h	9.3	13.5	16.9	40.8
	97	8-h	8.5	13.3	17.4	39.2
	97	12-h	8.4	12.3	17.3	36.2
	98	24-h	8.9	12.2	17.8	29.2
Outdoor ultrafine	98	1-h	13 100	20 800	30 700	84 700
particles	98	4-h	14 000	22 600	32 800	88 800
	98	8-h	11 100	18200	27 000	57 600
	98	12-h	9 900	14 400	21 100	46 500
	98	24-h	11 200	15 000	23 000	46 100

The longitudinal correlations between personal and outdoor PM$_{2.5}$ were moderate for daily and 1-h average concentrations prior to clinic visit, but lower for other averaging times (Table 3). Personal daily averages correlated poorly with the one hour personal exposure just before the clinic visit, but better with longer average exposures. All outdoor PM$_{2.5}$ averages inter-correlated at least moderately.

Spearman's correlation coefficients between daily (1-h) outdoor UF concentrations and outdoor and personal PM$_{2.5}$ measured just before the clinic visit were 0.32 (0.1) and 0.08 (0.08), respectively.

One-hour average personal $PM_{2.5}$ exposure prior to the clinic visit was significantly associated with the occurrence of ST segment depressions, and the odds ratio for 4-h average was also considerable although not statistically significant (Table 4). Four-hour average outdoor $PM_{2.5}$ concentration was statistically significantly associated with ST segment depressions, whereas daily outdoor $PM_{2.5}$ concentration was not associated with the end-point (Table 4). Ultrafine particles were not associated with ST segment depression, and exclusion of the extreme 1-h value did not change results.

Table 3. Spearman's correlation coefficients between different averaging times of personal and outdoor $PM_{2.5}$. Upper triangle: personal-personal; lower triangle: outdoor-outdoor; diagonal: personal-outdoor (longitudinal correlation).

Personal $PM_{2.5}$	1-hour	4-hour	8-hour	12-hour	22-hour	Outdoor vs.
22-hour	0.54	0.70	0.75	0.84	0.80	*24-hour*
12-hour	0.70	0.91	0.96	0.50	*0.93*	*12-hour*
8-hour	0.74	0.97	0.60	*0.98*	*0.79*	*8-hour*
4-hour	0.83	0.54	*0.94*	*0.92*	*0.78*	*4-hour*
1-hour	0.70	*0.93*	*0.79*	*0.78*	*0.69*	*1-hour*
Personal	*1-hour*	*4-hour*	*8-hour*	*12-hour*	*24-hour*	*Outdoor $PM_{2.5}$*

Looking at individual hourly lags of outdoor $PM_{2.5}$ (Figure 1), the highest odds ratio was observed for lag 2, but odds ratios until lag 10 were all positive.

Discussion

Among elderly persons with coronary heart disease, we observed an increased risk of exercise induced ST segment depressions in association with hourly variation in personal $PM_{2.5}$ exposure and outdoor levels within 24 hours before the exercise test. The associations were statistically significant for 1-h $PM_{2.5}$ exposure and 4-h outdoor concentration prior to the test. Variation in outdoor ultrafine particle concentrations was not associated with ST segment depressions during the same 24-h period.

We observed in the current study an association between ST segment depressions and $PM_{2.5}$ exposure and outdoor concentrations during a few hours before ST segment recording. Gold et al.[26] have recently reported among elderly an association for outdoor levels of black carbon in the 12-h period before ST segment recording, except during stress test period. In the study, there was no evidence of the effects
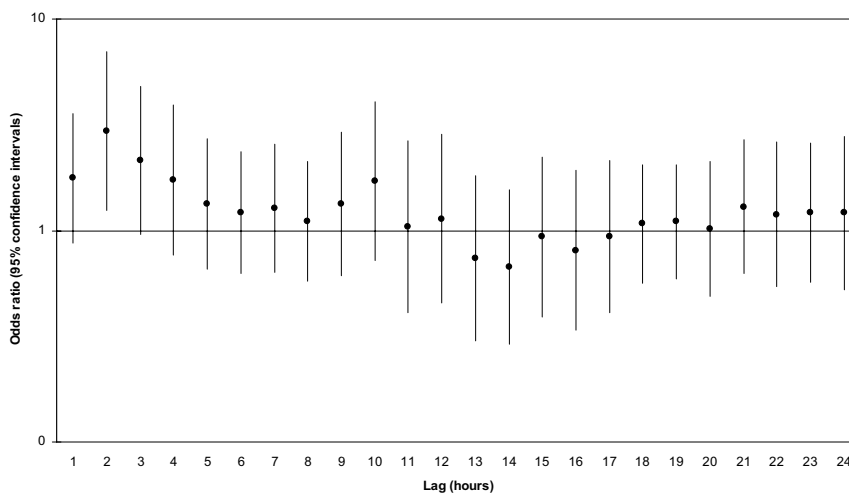
Figure 1. Odds ratios between 1-h outdoor PM$_{2.5}$ concentrations and ST segment depressions >0.1 mV. Odds ratios calculated for an increase of 10 μg/m^3 in PM$_{2.5}$.

Table 4. Odds ratios (ORs) for an association of personal and outdoor PM$_{2.5}$ and outdoor UF with the occurrence of ST segment depressions >0.1 mV. ORs calculated for an increase of 10 μg/m^3 in PM$_{2.5}$ and 10 000 particles/cm^3 in UF.

	Averaging time	N	>0.1 mV OR	>0.1 mV 95% Cl
Personal PM$_{2.5}$	1-hr	56	3.26	1.07-9.99
	4-hrs	57	2.42	0.75-7.83
	8-hrs	59	1.57	0.49-5.09
	12-hrs	59	1.96	0.44-8.64
	22-hrs	59	2.06	0.30-14.10
Outdoor PM$_{2.5}$	1-hr	90	1.77	0,87-3.58
	4-hrs	90	2.47	1.05-5.85
	8-hrs	91	1.83	0.80-4.20
	12-hrs	90	1.90	0.77-4.65
	24-hrs	90	1.60	0.59-4.39
Outdoor ultrafine particles	1-hr	92	1.22	0.79-1.89
	4-hrs	92	1.14	0.74-1.75
	8-hrs	92	1.19	0.71-1.98
	12-hrs	92	1.19	0.62-2.26
	24-hrs	92	1.06	0.53-2.16

of fine particles, or of delayed effects of black carbon. We have previously shown an association between 2-days lagged outdoor air pollution levels, including $PM_{2.5}$ and ultrafine particles, and the occurrence of ST segment depressions.[21] Taken together, our two studies suggest that there is both an immediate (within hours) and delayed (within days) effect of $PM_{2.5}$ on myocardial ischemia, as indicated by increased risk of ST segment depression. Our results are in line with a previous study by Peters et al.,[27] who suggested outdoor $PM_{2.5}$ levels to have independent immediate and delayed effects on the onset of myocardial infarction.

Both the initiation and progression of atherosclerosis and the onset of myocardial infarction and other acute forms of cardiovascular diseases have been found to include an important inflammatory component.[28] The effect of particulate air pollution on ST segment depression at 2-day lag could be explained by increased pulmonary and resulting systemic inflammation increasing blood viscosity and/or or impairing endothelial function leading to vasoconstriction, both mechanisms which would decrease oxygen supply to the heart.[29] However, it is unclear whether systemic inflammation could explain the rapid, transient increase in the occurrence of ST segment depressions after short-term $PM_{2.5}$ exposure. Instead, the effect may be linked to changes in autonomic nervous control of heart induced by particulate air pollution

In controlled human exposure studies even hourly exposure to PM has been associated with a decrease in heart rate variability among elderly subjects.[30] Heart rate variability and systemic inflammation have been proposed to be inversely associated,[31] but the observed rapid response in the current study is potentially explained by a direct induction of airway-mediated autonomic reflexes by pulmonary oxidative stress. Reactive oxygen species have recently been proposed to mediate the effect of particle exposure on high frequency component of HRV.[32] The following sympathetic stress may cause rapid vasoconstriction of coronary arteries or increases in cardiac demand. Sudden decrease in heart rate variability has been observed to precede ischemic events.[33] Consistent with this, we previously observed stronger effects of particulate air pollution on ST segment depression among persons not taking β-blocker medication, which would increase vagal activity.[34]

Hourly ultrafine particle concentrations, marker for traffic exhausts, were not associated with ST segment depression, although a delayed effect was observed in our earlier study.[21] It is likely that greater exposure misclassification on hourly than on daily level at least partly explains the discrepancy. In future studies, personal measurements of ultrafine particles should be conducted. The observation of an effect of very-short term $PM_{2.5}$ exposure on myocardial ischemia yet has implications concerning local traffic emissions, because especially during traffic peaks high ambient PM concentrations are encountered. Exposure to in-vehicle $PM_{2.5}$ has recently been reported to be more strongly associated with heart rate

variability and inflammatory markers than ambient or even road-side $PM_{2.5}$,[35] and just one hour exposure to traffic has been associated with myocardial infarction.[19] The observed association between hourly black carbon concentrations and ST segment depression in the study by Gold et al.[26] also underline the importance of traffic emissions.

A major strength of the current study was the use of personal measurements for $PM_{2.5}$. By linking actual exposures to ST segment depressions, we avoided exposure misclassification, inevitable for outdoor measurements, that is caused by varying infiltrations rates at homes and spatial variability of outdoor PM due to major roads.[36,37] However, personal $PM_{2.5}$ levels were not substantially more strongly associated with ST segment depressions than were outdoor measurements. The observation becomes understandable if we assume that outdoor $PM_{2.5}$ is mainly responsible for the effect. In that case, indoor sources would only blur the underlying association, and cancel some of the benefits of using personal measurements. The importance of indoor sources on $PM_{2.5}$ exposure became evident in our study by looking at the extreme exposures that were all linked to indoor sources. However, it should be noted that all the study participants lived within 5 km from the $PM_{2.5}$ outdoor measurement site. In most studies, study populations reside on much larger areas, in which case the benefits of personal measurements are likely to be clearer.

The main limitation in the study was the low number of persons with variation in ST segment depression, even when the study panel consisted of persons more likely to experience ischemia than general population. One should clearly not focus on the exact odds ratios in the study, but on general trends. The photometers used for personal measurements have their own limitations, caused mainly by sensitivity of results to changes in relative humidity and particle density.[38] We have previously reported a good correlation between gravimetric (filter collection method) and photometric $PM_{2.5}$ concentrations on daily level.[23] In the present study, we utilized the gravimetric method in the standardization of the photometric concentrations to decrease measurement error.

In conclusion, hourly increases in exposure to fine particles were associated with a rapid increase in the risk of ST segment depressions. Together with other recent studies, the observation suggests that ambient particles have both an immediate and a delayed effect on myocardial ischemia. The mechanisms of the two types of effects may differ.

References

1. Dominici F, Peng RD, Bell ML, Pham L, McDermott A, Zeger SL, Samet JM. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA* 2006;295:1127-1134.

2. Analitis A, Katsouyanni K, Dimakopoulou K, Samoli E, Nikoloulopoulos AK, Petasakis Y, Touloumi G, Schwartz J, Anderson HR, Cambra K, Forastiere F, Zmirou D, Vonk JM, Clancy L, Kriz B, Bobvos J, Pekkanen J. Short-term effects of ambient particles on cardiovascular and respiratory mortality. *Epidemiology* 2006;17:230-233.

3. von Klot S, Peters A, Aalto P, Bellander T, Berglind N, D'Ippoliti D, Elosua R, Hörmann A, Kulmala M, Lanki T, Löwel H, Pekkanen J, Picciotto S, Sunyer J, Forastiere F for the HEAPSS Study Group. Ambient air pollution is associated with increased risk of hospital cardiac readmissions of myocardial infarction survivors in European cities. *Circulation* 2005;112:3073-3079.

4. Goldberg MS, Burnett RT, Bailar JC 3rd, Tamblyn R, Ernst P, Flegel K, Brook J, Bonvalot Y, Singh R, Valois MF, Vincent R. Identification of persons with cardiorespiratory conditions who are at risk of dying from the acute effects of ambient air particles. *Environ Health Perspect* 2001;109 Suppl 4:487-494.

5. Schwartz J, Dockery DW, Neas LM. Is daily mortality associated specifically with fine particles? *J Air Waste Manag Assoc* 1996;46:927-939.

6. Hoek G, Brunekreef B, Goldbohm S, Fischer P, van den Brandt PA. Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. *Lancet* 2002;360:1203-1209.

7. Lanki T, de Hartog JJ, Heinrich J, Hoek G, Janssen NAH, Peters A, Stölzel M, Timonen KL, Vallius M, Vanninen E, Pekkanen J. Can we identify sources of fine particles responsible for exercise-induced ischemia on days with elevated air pollution? The ULTRA study. *Environmental Health Perspectives* 2006;114:655-660.

8. Brown DM, Donaldson K, Borm PJ, Schins RP, Dehnhardt M, Gilmour P, Jimenez LA, Stone V. Calcium and ROS-mediated activation of transcription factors and TNF-α cytokine gene expression in macrophages exposed to ultrafine particles. *Am J Physiol Lung Cell Mol Physiol* 2003; 286:L344-353.

9. Xia T, Korge P, Weiss JN, Li N, Venkatesen MI, Sioutas C, Nel A. Quinones and aromatic chemical compounds in particulate matter induce mitochondrial dysfunction: implications for ultrafine particle toxicity. *Environ Health Perspect* 2004;112:1347-1358.

10. Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, Luepker R, Mittleman M, Samet J, Smith SC Jr, Tager I; Expert Panel on Population and Prevention Science of the American Heart Association. Air pollution and cardiovascular disease: a statement for health care professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. *Circulation* 2004;109:2655-2671.

11. Lighty JS, Veranth JM, Sarofim AF. Combustion aerosols: factors governing their size and composition and implications to human health. *J Air Waste Manag Assoc* 2000;50:1565-1622.

12. Ghio AJ, Kim C, Devlin RB. Concentrated ambient air particles induce mild pulmonary inflammation in healthy human volunteers. *Am J Respir Crit Care Med* 2000;162:981-988.

13. Ruckerl R, Ibald-Mulli A, Koenig W, Schneider A, Woelke G, Cyrys J, Heinrich J, Marder V, Frampton M, Wichmann HE, Peters A. Air pollution and markers of inflammation and coagulation in patients with coronary heart disease. *Am J Respir Crit Care Med* 2006;173:432-441.

14. Pekkanen J, Brunner EJ, Anderson HR, Tiittanen P, Atkinson RW. Daily concentrations of air pollution and plasma fibrinogen in London. *Occup Environ Med* 2000;57:818-822.

15. Pope CA 3rd, Hansen ML, Long RW, Nielsen KR, Eatough NL, Wilson WE, Eatough DJ. Ambient particulate air pollution, heart rate variability, and blood markers of inflammation in a panel of elderly subjects. *Environ Health Perspect* 2004;112:339-345.

16. Timonen KL, Vanninen E, de Hartog J, Ibald-Mulli A, Brunekreef B, Gold DR, Heinrich J, Hoek G, Lanki T, Peters A, Tarkiainen T, Kreyling W, Pekkanen J. Effects of ultrafine and fine particulate and gaseous air pollution on cardiac autonomic control in subjects with coronary artery disease. The ULTRA study. *J Expo Sci Environ Epidemiol* 2006;16:332-341.

17. Gold DR, Litonjua A, Schwartz J, Lovett E, Larson A, Nearing B, Allen G, Verrier M, Cherry R, Verrier R. Ambient pollution and heart rate variability. *Circulation* 2000;101:1267-1273.

18. Henneberger A, Zareba W, Ibald-Mulli A, Ruckerl R, Cyrys J, Couderc JP, Mykins B, Woelke G, Wichmann HE, Peters A. Repolarization changes induced by air pollution in ischemic heart disease patients. *Environ Health Perspect* 2005;113:440-446.

19. Peters A, von Klot S, Heier M, Trentinaglia I, Hormann A, Wichmann HE, Lowel H, Cooperative Health Research in the Region of Augsburg Study Group. 2004. Exposure to traffic and the onset of myocardial infarction. *N Engl J Med* 351:1721-1730.

20. Janssen NA, de Hartog JJ, Hoek G, Brunegreef B, Lanki T, Timonen KL, Pekkanen J. Personal exposure to fine particulate matter in elderly subjects: relation between personal, indoor and outdoor concentrations. *J Air & Waste Manage Assoc* 2000;50:1133-1143.

21. Pekkanen J, Peters A, Hoek G, Tiittanen P, Brunekreef B, de Hartog J, Heinrich J, Ibald-Mulli A, Kreyling WG, Lanki T, Timonen KL, Vanninen E. Particulate air pollution and risk of ST segment depression during repeated submaximal exercise tests among subjects with coronary heart disease. The ULTRA study. *Circulation* 2002;106:933-938.

22. Pekkanen J, Timonen KL, Tiittanen P, Vallius M, Lanki T, Sinkko H, Ruuskanen J, Mirme A, Kulmala M, Vanninen E, Bernard A, Ibald-Mulli A, Wölke G, Staedeler M, Tuch Th, Kreyling W, Peters A, Heinrich J, de Hartog JJ, Oldenwening M, Kos G, ten Brink H, Khlystov A, van Wijnen J, Brunekreef B, Hoek G. ULTRA: Exposure and risk assessment for fine and ultrafine particles in ambient air. Study manual and data book. Publications of National Public Health Institute 2000. Available at http://www.ktl.fi/ultra.

23. Lanki T, Alm S, Ruuskanen J, Janssen NAH, Jantunen M, Pekkanen J. Photometrically measured continuous personal $PM_{2.5}$ exposure: Levels and correlation to a gravimetric method. *J Exposure Anal Environ Epidemiol* 2002: 12: 172-178.

24. Mirme A, Kreyling WG, Khlystov A, ten Brink H, Ruuskanen J, Tuch H, Pekkanen J. Intercomparison of aerosol spectrometers for ambient air monitoring. *Aerosol Sci Technol* 2002;36:866-876.

25. Wood SN, Augustin NH. GAMs with integrated model selection using penalized regression splines and applications to environmental modelling. *Ecol Model* 2002;157:157-77.

26. Gold DR, Litonjua AA, Zanobetti A, Coull BA, Schwartz J, MacCallum G, Verrier RL, Nearing BD, Canner MJ, Suh H, Stone PH. Air pollution and ST-segment depression in elderly subjects. *Environ Health Perspect* 2005;113:883-887.

27. Peters A, Dockery W, Muller JE, Mittleman MA. Increased particulate air pollution and the triggering of myocardial infarction. *Circulation 2001*;103:2810-2815.

28. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002;1135-1143.

29. Verrier RL, Mittleman MA, Stone PH. Air pollution. An insidious and pervasive component of cardiac risk. *Circulation* 2002;106:890-892.

30. Devlin RB, Ghio AJ, Kehrl H, Sanders G, Cascio W. Elderly humans exposed to concentrated air pollution particles have decreased heart rate variability. *Eur Respir J* 2003;21 Suppl. 40, 76-80.

31. Janszky I, Ericson M, Lekander M, Blom M, Buhlin K, Georgiades A, Ahnve S. Inflammatory markers and heart rate variability in women with coronary heart disease. *J Intern Med* 2004;256:421-428.

32. Schwartz J, Park SK, O'Neill MS, Vokonas PS, Sparrow D, Weiss S, Kelsey K. Glutathione-S-transferase M1, obesity, statins, and autonomic effects of particles: gene-by-drug-by-environment interaction. *Am J Respir Crit Care Med* 2005;172:1529-1533.

33. Pozzati A, Pancaldi LG, Di Pasquale G, Pinelli G, Bugiardini R. Transient sympathovagal imbalance triggers "ischemic" sudden death in patients undergoing electrocardiographic Holter monitoring. *J Am Coll Cardiol* 1996;27:847-852.

34. Cogliati C, Colombo S, Ruscone TG, Gruosso D, Porta A, Montano N, Malliani A, Furlan R. Acute beta-blockade increases muscle sympathetic activity and modifies its frequency distribution. *Circulation* 2004;110:2786-2791.

35. Riediker M, Cascio WE, Griggs TR, Herbst MC, Bromberg PA, Neas L, Williams RW, Devlin RB. Particulate matter exposure in cars is associated with cardiovascular effects in healthy young men. Am J Respir Crit Care Med 2004;169:934-940.

36. Sarnat SE, Coull BA, Schwartz J, Gold DR, Suh HH. Factors affecting the association between ambient concentrations and personal exposures to particles and gases. *Environ Health Perspect* 2006;114:649-654.

37. Lanki T, Ahokas A, Alm S, Janssen NAH, Hoek G, de Hartog JJ, Brunekreef B, Pekkanen J. Determinants of personal and indoor $PM_{2.5}$ and absorbance among elderly subjects with coronary heart disease. *J Expo Sci Environ Epidemiol*, in press (doi:10.1038/sj.jes.7500470)

38. Sioutas S, Kim S, Chang M, Terrel LL, Gong H Jr. Field evaluation of a modified DataRAM MIE scattering monitor for real-time $PM_{2.5}$ mass concentration measurements. *Atmos Environ* 2000;34:4829-4838.

9   CAN WE IDENTIFY SOURCES OF FINE PARTICLES RESPONSIBLE FOR EXERCISE-INDUCED ISCHEMIA ON DAYS WITH ELEVATED AIR POLLUTION? THE ULTRA STUDY

Lanki T,[1] de Hartog JJ,[2] Heinrich J,[3] Hoek G,[2] Janssen NAH,[2] Peters A,[3] Stölzel M,[3] Timonen KL,[4] Vallius M,[1] Vanninen E,[4,5] and Pekkanen J[1,5]

[1] Unit of Environmental Epidemiology, National Public Health Institute, Kuopio, Finland

[2] IRAS, Utrecht University, the Netherlands

[3] GSF-National Research Center for Environment and Health, Neuherberg, Germany

[4] Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital, Finland

[5] University of Kuopio, Finland

Abstract

Epidemiological studies have shown ambient particulate matter to have adverse effects on cardiovascular health. Effective mitigation of the health effects requires identification of the most harmful particle sources. The objective of our study was to evaluate relative effects of fine particles from different sources on exercise induced ischemia. We collected daily outdoor fine particle (particles <2.5 μm; $PM_{2.5}$) samples between autumn 1998 and spring 1999 in Helsinki, Finland. The mass of fine particles was apportioned between five sources. Forty-five elderly non-smoking persons with stable coronary heart disease visited a clinic biweekly for submaximal exercise testing, during which the occurrence of ST segment depressions was recorded. Levels of $PM_{2.5}$ originating from local traffic and long-range transport were associated with ST segment depressions >0.1 mV, odds ratios at two-day lag being 1.53 (95% confidence interval: 1.19-1.97) and 1.11 (1.02- 1.20) per 1 μg/m^3, respectively. In multi-pollutant models, where we used indicator elements for sources instead of source-specific $PM_{2.5}$, only absorbance (elemental carbon), indicator for local traffic and other combustion, was associated with ST segment depressions. Our results suggest that the fraction of particles originating from

combustion processes, notably traffic, is responsible for the exacerbation of ischemic heart diseases associated with particulate mass.

Introduction

For a long time it was assumed that ambient particulate matter damages primarily lungs (Dockery and Pope 1994; Pope 1989). Epidemiological evidence accumulated during the last decade shows that daily levels of particles are also associated with daily changes in mortality and hospitalizations due to cardiovascular diseases (Katsoyanni et al. 2001; Samet et al. 2000; Schwartz 1999; Zanobetti et al. 2000). Cohort studies suggest that cumulative effects of air pollution on cardiovascular health are even more important than acute effects (Pope et al. 2002, 2004). Although the relative risks associated with exposure to particulate matter are small compared to some other cardiovascular risk factors, the attributable health effects may be enormous due to ubiquitous nature of exposure. As an example, 6% of annual deaths has been assigned to particulate air pollution in 3 European countries (Künzli et al. 2000). Consequently, World Health Organization has in the 90's included air pollution on the list of ten major risks for death and disability (WHO 1996).

In general, air quality has markedly improved in developed countries during the last few decades. Unfortunately, no lower threshold has been observed for the effects of particulate matter (Daniels MJ et al. 2000), and further efforts to decrease the levels of particles are increasingly costly. Cost effective mitigation of health effects requires regulation of primarily those particle sources that are responsible for the effects. However, the constituents and characteristics of particulate matter responsible for the observed cardiovascular effects are unknown. Toxicological studies suggest the importance of transition metals (Goldsmith et al. 1998; Pagan et al. 2003), organic carbon compounds (Bonvallot et al. 2001; Urch et al. 2004), endotoxins (Long et al. 2001; Osornio-Vargar AR et al. 2003), and the smallest particle fraction, ultrafine particles (particles 0.01-0.1 μm in diameter) (Brown et al. 2003; Li et al. 2003). The few epidemiological studies that have compared the relative effects of different sources on cardiovascular health suggest that combustion particles are more important than crustal particles (Laden et al. 2000; Mar et al. 2000; Tsai et al. 2000).

The occurrence of ST segment depressions during stress test indicates myocardial ischemia (ACC/AHA 1997). We have previously shown in a panel of coronary heart disease patients that increases in the daily levels of ultrafine particles and fine particles (diameter $\leq 2.5\mu m$; $PM_{2.5}$) are associated with increased risk of ST segment depressions in Helsinki, Finland (Pekkanen et al. 2002). Our results provided an explanation for the associations observed in epidemiological studies between

ambient particles and hospitalizations and death due to ischemic heart diseases. We have recently apportioned $PM_{2.5}$ measurements of the earlier study between five major sources (Vallius et al. 2003). Using these data we now evaluate the relative, short-term effects of $PM_{2.5}$ from different sources on myocardial ischemia.

Materials and methods

Study population and protocol

The ULTRA study was conducted in Amsterdam, the Netherlands, Erfurt, Germany, and Helsinki, Finland, between autumn of 1998 and spring of 1999. In each city, we followed panels of elderly subjects with stable coronary heart disease for 6 months with biweekly clinic visits and daily symptom and medication diaries. At the same time, levels of particulate and gaseous air pollutants were monitored at fixed outdoor monitoring sites. We conducted all methods according to standard operating procedures (Pekkanen et al. 2000).

The main inclusion criteria for the study were a self-report on a doctor-diagnosed coronary artery disease, being a non-smoker and at least 50 years of age. The study subjects were characterized by a questionnaire and recording of a 12-lead standard resting ECG. For each subject, the clinic visit was scheduled for the same weekday and time of day. At every visit, ambulatory electrocardiogram was recorded during a standardized protocol, which included 6-minute submaximal exercise with a bicycle ergometer (Pekkanen et al. 2002).

Ethical committees in each country had approved the study protocol. All subjects gave a written informed consent before the study.

Recording of ST segment depressions

We have described the methodology used for the recording of ST segment depressions in detail elsewhere (Pekkanen et al. 2002). Briefly, the ambulatory electrocardiograms were recorded with Oxford MR-63 tape recorders (Oxford Instruments, Abington, U.K.), and the recordings were analyzed with the Oxford Medilog Excel II system (V7.5, Oxford Instruments, Abington, U.K.) in one core laboratory. ST depressions were measured at 63 msec after J-point. Only ST depressions having their start time during the exercise test were considered.

We used two endpoints in the present analyses: ST depressions larger than 0.1 mV regardless of the direction of the ST-slope (Rijneke et al. 1980), and ST depressions larger than 0.1 mV with horizontal or downward slope (i.e. stricter criteria)

(ACC/AHA 1997). The present analyses are limited to Helsinki, because there were only seven ST segment depressions > 0.1 mV in Amsterdam and five in Erfurt (Pekkanen et al. 2002). This was mainly due to the low heart rates achieved during the exercise tests. The low heart rates were mostly attributable to the fact that the study was done in the community setting and the field workers were very cautious in performing the exercise tests among coronary patients.

Exposure monitoring

In Helsinki, all study subjects lived within 5-km radius of the fixed outdoor $PM_{2.5}$ monitoring site. We collected daily noon-to-noon $PM_{2.5}$ filter samples with single-stage Harvard impactors 1.11.1998-30.4.1999. $PM_{2.5}$ concentrations were determined gravimetrically. After weighing, blackness of filters was measured and transformed into absorption coefficients, shortly absorbance (ABS). Absorbance is correlated with elemental carbon content of urban particulate matter (Cyrys et al. 2003; Janssen et al. 2000). We have reported the laboratory methods and quality control results elsewhere (Brunekreef et al. 2005; Janssen et al. 2000).

All $PM_{2.5}$ filter samples were analyzed for elemental composition with energy-dispersive X-ray fluorescence spectrometry. Automated Tracor Spectrace 5000 system (Tracor X-ray, Austin, TX, U.S.) was used for analyses in the Department of Chemistry, University of Antwerp (Belgium). The accuracy varied between 1 and 28% depending on the element and its concentration on the filter. Eighteen elements were analyzed. Details of the elemental analyses have been reported earlier (Brunekreef et al. 2005; Janssen et. al. 2005).

Number counts of ultrafine particles were measured with an electrical aerosol spectrometer developed in the Institute of Environmental Physics of the University of Tartu, Estonia (Tammet et al. 2002). The Helsinki Metropolitan Area Council provided the data on daily average temperature, and the Finnish Meteorological Institute the data on relative humidity.

Data analysis

We used principal component analysis and multivariate linear regression to apportion $PM_{2.5}$ mass between different sources. We identified source categories by examining the loadings of elements and other variables on the varimax (orthogonal) rotated principal components. We obtained estimates of daily source-specific $PM_{2.5}$ concentrations by regressing the measured $PM_{2.5}$ concentrations on absolute principal component scores (Thurston and Spengler 1985). Besides components of $PM_{2.5}$ (elemental concentrations and absorbance), daily data on ultrafine and

accumulation mode particles (diameter 0.1-1.0 μm), NO_2 and SO_2 were used to identify sources. Four days were excluded from the elemental data because of outliers leaving 164 days for analyses. Five main source categories were identified: local traffic (with contribution from other local combustion), long-range transported air pollution, crustal source, oil combustion, and salt source. The source apportionment methodology and results have been published recently (Vallius et al. 2003).

Air pollution concentrations of 0- to 3-day lags were evaluated. Lag 0 concentration was defined as the 24-hr average from noon the previous to noon of the day of the clinic visit; lag 1 concentration as the average concentration of the previous 24 hr and so on. A basic confounder model was built for ST segment depressions >0.1 mV without including particulate matter, and the same model was used for the horizontal or downward sloping ST segment depressions >0.1 mV. Loess functions were used to explore shapes and lags (0-3) of the covariates in S-Plus 2000 software (MathSoft Inc. 1999, Seattle, Washington, USA) (Hastie and Tibshirani 1990). Criteria for building the basic model were Akaike's information criteria and covariate-response plots. The protocol of statistical analyses is available at the ULTRA Study website (http://www.ktl.fi/ultra) (Pekkanen et al. 2000). Due to the recently raised questions on the usability of generalized additive models in S-Plus for air pollution research (Dominici et al. 2002), final analyses were conducted in the statistical package R using logistic regression (R-GAM function) with penalized splines (Eilers and Marx 1996; Wood 2001). The basic model included a dummy for each subject, linear terms for time trend, temperature (lag3) and relative humidity (lag3), and a penalized spline (df=3) for change in heart rate during exercise test.

As a sensitivity analysis, we evaluated the effect of extreme concentrations on results. For each $PM_{2.5}$ source, we calculated an outlier concentration corresponding to 3 times the interquartile range of each lag, and excluded all observations higher than the lowest of these outlier-concentrations from all the lags.

Varimax rotation used in principal component analysis forces the daily source-specific $PM_{2.5}$ concentrations to be non-correlating (Thurston and Spengler 1985), which does not always reflect reality. To allow correlation, we also constructed multi-pollutant models where indicator elements for sources were used instead of source-specific mass. For every source, the element with the highest correlation with source-specific mass was chosen as indicator.

Finally, we evaluated whether potentially toxic elements, not among the indicator elements, would be associated with ST segment depressions. Various two-pollutant models were also constructed using individual elements and ultrafine particles, but gaseous pollutants were not included in the models. Gaseous pollutants measured at a fixed outdoor monitoring site have been observed to reflect better exposures to

PM$_{2.5}$ than to gases themselves (Sarnat et al. 2005). Thus, interpretation of the models would have been difficult.

Results

There were 417 exercise tests performed during 511 visits among 47 subjects. Of the 417 exercise tests, we excluded 67 due to substandard quality of the recording and 8 due to missing data on covariates, leaving 342 exercise tests for analyses. There were altogether 45 study subjects in the final analyses, 24 of them were male. Mean (±SD) age of the subjects was 68.2 ± 6.5 years. Twenty-three of the subjects had had coronary by-pass surgery or percutaneous transluminal coronary angioplasty, 27 had history of myocardial infarction, and 31 used β-blockers. Details of the study panel have already been published (Pekkanen et al. 2002).

During the study, 164 valid outdoor samples were collected. Thirteen elements (K, V, Mn, Cu, Zn, Pb, Al, Si, S, Cl, Ca, Fe, Ni) were detectable in more than 50 % of samples, rest were excluded from analyses. In addition, Pb and Al were left out from current analyses due to low precision and reliability (Janssen et al. 2005). However, these elements were used in source-apportionment, because even less precisely detected elements can improve the apportionment of PM between sources (Vallius et al. 2003).

Descriptive statistics for components of PM$_{2.5}$ and ultrafine particles have been presented in Table 1. Sulfur was the most abundant element. Half of mass was apportioned to sulfur-rich long-range transported PM$_{2.5}$.

Many of the elements were highly correlated (Table 2). PM$_{2.5}$ was highly correlated with K, S, Zn, and absorbance, but not correlated with ultrafine particles. The highest correlation coefficients between elements and source-specific PM$_{2.5}$ were found between Si and crustal PM$_{2.5}$, S and long-range transported PM$_{2.5}$, Ni/V and PM$_{2.5}$ from oil combustion, Cl and PM$_{2.5}$ from salt source (salt source also characterized by high Pb concentrations), and ABS and traffic originating PM$_{2.5}$.

Median (minimum) daily temperature and relative humidity during the study period were -0.44 ^{o}C (-23.3) and 87.6 % (51.1), respectively. Temperature was negatively correlated with PM$_{2.5}$ from local traffic (r=-0.33) and oil combustion (r=-0.35), and relative humidity with PM$_{2.5}$ from oil combustion (r=-0.36) and crustal source (r=-0.55).

Table 1. Descriptive statistics for source-specific mass, elements, and ABS of PM$_{2.5}$, and UF (n=164).

	Average	25th percentile	Median	75th percentile	Maximum
Mass (µg/m^3)					
Crustal	0.6	0.0	0.4	1.1	5.3
Long-range transported	6.4	2.2	5.5	9.8	26.5
Oil combustion	1.6	0.6	1.3	2.3	12.2
Salt	0.9	0.3	0.8	1.2	5.9
Local traffic	2.9	1.7	2.5	3.4	12.0
Total	12.8	8.3	10.6	15.9	39.8
Elements (ng/m^3)					
Ca	38.5	22.7	32.3	47.3	154.4
Cl	98.9	8. 1	36.4	102.0	1556.0
Cu	1.9	0.6	1.6	2.8	8.9
Fe	75.1	39.3	66.7	100.3	297.0
K	108.2	60.0	93.1	141.0	540.3
Mn	4.2	2.2	3.4	5.2	14.5
Ni	3.4	1.7	2.9	4.4	18.7
S	1540.1	839.3	1383.9	2084.5	4296.6
Si	96.0	17.2	60.3	135.5	662.4
V	7.5	3.2	6.6	9.8	26.8
Zn	20.5	11.3	16.8	25.1	75.3
ABS (m^{-1}*10^{-5})	2.0	1.4	1.9	2.5	4.9
UF (cm^{-3})	16.900	11.000	14.700	20.500	50.300

Associations between levels of source-specific PM$_{2.5}$ and the occurrence of ST segment depressions have been presented in table 3. PM$_{2.5}$ originating from local traffic as well as long-range transported PM$_{2.5}$ were associated with ST segment depressions > 0.1 mV. In addition, when the stricter criterion for ST segment depressions was used, a suggestive association of PM$_{2.5}$ originating from oil combustion emerged. The highest observed odds ratios were for PM$_{2.5}$ from crustal source and from salt source at lag 3, but the associations were not consistent or statistically significant.

Table 2. Spearman's correlation coefficients between elements of PM$_{2.5}$, UF, and source-specific PM$_{2.5}$ (n=164).

	PM$_{2.5}$	ABS	Ca	Cl	Cu	Fe	K	Mn	Ni	S	Si	V	Zn	UF
ABS	0.70													
Ca	0.17	0.30												
Cl	-0.03	0.02	0.11											
Cu	0.42	0.68	0.42	-0.05										
Fe	0.38	0.59	0.69	-0.18	0.71									
K	0.84	0.73	0.40	-0.10	0.52	0.56								
Mn	0.49	0.65	0.48	-0.17	0.65	0.79	0.60							
Ni	0.54	0.52	0.37	-0.07	0.39	0.41	0.59	0.13						
S	0.85	0.45	0.01	-0.28	0.23	0.21	0.70	0.37	0.43					
Si	0.10	0.29	0.71	-0.20	0.45	0.79	0.34	0.54	0.29	-0.26				
V	0.59	0.42	0.31	-0.04	0.21	0.29	0.57	0.36	0.88	0.52	0.18			
Zn	0.77	0.80	0.29	-0.10	0.66	0.59	0.84	0.73	0.59	0.62	0.30	0.53		
UF	0.13	0.57	0.39	-0.11	0.48	0.47	0.24	0.45	0.33	-0.05	0.36	0.16	0.34	
Source-specific PM$_{2.5}$														
Crustal	-0.01	0.14	0.80	-0.08	0.36	0.72	0.25	0.49	0.21	-0.12	0.88	0.12	0.19	0.23
Long range transported	0.82	0.46	-0.06	-0.18	0.26	0.20	0.70	0.38	0.27	0.90	-0.06	0.38	0.64	-0.19
Oil combustion	0.35	0.24	0.17	-0.12	0.06	0.10	0.37	0.20	0.86	0.35	0.11	0.86	0.34	0.20
Salt	0.19	0.07	0.19	0.54	-0.03	-0.17	0.11	-0.11	0.11	0.03	-0.13	0.15	0.07	-0.04
Local traffic	0.26	0.74	0.20	0.04	0.71	0.47	0.30	0.54	0.21	0.02	0.20	0.04	0.50	0.79

All correlations >0.17 or <-0.17 are statistically significant at $p < 0.05$.

Table 3. Adjusted odds ratios (OR)[a] between daily source-specific PM$_{2.5}$ concentrations and the occurrence of ST segment depressions.

Source-specific PM$_{2.5}$		>0.1 mV (n=62)[b]		>0.1mV+slope (n=46)[c]	
	Lag	OR	95% CI[d]	OR	95% CI
Crustal	Lag 0	0.80	0.47- 1.36	0.76	0.42- 1.35
	Lag 1	0.66	0.40- 1.10	0.41	0.22- 0.79
	Lag 2	1.18	0.68- 2.06	1.17	0.65- 2.09
	Lag 3	1.87	0.85- 4.09	1.60	0.72- 3.59
Long-range	Lag 0	0.94	0.84- 1.05	0.98	0.86- 1.10
transport	Lag 1	1.00	0.92- 1.08	1.03	0.95- 1.12
	Lag 2	1.11	1.02- 1.20	1.11	1.02- 1.21
	Lag 3	1.06	0.95- 1.18	1.02	0.95- 1.10
Oil combustion	Lag 0	0.87	0.57- 1.32	0.95	0.61- 1.49
	Lag 1	1.04	0.75- 1.45	1.13	0.76- 1.68
	Lag 2	1.10	0.83- 1.46	1.33	0.98- 1.80
	Lag 3	1.12	0.79- 1.58	1.29	0.90- 1.86
Salt	Lag 0	1.03	0.57- 1.85	1.15	0.56- 2.38
	Lag 1	0.72	0.37- 1.40	0.90	0.44- 1.81
	Lag 2	0.66	0.31- 1.40	1.39	0.63- 3.08
	Lag 3	1.55	0.83- 2.89	1.93	1.00- 3.72
Local traffic	Lag 0	0.91	0.69- 1.21	0.89	0.64- 1.23
	Lag 1	1.22	0.88- 1.69	1.21	0.86- 1.71
	Lag 2	1.53	1.19- 1.97	1.37	1.03- 1.83
	Lag 3	0.98	0.78- 1.23	1.03	0.80- 1.32

ORs calculated for an increase of 1 μg/m^3 in exposure.
[a] The statistical model included the source-specific PM$_{2.5}$ concentration, a dummy for each subject, linear terms for time trend, temperature (lag 3) and relative humidity (lag 3), and a penalized spline (df=3) for change in heart rate during exercise test.
[b] ST segment depression >0.1 mV; number of events at minimum (lag 0).
[c] ST segment depressions >0.1 mV with horizontal or downward slope; number of events at minimum (lag 0).
[d] CI, confidence interval.
Number of measurements= 312 for lag 0, 322 for lag 1, 314 for lag 2, and 311 for lag 3.

Exclusion of extreme concentrations (at maximum 13 measurements per lag) from source-specific PM$_{2.5}$ changed the results only for oil combustion. Association between oil combustion and ST segment depressions at lag 2 vanished, and for the strict criteria for ST segment depression, association got weaker.

In a multi-pollutant model that included indicator elements for all sources, only absorbance, marker for local traffic, was associated with ST segment depressions (table 4). The confidence intervals were rather wide, and wider than in single-pollutants models (data not shown), obviously due to inclusion of several correlating variables in the same model.

In the single-pollutant models most of the individual elements, i.e. Cu, Fe, K, Mn, Ni, S, and Zn, were significantly (p<0.05) associated with ST segment depressions >0.1 mV at lag 2 (data not shown), possibly due to high intercorrelations. However, when potentially toxic elements (Cu, Fe, Zn, V) were included in two-pollutant models together with absorbance, none of them was associated with ST segment depressions. In all two-pollutant models, statistically significant association between absorbance and ST segment depressions >0.1 mV remained at lag 2, and odds ratios for absorbance varied only slightly: from 3.93 to 5.03 (data not shown).

Interquartile range of long-range transported $PM_{2.5}$ was much higher than interquartile ranges of other source-specific masses (table 1). We therefore also calculated odds ratios at lag 2 per interquartile range of source-specific $PM_{2.5}$ for ST segment depressions >0.1 mV (figure 1). For comparison, odds ratios for the association of (total) PM2.5 , ultrafine particles and absorbance have also been presented.

Finally, we tested whether the association of ultrafine particles with ST segment depressions >0.1 mV is robust to adjustment for absorbance. The effect of absorbance remained, but ultrafine particles were no more significantly associated with ST segment depressions at lag 2. Odds ratio (95% CI) for absorbance was 3.44 (1.25-9.50), and for ultrafine particles 1.38 (0.53-3.61).

Table 4. Odds ratios (ORs) for the association of indicator elements of PM$_{2.5}$ sources with the occurrence of ST segment depressions in multipollutant models.[a]

Source-indicator	Lag	>0.1 mV (n=62)[b]		>0.1mV+slope (n=46)[c]	
		OR	95% CI[d]	OR	95% CI
Si (crustal)	Lag 0	0.73	0.39- 1.38	0.67	0.33- 1.36
	Lag 1	0.48	0.25- 0.93	0.34	0.15- 0.81
	Lag 2	0.78	0.35- 1.71	0.81	0.33- 2.00
	Lag 3	1.95	0.69- 5.48	1.90	0.64- 5.65
S (long-range transport)	Lag 0	0.70	0.25- 1.95	0.84	0.29- 2.47
	Lag 1	0.58	0.23- 1.47	0.89	0.34- 2.32
	Lag 2	1.08	0.44- 2.63	1.36	0.54- 3.45
	Lag 3	1.60	0.73- 3.48	1.12	0.53- 2.40
Ni (oil combustion)	Lag 0	0.78	0.30- 2.04	1.10	0.36- 3.37
	Lag 1	1.20	0.58- 2.46	1.16	0.45- 2.96
	Lag 2	1.15	0.61- 2.18	1.64	0.84- 3.20
	Lag 3	1.02	0.41- 2.54	1.63	0.64- 4.14
Cl (salt)	Lag 0	1.03	0.79- 1.34	1.13	0.80- 1.62
	Lag 1	0.88	0.56- 1.38	0.99	0.58- 1.68
	Lag 2	1.02	0.62- 1.69	1.55	0.87- 2.76
	Lag 3	1.27	0.85- 1.91	1.45	0.94- 2.25
ABS (local traffic)	Lag 0	0.92	0.36- 2.37	0.74	0.25- 2.23
	Lag 1	1.83	0.73- 4.59	1.76	0.62- 5.00
	Lag 2	4.46	1.69- 11.79	4.86	1.55- 15.26
	Lag 3	0.92	0.40- 2.12	0.97	0.39- 2.41

ORs calculated for an increase of interquartile range of pollutant.
[a] The statistical model included all five indicator elements, a dummy for each subject, linear terms for time trend, temperature (lag3) and relative humidity (lag3), and a a penalized spline (df=3) for heart rate during exercise test.
[b] ST segment depression >0.1 mV; number of events at minimum (lag 0).
[c] ST segment depressions >0.1 mV with horizontal or downward slope; number of events at minimum (lag 0).
[d] CI, confidence interval.
Number of measurements= 312 for lag 0, 322 for lag 1, 314 for lag 2, and 311 for lag 3.
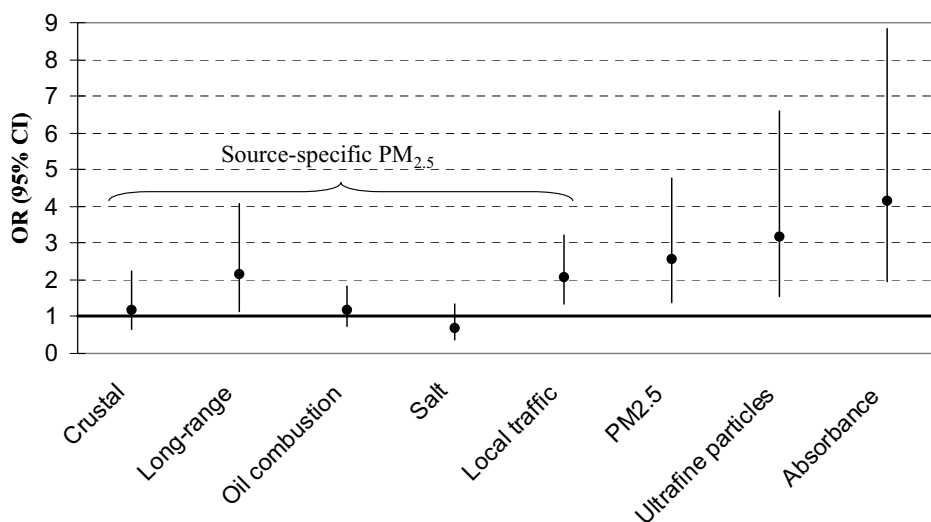
Figure 1. ORs and 95% CIs for 2-day lag for the association of source-specific $PM_{2.5}$, (total) $PM_{2.5}$, UF, and $PM_{2.5}$ ABS with the occurrence of ST segment depressions >0.1 mV. ORs were calculated for an increase of interquartile range of pollutant.

Discussion

Exposure to air pollution, especially particulate matter, has been linked to exacerbations of ischemic and arrhythmic cardiac diseases and congestive heart failure (Kwon et al. 2001; Le Tertre et al. 2002; Peters et al. 2000; Zanobetti et al. 2000), and triggering of the onset of myocardial infarction (Peters et al. 2001, 2004). Promotion of atherosclerosis is likely to be involved in the chronic pathways of air pollution effect (Brook et al. 2004). The plausibility of a causal association is increased by the established association between passive smoking and heart disease (Sarnoya and Glantz 2004). Our research team has previously published evidence on the association between $PM_{2.5}$ and myocardial ischemia, as indicated by the occurrence of exercise induced ST segment depressions among patients with coronary heart disease (Pekkanen et al. 2002). The observed association contributed to the emerging body of evidence providing a plausible biological link between levels of particulate air pollution and adverse cardiac outcomes (Verrier et al. 2002). The same data were used in the present study.

Ambient particulate matter is a very heterogeneous mixture of organic and inorganic components from multiple sources, and it is unlikely that all components have similar effects on cardiovascular system. Our current results suggest that the composition of $PM_{2.5}$ originating from local traffic is the most toxic, as the odds ratio per microgram of particle mass was high and the association statistically significant. However, the effect of long-range transported $PM_{2.5}$ was comparable to the effect of traffic-$PM_{2.5}$ when estimate was calculated per measured interquartile range of the pollutant. This is due to greater daily variability in the levels of long-range transported $PM_{2.5}$, and implies that by reducing high concentration days of either of the sources, equal benefits are attainable. Associations between other sources and ST segment depressions were less consistent and not statistically significant, although high odds ratios were observed. $PM_{2.5}$ originating from local traffic correlated highly with ultrafine particles ($r=0.79$), whereas long-range transported $PM_{2.5}$ correlated highly with $PM_{2.5}$ ($r=0.82$). Considering this, current results are in line with our previous study (Pekkanen et al. 2002), where we found levels of ultrafine particles and $PM_{2.5}$ to be independently associated with ST segment depressions.

There are few earlier studies that have compared health effects of $PM_{2.5}$ from different sources have been compared, and all of them are mortality studies in the United States. The studies suggest effect of $PM_{2.5}$ from a variety of combustion sources, and fewer effects of soil-originating $PM_{2.5}$. In a time-series study of six eastern U.S. cities (Laden et al. 2000), only $PM_{2.5}$ from traffic was weakly associated with increased daily mortality from ischemic heart disease, whereas both traffic and coal combustion were associated with increased total mortality. There was also a suggestion of a positive effect of oil combustion originating $PM_{2.5}$ on total mortality in the cities where the source was identified. In Phoenix (Mar et al. 2000), cardiovascular mortality was associated with $PM_{2.5}$ from traffic, biomass combustion, and regional pollution (indicated by sulfate). Total mortality was associated positively, although inconsistently, with regional sulfate. At three sites in New Jersey (Tsai et al. 2000), both total and cardiorespiratory mortality were associated with several sources of inhalable particles (diameter <15 μm) including, site-dependently, traffic and oil combustion, industry, and sulfate aerosol.

The source-apportionment method as used in our study yields non-correlating source-specific $PM_{2.5}$ concentrations. In an alternative approach, we constructed multi-pollutant models where indicators of sources were used instead of source-specific masses, and thus sources were allowed to correlate. In these models only absorbance (measure of elemental carbon), the chosen indicator for local traffic, was associated with ST segment depressions, whereas the effect of long-range $PM_{2.5}$, as represented by sulfur, disappeared. Absorbance correlated in our study both with

local traffic and long-range transported $PM_{2.5}$, r=0.74 and r=0.46, respectively. Thus, results suggest that the effect of long-range $PM_{2.5}$ is more related with carbon products than secondary sulfate. Absorbance is associated with a variety of combustion processes, but ambient concentrations are mostly affected by diesel particles (Gray and Cass 1998).

It has been suggested that transition metals and/or organic carbon compounds adsorbed onto the elemental carbon core formed in incomplete combustion are responsible for the cellular changes associated with PM (Chin BY et al. 1998; Obot et al. 2002). Capability to induce oxidative stress in lungs is common to transition metals and organic carbon compounds (Kelly 2003). In the present study most of the elements were associated with ST segment depressions, probably due to high intercorrelations. We did not find evidence for an effect of any of the potentially toxic transition metals when adjusting for absorbance.

Recently, some toxicological studies have suggested that the effects of ultrafine particles on human health would be due to organic chemicals (Li et al. 2003; Xia et al. 2004). On the other hand, the composition of ultrafine particles might not be decisive, but even inert particles in the ultrafine particle size range seem to be capable of inducing oxidative stress due to great number, large surface area and high penetration (Brown et al. 2003; Donaldson et al. 2001). When we adjusted ultrafine particles for absorbance, the association of ultrafines with ST depressions weakened. Two-pollutant models of correlating variables should be interpreted with caution, but the results suggest that carbon content of particles may be more important than size. Consequently, the apparently independent effects of $PM_{2.5}$ and ultrafines which we observed previously could be explained by considering the two pollutants as indicators of two combustion sources with different temporal variation — long-range transport and local traffic.

We have previously shown in this same study population that outdoor concentrations of absorbance correlate longitudinally (the relevant measure in time-series studies) highly with personal exposure, even better than $PM_{2.5}$ (Janssen et al. 2000). There is a general lack of such information for ultrafine particles, and it is possible that central outdoor measurements reflect worse day-to-day changes in exposure to ultrafines than to absorbance (Pekkanen and Kulmala 2004). This could weaken the association of ultrafines with ST segment depressions in the two-pollutant model. However, most of the study participants lived very close (within 2 km) to the central monitoring site, which is likely to improve not only spatial but also longitudinal correlation.

Particulate matter can increase cardiovascular disease risk through several pathways, which have different lags. It is hypothesized that the local inflammation in lungs

caused by particulate matter starts a cascade of events which leads to systemic inflammation as indicated by increased levels of inflammatory mediators in blood (Brook et al. 2004). The systemic inflammation in turn might transfer the myocardium and myocardial circulation into state which is vulnerable to various triggers of acute coronary syndrome (Muller et al. 1994). In our study, the effect of absorbance on ST segment depressions was delayed, strongest association being observed at 2 day lag, which is in agreement with systemic inflammation. There is evidence that particulate matter can act also as a trigger of acute events. $PM_{2.5}$ has been observed to increase risk of myocardial infarction both several hours and several days after exposure (Peters et al. 2001). In a recent study, an association was found between exposure to traffic and the onset of myocardial infarction within one hour afterward (Peters et al. 2004). Chronic exposure to traffic related air pollution has also been associated with adverse effects on health (Finkelstein et al. 2004; Gauderman et al. 2004; Hoek et al. 2002).

Low numbers posed two major limitations in our study. Low number of study subjects calls for caution when comparing the magnitudes of odd ratios. Modest number of elements available for analyses leaves room for speculations about unidentified harmful constituents. Above all, we were not able to analyze organic compounds. Newer, more sophisticated methods of source-apportionment could also be used in future. However, different source-apportionment methods usually produce similar main sources, although e.g. traffic is a more difficult source due to lack of unique elemental tracers (Thurston and Spengler 1985). We used ultrafine particles and gaseous pollutants in the source-apportionment, which clearly improved the results (Vallius et al. 2003). No method totally bypasses the fact that meteorology drives the concentrations of pollutants from all sources into same direction. In our case, local traffic partly included emissions from other, non-specified local combustion processes due to common meteorology. In any case, any source-specific $PM_{2.5}$ in our study should be considered merely as a marker of harmful factor in particulate matter, causal factors are still to be identified.

An unavoidable limitation in the study was the exclusion of summer time, because the elderly in Helsinki tend to spend most of summer at summer cottages on countryside. It is difficult to say, whether the effect estimates would have been higher or lower during summer than during the cooler seasons. Exposure to ambient particles would probably have been higher during summer due to more frequent opening of windows at homes and more frequent engagement in outdoor activities. On the other hand, cold temperatures are associated with increased rate of ischemic events (Barnet et al. 2005), and there is some evidence that effects of air pollution on ischemic heart diseases are higher during cool season (Wong et al. 2002).

Airborne particulate matter has conventionally been measured and regulated based primarily on mass. Effective reduction of health effects associated with mass of particles requires identification of the most harmful particle sources. Our results suggest that the fraction of particulate matter originating from combustion processes, notably traffic, may be responsible for the observed effect of particulate air pollution on ischemic heart diseases.

References

ACC/AHA. 1997. Guidelines for Exercise testing. A Report of the American College of Cardiology/American Heart Association Task Force of Practice Guidelines (Committee on Exercise Testing). J Am Coll Cardiol 30:260-315.

Barnet AG, Dobson AJ, McElduff P, Salomaa V, Kuulasmaa K, Sans S, for the WHO MONICA project. 2005. Cold periods and coronary events: an analyses of populations world-wide. J Epidemiol Community Health 59:551-557.

Barnoya J, Glantz SA. 2004. Secondhand smoke: the evidence of danger keeps growing. Am J Med 116:201-202.

Bonvallot V, Baeza-Squiban A, Baulig A, Brulant S, Boland S, Muzeau F, et al. 2001. Organic compounds from diesel exhaust particles elicit a proinflammatory response in human airway epithelial cells and induce cytochrome p450 1A1 expression. Am J Respir Cell Mol Biol 25:515-521.

Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, et al. 2004. Air pollution and cardiovascular disease: a statement for health care professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. Circulation 109:2655-2671.

Brown DM, Donaldson K, Borm PJ, Schins RP, Dehnhardt M, Gilmour P, et al. 2003. Calcium and ROS-mediated activation of transcription factors and TNF-α cytokine gene expression in macrophages exposed to ultrafine particles. Am J Physiol Lung Cell Mol Physiol 286:L344-353.

Brunekreef B, Janssen NAH, de Hartog JJ, Oldenwening M, Meliefste K, Hoek G, et al. 2005. Associations between ambient, personal and indoor exposure to fine particulate matter and its constituents in Dutch and Finnish panels of cardiovascular patients. Res Rep Health Eff Inst 127:1-70; discussion 71-79.

Chin BY, Choi ME, Burdick MD, Strieter RM, Risby TH, Choi AM. 1998. Induction of apoptosis by particulate matter: Role of TNF-[*] and MAPK. Am J Physiol 275:L924-949.

Cyrys J, Heinrich J, Hoek G, Meliefste K, Lewne M, Gehring U, et al. 2003. Comparison between different traffic-related particle indicators: Elemental carbon (EC), PM(2.5) mass, and absorbance. J Expo Anal Environment Epidemiol 13:134-143.

Daniels MJ, Dominici F, Samet JM, Zeger SL. 2000. Estimating particulate matter-mortality dose-response curves and threshold levels: an analysis of daily time-series for the 20 largest US cities. Am J Epidemiol 152:397-406.

Dockery DW, Pope CA 3rd. 1994. Acute respiratory effects of particulate air pollution. Annu Rev Public Health 15:107-132. Review.

Dominici F, McDermott A, Zeger SL, Samet JM. 2002. On the use of generalized additive models in time-series studies of air pollution and health. Am J Epidemiol 156:193-203.

Donaldson K, Stone V, Clouter A, Renwick L, MacNee W. 2001. Ultrafine particles. Occup Environ Med 58:211-216.

Eilers PHC, Marx BD. 1996. Flexible Smoothing with B-splines and Penalties. Statistical Science 11:89-121.

Finkelstein MM, Jerrett M, Sears MR. Traffic air pollution mortality rate advancement periods. Am J Epidemiol. 2004;160:173-7.

Gauderman WJ, Avol E, Gilliland F. The effect of air pollution on lung development from 10 to 18 years of age. N Engl J Med. 2004;351:1057-67.

Goldsmith CA, Imrich A, Danaee H, Ning YY, Kobzik L. 1998. Analysis of air pollution particulate-mediated oxidant stress in alveolar macrophages. J Toxicol Environ Health A 54:529-545.

Gray HA, Cass GR. 1998. Source contributions to atmospheric fine carbon particle concentrations. Atmos Environ 32:3805-3825.

Hastie T, Tibshirani R. 1990. Generalized additive models. London, United Kingdom: Chapman and Hall Ltd.

Hoek G, Brunekreef B, Goldbohm S, et al. Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. Lancet. 2002;360:1203-9.

Janssen NAH, de Hartog JJ, Hoek G, Brunekreef B, Lanki T, Timonen KL, et al. 2000. Personal exposure to fine particulate matter in elderly subjects: Relation between personal, indoor and outdoor concentrations. J Air Waste Manag Assoc 50:1133-1143.

Janssen NAH, Lanki T, Hoek G, Vallius M, de Hartog JJ, Van Grieken R, et al. 2005. Associations between ambient, personal, and indoor exposure to fine particulate matter constituents in Dutch and Finnish panels of cardiovascular patients. Occup Environ Med 62:868-877.

Janssen NAH, van Vliet P, van Aarts F, Harssema H, Brunekreef B. 2001. Assessment of exposure to traffic-related air pollution of children attending schools near motorways. Atmos Environ 35:3875-3884.

Katsouyanni K, Touloumi G, Samoli E, Gryparis A, Le Tertre A, Monopolis Y, et al. 2001. Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. Epidemiology 12:521-531.

Kelly FJ. 2003. Oxidative stress: its role in air pollution and adverse health effects. Occup Environ Med 60:612-616.

Kwon HJ, Cho SH, Nyberg F, Pershagen G. 2001. Effects of ambient air pollution on daily mortality in a cohort of patients with congestive heart failure. Epidemiology 12:413-419.

Künzli N, Raiser K, Medina S, Studnicka M, Chanel O, Filliger P, et al. 2000. Public-health impact of outdoor and traffic-related air pollution: a European assessment. Lancet 356:795-801.

Laden F, Neas LM, Dockery DW, Schwartz J. 2000. Association of fine particulate matter from different sources with daily mortality in six U.S. cities. Environ Health Perspect 108:941-947.

Le Tertre A, Medina S, Samoli E, Forsber B, Michelozzi P, Boumghar A, et al. 2002. Short-term effects of particulate air pollution on cardiovascular diseases in eight European cities. J Epidemiol Community Health 56:773-779.

Li N, Sioutas C, Cho A, Schmitz D, Misra C, Sempf J, et al. 2003. Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage. Environ Health Perspect 111:455-460.

Long CM, Suh HH, Kobzik L, Catalano PJ, Ning YY, Koutrakis P. 2001. A pilot investigation of the relative toxicity of indoor and outdoor fine particles: in vitro effects of endotoxin and other particle properties. Environ Health Perspect 109:1019-1026.

Mar TF, Norris GA, Koenig JQ, Larson TV. 2000. Association between air pollution and mortality in Phoenix, 1995-1997. Environ Health Perspect 108:347-353.

Muller JE, Abela GS, Nesto RW, Tofler GH. 1994. Triggers, acute risk factors and vulnerable plaques: the lexicon of a new frontier. J Am Coll Cardiol 23:809-813.

Obot CJ, Morandi MT, Beebe TP, Hamilton RF, Holian A. 2002. Surface components of airborne particulate matter induce macrophage apoptosis through scavenger receptors. Toxicol Appl Pharmacol 184:98-106.

Osornio-Vargas ÁR, Bonner JC, Alfaro-Moreno E, Martinez L, Garcia-Cuellar C, Ponce-de-Leon RS, et al. 2003. Proinflammatory and cytotoxic effects of Mexico city air pollution particulate matter in vitro are dependent on particle size and composition. Environ Health Perspect 111:1289-1293.

Pagan I, Costa DL, McGee JK, Richards JH, Dye JA. 2003. Metals mimic airway epithelial injury induced by in vitro exposure to Utah Valley ambient particulate matter extracts. J Toxicol Environ Health A 66:1087-1112.

Pekkanen J, Kulmala M. 2004. Exposure assessment of ultrafine particles in epidemiologic time-series studies. Scand J Work Environ Health 30 Suppl 2:9-18.

Pekkanen J, Peters A, Hoek G, Tiittanen P, Brunekreef B, de Hartog J, et al. 2002. Particulate air pollution and risk of ST-segment depression during repeated submaximal exercise tests among subjects with coronary heart disease. The exposure and risk assessment for fine and ultrafine particles in ambient air (ULTRA) study. Circulation 20:933-938.

Pekkanen J, Timonen KL, Tiittanen P, Vallius M, Lanki T, Sinkko H, et al. 2000. ULTRA: Exposure and risk assessment for fine and ultrafine particles in ambient air. Study manual and data book. Publications of National Public Health Institute 2000. Available at http://www.ktl.fi/ultra. Accessed August 10, 2005.

Peters A, Dockery W, Muller JE, Mittleman MA. 2001. Increased particulate air pollution and the triggering of myocardial infarction. Circulation 103:2810-2815.

Peters A, Liu E, Verrier RL, Schwartz J, Gold DR, Mittleman M, et al. 2000. Air pollution and incidence of cardiac arrhythmia. Epidemiology 11:11-17.

Peters A, von Klot S, Heier M, Trentinaglia I, Hormann A, Wichmann HE, Lowel H, Cooperative Health Research in the Region of Augsburg Study Group. 2004. Exposure to traffic and the onset of myocardial infarction. N Engl J Med 351:1721-1730.

Pope CA 3rd. 1989. Respiratory disease associated with community air pollution and a steel mill, Utah Valley. Am J Public Health 79:623-628.

Pope CA 3rd, Burnett RT, Thun MJ, Eugenie EE, Krewski D, Ito K, et al. 2002. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA 287:1132-1141.

Pope CA 3rd, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, et al. 2004. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. Circulation 109:71-77.

Rijneke RD, Ascoop CA, Talmon JL. 1980. Clinical significance of upsloping ST segments in exercise electrocardiography. Circulation 61:671-678.

Sarnat JA, Brown KW, Schwartz J, Coull BA, Koutrakis P. 2005. Ambient gas concentrations and personal particulate matter exposures. Implications for studying the health effects of particles. Epidemiology 16:385-395.

Samet JM, Dominici F, Curriero FC, Coursac I, Zeger SL. 2000. Fine particulate air pollution and mortality in 20 U.S. cities, 1987-1994. N Engl J Med 343:1742-1749.

Schwartz J. 1999. Air pollution and hospital admissions for heart disease in eight U.S. counties. Epidemiology 10:1-4.

Tammet H, Mirme A, Tamm E. 2002. Electrical aerosol spectrometer of Tartu University. Atm Res 62:315-324.

Thurston GD, Spengler JD. 1985. A quantitative assessment of source contributions to inhalable particulate matter pollution in metropolitan Boston. Atm Environ 19:9-25.

Tsai FC, Apte MG, Daisey JM. 2000. An exploratory analysis of the relationship between mortality and the chemical composition of airborne particulate matter. Inhal Toxicol 12:121-135.

Urch B, Brook JR, Wasserstein D, Brook RD, Rajagopalan S, Corey P, et al. 2004. Relative contributions of $PM_{2.5}$ chemical constituents to acute arterial vasoconstriction in humans. Inhal Toxicol 16:345-352.

Vallius M, Lanki T, Tiittanen P, Koistinen K, Ruuskanen J, Pekkanen J. 2003. Source apportionment of urban ambient PM2.5 in two successive measurement campaigns in Helsinki, Finland. Atm Environment 37:615-623.

Verrier RL, Mittleman MA, Stone PH. 2002. Air pollution. An insidious and pervasive component of cardiac risk. Circulation 106:890-892. (editorial)

WHO Ad Hoc Committee on Health Research Relating to Future Intervention Options. 1996. Investing in health research and development. Geneva, Switzerland: World Health Organization.

Wood S. 2001. mgcv: GAMs and Generalized Ridge Regression for R. R News. Vol. 1/2, June 2001:20-25.

Wong C-M, Atkinson RW, Anderson RH, Hedley AJ, Ma S, Chau P Y-K, et al. 2002. A tale of two cities: effects of air pollution on hospital admission in Hong Kong and London compared. Environ Health Perspect 110:67-77.

Xia T, Korge P, Weiss JN, Li N, Venkatesen MI, Sioutas C, et al. 2004. Quinones and aromatic chemical compounds in particulate matter induce mitochondrial dysfunction: implications for ultrafine particle toxicity. Environ Health Perspect 112:1347-358.

Zanobetti A, Schwartz J, Dockery DW. 2000. Airborne particles are a risk factor for hospital admissions for heart and lung disease. Environ Health Perspect 108:1071-1077.

10 ASSOCIATIONS BETWEEN SOURCE-SPECIFIC PM$_{2.5}$ AND HEART RATE VARIABILITY ARE MODIFIED BY BETA-BLOCKER USE IN PATIENTS WITH CORONARY HEART DISEASE

de Hartog JJ,[1,2] Lanki T,[3] Timonen KL,[4] Hoek G,[2] Janssen NAH,[1,2] Ibald-Mulli A,[5] Peters A,[5] Heinrich J,[5] Tarkiainen T,[6] van Grieken R,[7] van Wijnen J,[8] Brunekreef B,[2,9] and Pekkanen J [3,10]

1 RIVM, National Institute for Public Health and Environment, Bilthoven, The Netherlands

2 IRAS, Institute for Risk Assessment Sciences, Utrecht University, The Netherlands

3 Environmental Epidemiology Unit, National Public Health Institute (KTL), Kuopio, Finland

4 Department of Clinical and Nuclear Medicine, Kuopio University and Kuopio University Hospital, Finland

5 Institute of Epidemiology, GSF-National Research Center for Environment and Health, Neuherberg, Germany

6 Department of Clinical Physiology and Nuclear Medicine, Mikkeli Central Hospital, Etelä-Savo Hospital District, Mikkeli, Finland

7 Department of Chemistry, University of Antwerp, Belgium

8 Department of Environmental Medicine, Municipal Health Service Amsterdam, The Netherlands

9 Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands.

10 School of Public Health and Clinical Nutrition, University of Kuopio, Finland

Abstract

It has been hypothesized that ambient particulate air pollution is able to modify the autonomic nervous control of the heart, measured as heart rate variability (HRV). We have previously reported heterogeneous associations between PM$_{2.5}$ and HRV across three ULTRA study centres. Therefore, we evaluate whether exposure misclassification, effect modification by beta-blocker medication or differences in particle composition could explain the inconsistencies.

Subjects with coronary heart disease visited clinics biweekly in Amsterdam, the Netherlands, Erfurt, Germany, and Helsinki, Finland during 6-8 months. The standard deviation of NN intervals (SDNN) and high frequency (HF) power of HRV

were measured with ambulatory ECG during a paced breathing period. Outdoor levels of $PM_{2.5}$ were measured at a central site. In Amsterdam and Helsinki, indoor and personal $PM_{2.5}$ were measured during the 24 hours preceding the clinic visit. $PM_{2.5}$ was apportioned between sources using principal component analyses. Associations of outdoor/indoor/personal $PM_{2.5}$, elements of $PM_{2.5}$ and source-specific PM2.5 with HRV were analyzed with linear regression.

We obtained 1266 successful HRV recordings from 122 subjects. Indoor or personal $PM_{2.5}$ at lag 0 were not associated with HRV. Increased outdoor $PM_{2.5}$ was associated with decreased SDNN and HF at lags 2 and 3, but only among persons not on beta-blocker medication. Traffic related $PM_{2.5}$ was associated with decreased SDNN, and long-range transported $PM_{2.5}$ with decreased SDNN and HF, most strongly among persons not using beta-blockers. Indicators for $PM_{2.5}$ from traffic and long-range transport (light absorbance and sulfur, respectively) were also associated with decreased HRV.

Our results suggest that $PM_{2.5}$ from combustion sources, both local traffic and long-range transport, influences HRV primarily among persons not on beta-blocker medication.

Introduction

Increased cardiovascular mortality and morbidity have been reported in association with increases in daily ambient levels of particulate matter (PM) in epidemiological studies.[1-3] However, it is not known which constituents of particles are responsible for the effects associated with particle mass. The source of particles defines their composition. Recent epidemiological studies suggest that particles from combustion sources are especially harmful.[4,5] Transition metals and organic carbon compounds were shown to be toxic in toxicological studies.[6,7] These can be found in abundance in combustion particles.

The relative importance of different pathways from particle exposure to effects on the cardiovascular system is not clear, but exposure to particles has been associated both with increased systemic inflammation and changes in autonomic nervous control of the heart.[8] The latter is most often measured indirectly as heart rate variability (HRV).[9] A decreased overall HRV is proven to be a strong independent predictor of cardiac mortality in subjects with existing cardiovascular disease.[10,11] Several studies have shown decreased indices of HRV on days with increased outdoor levels of respirable particles (aerodynamic diameter <10 μm, [PM_{10}])[12,13] and fine particles (<2.5 μm, [$PM_{2.5}$]).[14,15]

In the ULTRA study, levels of outdoor air pollution were monitored for 6-8 months in 1998-1999 in three European cities. At the same time, panels of patients with coronary heart disease were followed up with measurements of HRV. We have previously reported that the levels of ultrafine particles (<0.1 µm) are associated with changes in the balance between sympathetic and vagal nervous input to the heart.[16] However, $PM_{2.5}$ or ultrafine particles were not consistently associated with decreased HRV in the different study centres. In the present paper, we evaluate whether exposure misclassification, effect modification by medication, or variable particle composition could explain the inconsistencies. Personal and indoor $PM_{2.5}$ were measured in Amsterdam and Helsinki in order to obtain more accurate estimates of exposure. Possible effect modification by beta-blocker (β-adrenergic antagonist) medication was evaluated in light of the limited number of earlier studies.[17,18] Finally, we linked for the first time source-specific $PM_{2.5}$ with HRV to evaluate the importance of particle composition for cardiovascular effects of PM.

Methods

Heart rate variability was measured at biweekly clinic visits in panels of elderly subjects with coronary heart disease in Amsterdam, The Netherlands, Erfurt, Germany, and Helsinki, Finland, in 1998-1999. In Amsterdam, 37 panelists were followed up for 8 months and in Erfurt and Helsinki 47 panelists for 6 months. The visits of every subject were scheduled always for the same weekday and for the same time. The medication of the subjects was not changed for the clinic visits. Concurrently with the visits, outdoor levels of $PM_{2.5}$ were measured at one central site in each city. In Helsinki and Amsterdam, also indoor and personal measurements of $PM_{2.5}$ were performed during the 24 hours preceding the clinic visit. All measurements in the study were performed according to Standard Operating Procedures.[19,20]

The main inclusion criteria for the study were a self-report of a physician-diagnosed coronary heart disease, being a non-smoker, and aged 50 years or more. Ethical committees in each study centre approved the study protocol. A written informed consent was obtained from all subjects.

At the clinic visits HRV was recorded with an ambulatory ECG recorder (Holter) using a standardized protocol.[16] Breathing frequency strongly affects HRV, and for that reason HRV recorded during a 5 min period of paced breathing in supine position (frequency of 0.2 Hz; 2.5 seconds inhalation and 2.5 seconds exhalation; the period came after 5 minutes of rest in supine position) has been used for the analyses. The ECGs were recorded with Oxford MR-63 tape recorders (Oxford Instruments, Abington, U.K.) and the recordings were analysed with the Oxford

Exel Medilog II V7.5 system (Oxford Instruments, Abington, U.K.). Details of the analyses have been published before.[16,21]

We used two common indices of HRV in the present analyses: the standard deviation of NN intervals (SDNN), which is a time-domain measure of overall HRV, and high frequency (HF) power (0.15 to 0.4 Hz) of HRV, which is a frequency domain measure thought to reflect mainly the vagal (parasympathetic) part of the autonomic nervous input to the heart.[9]

Harvard impactors were used to collect filter samples of outdoor $PM_{2.5}$, GK2.05 cyclones and battery-operated AFC400S pumps (both from BGI Inc., Waltham, MA, USA) were used for the collection of personal $PM_{2.5}$ samples. The filters were weighted to determine mass of $PM_{2.5}$, and the reflectance was measured with a reflectometer (Model 43, Diffusion Systems Ltd., UK). The reflectance was transformed into absorbance (absorption coefficient [ABS]), which is an indicator for elemental carbon. Finally, elemental composition of the samples was determined using energy-dispersive X-ray fluorescence spectrometry. All methods have been described in detail in previous papers.[20,22,23]

Principal component analysis and multivariate linear regression were used to apportion $PM_{2.5}$ mass to different sources,[24] obtaining estimates of daily source-specific $PM_{2.5}$ concentrations. Besides components of $PM_{2.5}$ (elemental concentrations and absorbance), daily data on ultrafine (diameter <0.1 μm) and accumulation mode particles (0.1-1.0 μm), NO_2 and SO_2 were used to identify sources. Four to six main source categories were identified in each city: local traffic (with contribution from other local combustion sources), long-range transported (secondary) air pollution, industry, crustal, oil combustion, and salt.[24]

Data were analyzed using the SAS statistical package and mixed models (PROC MIXED) taking into account repeated observations and assuming constant correlation between observations within a subject. A basic model was first built without including particulate air pollution in the model. Criteria for building the basic model were Akaike's information criteria and covariate-response plots. The same basic models as in the previous paper have been used.[16] Lag 0 was defined as the 24-h period from the noon of the day of the clinic visit to previous day's noon, lag 1 was the previous 24-h period and so on. In Amsterdam, the model included linear terms for time trend, temperature (lag 2), relative humidity (lag 3), and barometric pressure. In Erfurt the model included linear terms for time trend, relative humidity (lag 3), and barometric pressure (lag 2). Temperature (lag 3) was modelled with linear, squared and cubic terms. The basic model for Helsinki included linear terms for time trend, relative humidity (lag 1), and barometric

pressure (lag 1). Temperature (lag 3) was modelled with linear and squared terms. In all cities, the model included weekday as a categorical variable.

For the comparison of the effects of outdoor, indoor and personal $PM_{2.5}$ on HRV, only the days with all three types of measurements were included in the analyses. Associations of source-specific $PM_{2.5}$ with HRV were analyzed using multi-pollutant models that included at the same time all identified sources and the unidentified $PM_{2.5}$ fraction. Multi-pollutant models were not used for elements of $PM_{2.5}$ because of high inter-correlations. We analyzed data only for the elements that are either indicators for the $PM_{2.5}$ sources or that have been found harmful in toxicological studies. The indicators were chosen based on the elemental profiles of sources:[24] absorbance for local traffic, S for long-range transported particles, V for oil combustion (not used for Erfurt because oil source not identified there, and >50% of concentrations below detection limit), Ca for soil particles, and Cl for salt particles (not in Erfurt). Elements considered because of potential toxicity were the transition metals Cu, Fe and Zn.

HF was log-transformed for the analyses and the effect of particulate air pollution on the endpoint was estimated as percent change: $[e^{(\beta x SE)}-1]$ x100%, where β is the estimated regression coefficient and SE is its standard error. Effect estimates for the elements are presented for increases that are close to study mean Inter Quartile Ranges (IQRs), i.e. the differences between the 25th and 75th percentiles of the exposure distributions. Pooled effect estimates were calculated as a weighted average of the center-specific estimates using the inverse of center-specific variances as weights. The heterogeneity of effect estimates between centers was tested with a χ^2-test.[25]

Effect of extreme source-specific $PM_{2.5}$ values on the results was evaluated by excluding for the analyses from each lag the concentrations that were more than 3 times the interquartile range of the lag.

Results

There were a total of 424 clinical visits in Amsterdam, 491 in Erfurt and 519 in Helsinki. Although special care was given to attachment of the electrodes, some ECG-recordings were unsuccessful. There were 366 successful recordings (from 33 patients) in Amsterdam, 432 (44) in Erfurt and 468 (45) in Helsinki.

In Helsinki, the proportion of males and females was almost equal, but in Amsterdam the panel contained mostly males and in Erfurt almost exclusively males (Table 1). About two thirds of the study subjects in Erfurt and Helsinki had daily beta-blocker medication, whereas only about one third of the subjects was on

medication in Amsterdam. Except for SDNN in Amsterdam, HRV indices were lower among beta-blocker users than among non-users.

Table 1. Characteristics of the three study panels.

	Amsterdam The Netherlands (n=33)[*]		Erfurt Germany (n=44)		Helsinki Finland (n=45)	
Sex / Female (%)	11	(34)	4	(9)	21	(47)
Mean age (range)	70.9	(54-83)	64.3	(40-78)	68.2	(54-83)
Mean BMI [†] (range)	27.6	(21-34)	27.3	(22-33)	28.9	(20-36)
Past myocardial infarction (%)	22	(69)	30	(68)	27	(60)
Angina Pectoris (%)	21	(66)	24	(55)	29	(64)
CABG or PTCA conducted [†] (%)	17	(53)	31	(70)	23	(51)
Daily beta-blocker medication (%)	13	(39)	34	(77)	31	(69)
Mean [‡] SDNN (sd[†]) [ms]						
Beta-blocker users	46.7	(17.8)	29.9	(8.8)	35.3	(10.7)
Non-users	40.0	(11.9)	41.2	(12.1)	38.8	(11.7)
Mean [‡] HF (sd[†]) [ms^2]						
Beta-blocker users	414	(289)	280	(237)	600	(376)
Non-users	504	(307)	547	(396)	629	(409)

[*] Number of patients available for analyses
[†] BMI, body mass index, weight[kg]/height[m^2]; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; sd, standard deviation.
[‡] Average of individual means and standard deviations

Outdoor levels of $PM_{2.5}$ were lower in Helsinki than in Amsterdam and Erfurt (Table 2). In Helsinki, about half of $PM_{2.5}$ was of secondary origin, i.e. could be considered long-range transported, in Amsterdam and Erfurt this was about one third. Industrial sources of $PM_{2.5}$ were not identified in Helsinki.[24] Oil combustion and salt as sources of $PM_{2.5}$ were not identified in Erfurt, and the indicator elements for these sources have not been included.

Table 2. Outdoor levels of PM$_{2.5}$, its components, and temperature, at central measurement sites in the three cities.

	Amsterdam The Netherlands				Erfurt Germany				Helsinki Finland			
	p25 *	p50	p75	p95	p25	p50	p75	p95	p25	p50	p75	p95
PM$_{2.5}$ (µg/m^3)	10.4	16.7	23.9	47.0	10.8	16.3	26.7	62.3	8.3	10.6	15.9	25.8
Source-specific PM$_{2.5}$ (µg/m^3)												
Local traffic	3.5	6.1	9.3	20.4	4.1	7.0	10.0	18.4	1.7	2.6	3.4	6.5
Long-range transported	0.3	5.1	11.6	21.8	3.1	5.4	9.8	31.9	2.2	5.5	9.8	15.9
Oil combustion	0.9	1.6	3.1	5.9	NA	NA	NA	NA	0.6	1.3	2.3	4.2
Industry	-2.6	-0.5	3.0	9.2	-3.6	-1.6	2.2	24.7	NA	NA	NA	NA
Crustal	0.7	1.4	2.1	3.6	1.8	2.7	4.8	13.8	0.0	0.4	1.1	2.2
Salt	0.1	0.2	0.8	1.8	NA	NA	NA	NA	0.3	0.8	1.2	2.4
Absorbance (m^{-1}x10^{-5})	0.9	1.5	2.2	3.4	1.3	2.0	3.4	5.1	1.4	1.89	24.7	3.56
Elements (ng/m^3)												
S	936	1340	2240	3650	600	862	1530	3740	839	1380	2080	3400
V	2.5	4.1	7.8	14.7	NA	NA	NA	NA	3.2	6.69	9.8	16.4
Zn	8.7	18.2	33.9	65.2	22.6	40.2	75.1	199	11.3	16.8	25.1	47.3
Ca	26.9	37.1	51.8	76.9	34.6	47.0	72.2	193	22.7	32.3	47.3	87.0
Cl	33.8	116	432	990	NA	NA	NA	NA	8.1	36.4	102	386
Fe	47.1	70.7	107	175	38.6	59.9	112	248	39.3	66.7	100	165
Cu	1.4	2.5	4.7	9.0	0.6	2.5	4.9	10.4	0.6	1.6	2.8	5.1
Temperature (^{o}C)	4.4	7.9	12.3	16.9	-0.1	3.9	6.7	11.2	-5.0	-0.6	2.5	8.8

The number of measurements available for analyses was 223 in Amsterdam, 156 in Erfurt, and 164 in Helsinki.
* p25, 25th percentile; p50, 50th percentile i.e. median; p75, 75th percentile; p95, 95th percentile

PM$_{2.5}$ (total) correlated most strongly with long-range transported PM$_{2.5}$, and the correlation with sulfur, the indicator element for this source, was even higher (Table 3). Transition metals Zn, Fe and Cu correlated highly with absorbance, the correlation being highest for Cu in Amsterdam (r=0.83) and lowest for Fe in Helsinki (r=0.49) (data not shown).

The medians of individual averages (n of measurements) of outdoor, indoor and personal PM$_{2.5}$ in Amsterdam were 21.0 (417), 14.9 (411) and 15.3 (338) µg/m3, respectively. The respective PM$_{2.5}$ levels in Helsinki were 12.0 (478), 10.2 (503) and 10.0 (336) µg/m^3.[22]

Table 3. Correlation[*] of total $PM_{2.5}$ with source-specific $PM_{2.5}$ and elements in the three cities.

| | Source-specific $PM_{2.5}$ | | | | | | Elements of PM_2 | | | | | | | |
	Traffic	LRT[†]	Oil	Industry	Crustal	Salt	ABS	S	V	Zn	Ca	Cl	Fe	Cu
Amsterdam, The Netherlands														
$PM_{2.5}$	0.50	0.62	0.18	0.27	-0.15	0.04	0.73	0.84	0.27	0.81	0.04	0.14	0.68	0.63
Erfurt, Germany														
$PM_{2.5}$	0.32	0.57	NA	0.41	0.19	NA	0.81	0.85	NA	0.82	0.51	0.63	0.81	0.70
Helsinki, Finland														
$PM_{2.5}$	0.26	0.82	0.35	NA	-0.01	0.19	0.70	0.85	0.59	0.77	0.17	-0.03	0.38	0.42

The number of measurements available for analyses was 223 in Amsterdam, 156 in Erfurt, and 164 in Helsinki.
[*] Spearman's correlation coefficients; [†] long-range transported

Outdoor, indoor and personal $PM_{2.5}$ were not associated with SDNN at lag 0 (Figure 1). There was a suggestive positive association of outdoor and personal $PM_{2.5}$ with HF.

Increased concentrations of $PM_{2.5}$ were associated with decreased SDNN and HF especially at longer lags among study subjects not on daily beta-blocker medication (Figure 2). The city-specific estimates were not heterogeneous. There was a positive association at single (1-day) lag between $PM_{2.5}$ and HF among subjects that were on medication.

Increases in $PM_{2.5}$ originating from local traffic were consistently associated with decreased SDNN; somewhat more strongly among study subjects not using beta-blockers than in the whole study panel (Table 4). However, none of the associations reached statistical significance. Long-range transported $PM_{2.5}$ was associated with decreased SDNN and HF at lags 2 and 3 among persons not having daily beta-blocker medication. Among all subjects, there was heterogeneity in the effect estimate at a 2-day lag for HF because of negative associations in Amsterdam and Helsinki (the latter significant), and a positive association in Erfurt (data not shown). There was evidence of the effect of $PM_{2.5}$ from oil combustion only for SDNN among non-medicated subjects. Crustal $PM_{2.5}$ was associated with increased HF irrespective of medication use at lag 2.

The fraction of $PM_{2.5}$ that could not be linked to any particular source category was positively associated at 0-day lag with SDNN (estimate 0.18; 95% CIs 0.00-0.35) and HF (1.53; 0.48-2.59) among all study subjects, but the association was not evident among subjects not using beta-blockers.
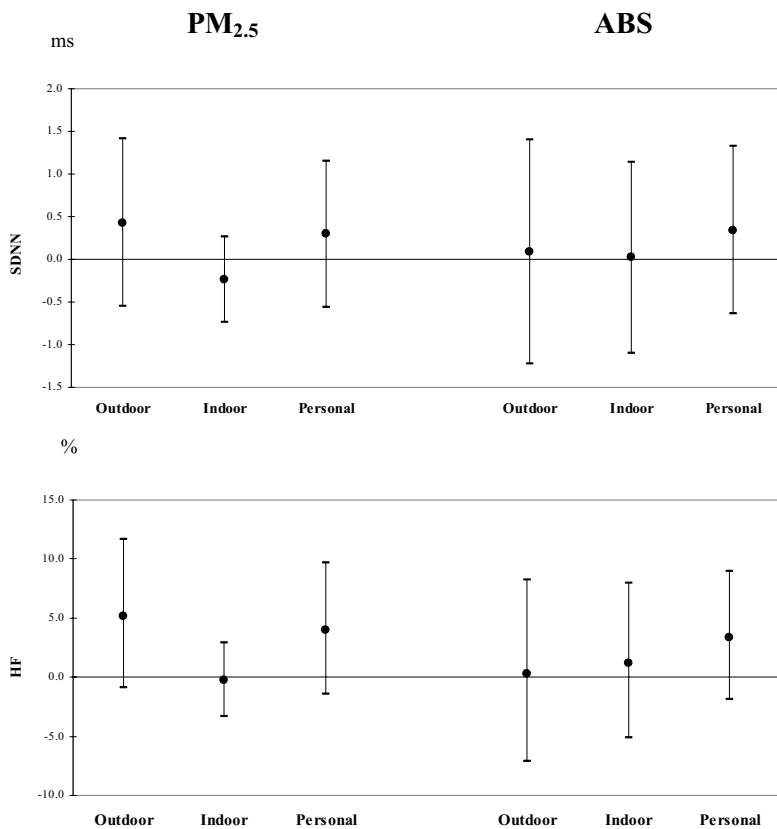
Figure 1. Pooled effect estimates with 95% confidence intervals for two study panels (Amsterdam and Helsinki) for the association outdoor, indoor, and personal PM$_{2.5}$ at 0-day lag with heart rate variability. Effect estimates are calculated for an increase of 10 µg/m^3 for PM$_{2.5}$ and 1 m^{-1} x10^5 for absorbance.
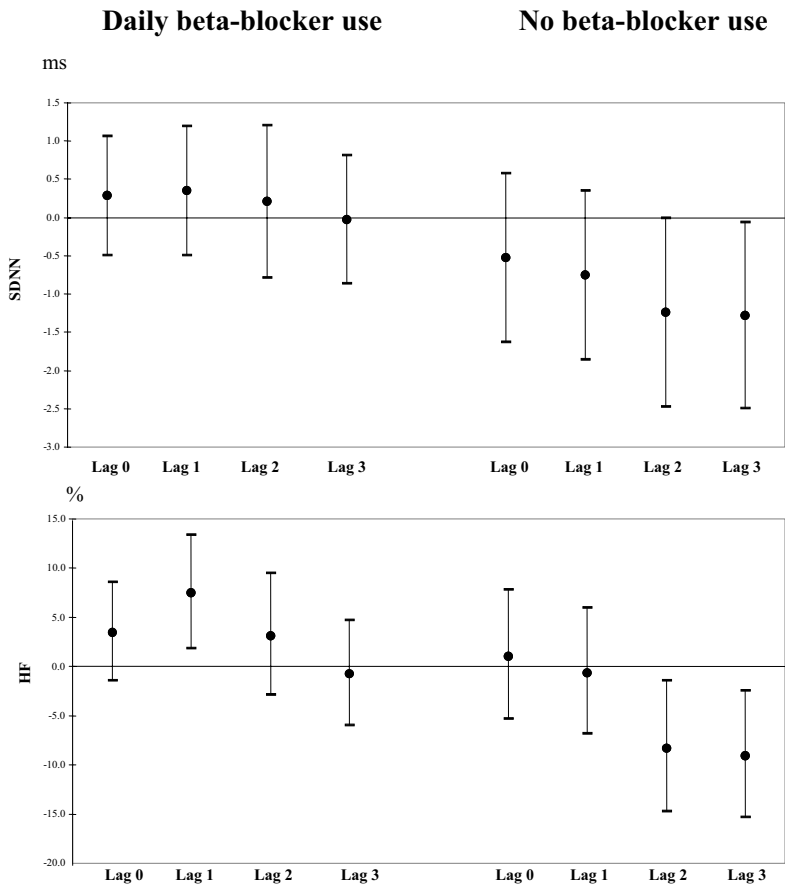
Figure 2.   Pooled effect estimates with 95% confidence intervals for the three study panels for the association of outdoor PM$_{2.5}$ with heart rate variability stratified by beta-blocker use. Effect estimates are calculated for an increase of 10 μg/m^3 for PM$_{2.5}$.

Table 4. Pooled effect estimates in the three study panels for the associations of source-specific PM$_{2.5}$ with heart rate variability in multi-pollutant models.

	SDNN (ms)						HF (%)					
	All subjects			Subjects without β-blockers			All subjects			Subjects without β-blockers		
	β[*]	95% CI[†]		β	95% CI		β	95% CI		β	95% CI	
Local traffic												
Lag 0	-0.05	-0.26	0.15	0.11	-0.23	0.44	0.11	-1.05	1.28	0.31	-1.65	2.30
Lag 1	-0.12	-0.36	0.12	-0.27	-0.59	0.05	0.43	-0.91	1.79	-0.21	-2.16	1.77
Lag 2	-0.28	-0.57	0.01	-0.45	-0.90	0.01	-0.13	-1.74	1.50	-0.67	-3.34	2.07
Lag 3	-0.20	-0.45	0.06	-0.35	-0.69	0.00	-0.64	-2.03	0.78	-1.43	-3.40	0.58
Long-range transport												
Lag 0	0.00	-0.10	0.09	-0.03	-0.19	0.14	0.12	-0.43	0.67	-0.18[‡]	-1.13	0.77
Lag 1	-0.04	-0.14	0.06	0.00	-0.15	0.16	0.19	-0.38	0.77	0.06	-0.86	0.99
Lag 2	-0.05	-0.17	0.07	-0.11	-0.30	0.07	-0.69[‡]	-1.35	-0.02	-1.06	-2.14	0.03
Lag 3	0.00	-0.13	0.12	-0.20	-0.39	-0.01	-0.54	-1.23	0.15	-1.98	-3.07	-0.88
Oil combustion[§]												
Lag 0	-0.02	-0.74	0.70	-0.46	-1.34	0.41	3.20	-0.48	7.03	1.43	-3.83	6.97
Lag 1	-0.29	-1.04	0.45	-1.08	-2.09	-0.06	1.05	-2.70	4.94	-3.04	-8.80	3.08
Lag 2	0.36	-0.42	1.13	0.22	-0.89	1.33	1.50	-2.36	5.51	0.10	-6.34	6.98
Lag 3	0.00	-0.77	0.77	-0.43	-1.27	0.42	0.49	-3.25	4.38	-0.42	-5.32	4.73
Industry[§]												
Lag 0	-0.07	-0.23	0.09	-0.17	-0.43	0.10	0.13	-0.80	1.07	0.08	-1.44	1.62
Lag 1	0.03	-0.12	0.19	-0.14	-0.44	0.16	0.62	-0.34	1.59	-0.08	-1.79	1.65
Lag 2	0.02	-0.12	0.16	-0.08	-0.34	0.18	0.05	-0.82	0.94	-1.03	-2.53	0.49
Lag 3	-0.04	-0.17	0.09	0.12	-0.19	0.42	-0.05	-0.87	0.77	0.68	-0.98	2.37
Crustal												
Lag 0	-0.02	-0.36	0.31	-0.05	-0.84	0.75	0.01	-2.07	2.15	0.80	-3.47	5.26
Lag 1	0.11	-0.35	0.56	0.07	-0.97	1.11	1.57	-1.28	4.50	1.93	-3.86	8.06
Lag 2	0.18	-0.37	0.73	0.35	-0.82	1.52	4.72	1.16	8.41	5.67	-1.11	12.91
Lag 3	0.11	-0.43	0.66	0.20	-1.05	1.45	0.93	-2.43	4.41	2.68	-4.02	9.84
Salt[§]												
Lag 0	1.07	-0.66	2.80	-0.03	-2.61	2.55	5.20	-3.83	15.08	4.33	-10.46	21.56
Lag 1	-0.19	-1.92	1.55	-0.64	-3.29	2.00	-1.43	-9.86	7.78	4.33	-10.68	21.87
Lag 2	-0.33	-2.13	1.47	-0.44	-2.88	2.00	-1.06	-9.69	8.38	-6.55	-18.85	7.62
Lag 3	1.47	-0.28	3.22	2.17	-0.07	4.41	6.70	-2.30	16.52	2.74	-9.65	16.83

The number of observations in the analyses was 1195 for SDNN and 1183 for HF.

[*] β, effect estimate for an increase of 1 µg/m^3 in source-specific PM$_{2.5}$; [†] CI, confidence interval; [‡] Pooled effect estimates have heterogeneous underlying centre-specific effect estimates (significance test <0.05); [§] oil combustion source and salt source of PM$_{2.5}$ not identified in Erfurt, industrial source of PM$_{2.5}$ not identified in Helsinki; estimates of only two cities pooled

The positive association between unidentified $PM_{2.5}$ fraction and SDNN disappeared, when extreme source-specific $PM_{2.5}$ concentrations were excluded from the analyses. After exclusion, the city-specific estimates were no more heterogeneous for the association of long-range transported $PM_{2.5}$ with HF at lag 2 among all study subjects. Overall, exclusions of extreme values did not lead to more interpretable results.

Among persons not having daily beta-blocker medication, increases in absorbance (local traffic) and S (long-range transport) were consistently associated with decreased SDNN and HF (Table 5). The associations between V (oil combustion) and HRV were less consistent, and for the other source indicators there was no evidence of an effect. However, for the transition metals included because of potential toxicity, there was some evidence of negative associations with HRV at longer lags.

Discussion

In this panel study, conducted among persons with coronary heart disease in three European cities, personal, indoor or outdoor $PM_{2.5}$ measured during the 24 hours preceding clinic visit (lag 0) were not associated with heart rate variability (HRV). However, at 2- and 3-day lags we observed that daily increases in outdoor levels of $PM_{2.5}$ were associated with decreased HRV, but only among persons not on beta-blocker medication. When we linked source-specific $PM_{2.5}$ to HRV, we observed increases in traffic related $PM_{2.5}$ to be associated with decreased SDNN, especially among persons who were not on beta-blocker medication. Daily increases in the long-range transported $PM_{2.5}$ were associated both with decreased HF and SDNN, more strongly or exclusively among non-medicated persons. In separate analyses, indicator elements for these two sources, absorbance and S, were also negatively associated with HRV among persons not on medication. There was also evidence for a negative association of transition metals with HRV.

Table 5. Pooled effect estimates in the three study panels for the associations of elements of PM$_{2.5}$ with HRV among study subjects without daily beta-blocker medication.

		SDNN (ms)			HF (%)		
		β[*]	95% CI[†]		β	95% CI	
ABS	Lag 0	-0.64	-2.25	0.97	-2.54	-11.15	6.91
	Lag 1	-1.59	-3.11	-0.06	-4.94	-13.04	3.91
	Lag 2	-1.36	-2.99	0.27	-7.13	-15.51	2.08
	Lag 3	-1.44	-3.15	0.27	-7.83	-16.27	1.45
S	Lag 0	-0.71	-1.98	0.56	-2.70	-9.71	4.84
	Lag 1	-0.76	-1.99	0.47	-3.61	-10.36	3.64
	Lag 2	-1.44	-2.84	-0.04	-10.56	-17.63	-2.87
	Lag 3	-1.54	-3.02	-0.06	-13.05	-20.18	-5.29
V[§]	Lag 0	-0.46	-1.85	0.93	3.68	-4.72	12.82
	Lag 1	-1.97	-3.56	-0.39	-6.24	-14.71	3.07
	Lag 2	-0.16[‡]	-1.72	1.39	-4.58	-12.97	4.61
	Lag 3	-0.43	-1.78	0.91	-2.09	-9.64	6.09
Zn	Lag 0	-0.02	-0.06	0.02	0.04	-0.18	0.26
	Lag 1	-0.78	-2.11	0.54	0.13	-6.92	7.72
	Lag 2	-0.92	-2.20	0.37	-3.78	-10.41	3.35
	Lag 3	-0.28	-1.53	0.96	-6.41	-12.60	0.22
Ca	Lag 0	-0.72	-2.17	0.73	-0.37	-8.12	8.04
	Lag 1	-0.47	-2.16	1.21	2.10	-7.18	12.31
	Lag 2	0.35	-1.47	2.18	5.60	-4.98	17.35
	Lag 3	0.01	-2.03	2.05	-0.01	-10.58	11.81
Cl[§]	Lag 0	0.07	-0.48	0.61	2.34	-1.00	5.79
	Lag 1	0.00	-0.63	0.64	1.46	-2.39	5.46
	Lag 2	0.32	-0.22	0.85	1.71	-1.56	5.08
	Lag 3	0.37	-0.13	0.87	0.81	-2.21	3.91
Fe	Lag 0	0.00	-0.03	0.02	0.01	-0.13	0.15
	Lag 1	-1.09	-2.85	0.67	0.13	-9.70	11.04
	Lag 2	-1.51	-3.58	0.56	-3.31	-14.26	9.05
	Lag 3	-1.77	-3.86	0.32	-9.93	-20.26	1.72
Cu	Lag 0	-0.29	-1.26	0.68	-0.97	-6.40	4.77
	Lag 1	-0.20	-1.19	0.78	2.34	-3.49	8.52
	Lag 2	-1.55	-2.71	-0.39	-4.16	-10.53	2.67
	Lag 3	-0.54	-1.59	0.51	-4.41	-9.91	1.43

[*] β, effect estimate, calculated for an increase of 1 m^{-1}x10^{-5} in absorbance, 1 µg/m^3 in S, 4 ng/m^3 in V, 30 ng/m^3 in Ca and Zn, 100 ng/m^3 in Cl, 70 ng/m^3 in Fe, and 2 ng/m^3 in Cu; [†] CI, confidence interval ; [‡] Pooled effect estimates have heterogeneous underlying centre-specific effect estimates (significance test <0.05); [§] V and Cl not used in in Erfurt; estimates of only two cities pooled

We have previously reported that outdoor levels of $PM_{2.5}$ were not consistently associated with HRV in the three study panels.[16] However, people spend most of their time indoors, and persons with compromised health, like the panel members in our study, even more so.[20] Consequently, outdoor levels of particulate air pollution measured at a central site may not be perfect proxies for variation in personal PM exposure. However, we did not find personal or indoor $PM_{2.5}$ to be associated with decreased HRV. Unfortunately, we only had personal and indoor measurements in the 24 hours preceding the clinic visit, and $PM_{2.5}$ mass and composition during that time period were not associated with HRV. Our observation thus only indicates that the lack of association at 0-day lag for outdoor $PM_{2.5}$ was not due to exposure misclassification. It should be noted that in some studies the effects of PM on HRV have been observed even within hours of exposure.[26,27] However, the use of daily averages to measure $PM_{2.5}$ exposure in our study prevented us from detecting possible immediate effects of PM.

Beta-blockers have been shown to enhance heart rate variability in patients with coronary heart disease.[28,29] Consistent with this, we observed increased outdoor levels of $PM_{2.5}$ to be associated with decreased SDNN and HF (at 2- and 3-day lags) only among persons not using beta-blockers. Effect modification by medication use thus seems to explain the lack of associations between $PM_{2.5}$ and HRV in our previous analysis.[16] The interpretation of earlier studies evaluating the importance of beta-blocker use for the effects of ambient particles on HRV is somewhat difficult, because of the differences in the disease status between the users and non-users of beta-blockers. In a study by Park et al. conducted among veteran men,[17] beta-blocker users were all hypertensive, whereas only half of the non-users had hypertension. No clear effect of $PM_{2.5}$ (adjusted for O_3) on SDNN or HF was observed in either medication group. However, the low frequency component of HRV decreased in association with $PM_{2.5}$ only among persons not using beta-blockers. In a study by Wheeler et al.,[18] all but one of the beta-blocker users were myocardial infarction survivors, whereas most non-users had chronic obstructive pulmonary disease. Effect modification by beta-blocker use was reported only for SDNN, which decreased in association with $PM_{2.5}$ among users and increased among non-users. In the present study, all patients had coronary heart disease, and our results suggest that the use of beta-blockers modifies the effect of PM on HRV even in this more homogeneous patient group. Medication use is obviously never independent of disease status. Consequently, the suggestive increase in HF in association with $PM_{2.5}$ among beta-blocker users in our study may indicate either that the use of medication changes the direction of the association, or that those with less severe heart disease differ in their response to particulate air pollution.

Clinical studies have related decreased HRV in cardiac patients with increased risk of mortality over relatively long periods of follow-up.[9] To what extent short-term decreases in HRV measures predict short-term mortality is not known. However, vagal withdrawal is observed few minutes before transient ischemic events,[30,31] suggesting that short-term changes in HRV are not harmless. In a large study among elderly subjects,[32] increased HRV has been even more strongly associated with decreased survival than decreased HRV. Taking this into account, our study cannot be straightforwardly interpreted as showing that beta-blocker use is protective against the effects of particulate air pollution on cardiovascular health, because there was a suggestive increase in HF in association with $PM_{2.5}$ among medicated persons.

There was some indication of the effects of traffic related $PM_{2.5}$ with SDNN, and long-range transported $PM_{2.5}$ with HF and SDNN even before taking into account medication, but after considering beta-blocker use the associations became stronger. Some earlier studies have evaluated the effects of traffic related particles on HRV without conducting source-apportionment. Absorbance, considered as an indicator for traffic originating particles, has been more strongly associated with HRV among elderly subjects than $PM_{2.5}$.[15] In-vehicle $PM_{2.5}$ has been more strongly associated with HRV in healthy young men than were ambient or roadside $PM_{2.5}$.[33] The in-vehicle $PM_{2.5}$ was further apportioned between different sources,[34] and strongest associations were observed between $PM_{2.5}$ from brake wear and engine emissions and HRV.

Schwartz et al.[15] have evaluated indirectly the effects of secondary particles on HRV and found no effect. They regressed $PM_{2.5}$ against black carbon concentrations and interpreted residuals to represent the fraction of secondary particles that varied independently from primary combustion particles. It is possible that the effects of long-range transported $PM_{2.5}$ on HRV in our study are related to primary combustion particles generated e.g. by regional traffic. In any case, the effect estimates (for SDNN) per microgram of particle mass were clearly higher for local traffic related $PM_{2.5}$ than for long-range transported particles. However, there was also some evidence of the effects of $PM_{2.5}$ from oil combustion on SDNN. The results are consistent with our previous study, where $PM_{2.5}$ from traffic and other local combustion was most strongly associated with the occurrence of ST segment depressions in Helsinki, but also long-range transported particles and possibly oil combustion were contributing to the effects of $PM_{2.5}$.[5]

In the last part of our analyses, we evaluated the associations of HRV with elements of $PM_{2.5}$, and absorbance, a proxy for elemental carbon content of particles. In these analyses, decreased HRV was associated with absorbance and S, which were considered as markers for local traffic and long-range transported $PM_{2.5}$, respectively. The finding thus confirmed the analyses conducted using source-specific $PM_{2.5}$. However, it should be noted that also long-range transported $PM_{2.5}$

contains traffic originating PM and elemental carbon. There was also evidence of the negative associations of V (oil combustion), Zn (e.g. industry), Fe, and Cu with HRV, but the associations were mostly non-significant. Transition metals are typically associated with combustion processes, so it was not a surprise that absorbance was highly correlated with Zn, Fe and Cu. It has been suggested organic carbon compounds and transition metals attached to elemental carbon core (approximated by absorbance) are responsible for the effects of particulate matter on health.[35]

Toxicological studies have often observed cellular defences to be even more responsive to the coarse particle fraction (PM_{10}-$PM_{2.5}$) than to finer size fractions.[36,37] The ambient levels of coarse particles are typically dominated by crustal material, whereas $PM_{2.5}$ levels are more influenced by combustion emissions. In a recent study,[38] coarse particles were associated with decreased HRV whereas $PM_{2.5}$ was not. Interestingly, we found increases in HF in association with increased outdoor levels of crustal $PM_{2.5}$. On the other hand, the chosen indicator element for crustal $PM_{2.5}$, calcium, was not associated with HF. In the absence of coarse PM data in our study, we cannot contribute to this particular debate further.

Our study has both strengths and weaknesses. The study had rather stringent inclusion criteria for the study subjects in order to obtain a homogeneous cardiac panel, presumably vulnerable for the effects of air pollution.[39] The three study centres used common standard operating procedures and standardized equipment, and Holter recordings were analyzed in a single lab. HRV was recorded during paced breathing period to avoid influence of breathing patterns on the results. However, because we measured outdoor levels of source-specific $PM_{2.5}$ instead of actual exposure, exposure misclassification may have biased the results. We have previously reported considerable longitudinal correlations between outdoor and personal $PM_{2.5}$, absorbance (traffic) and S (long-range transport), but correlations have been lower for Ca (soil), Cl (salt) and Cu.[40] Finally, it should be emphasized that our source-specific $PM_{2.5}$ levels are not always products of homogeneous sources but rather of broader sources categories.

In conclusion, we found $PM_{2.5}$ originating from local traffic and other local combustion, but also long-range-transported $PM_{2.5}$ to be associated with decreased indices of heart rate variability. The effects were stronger among persons not using beta-blocker medication. Differences in the composition of particles and medication use or disease severity of study subjects may explain some inconsistencies between previous studies on HRV.

Acknowledgements

References

1. Samet JM, Dominici F, Curriero FC, et al. Fine particulate air pollution and mortality in 20 U.S. cities, 1987-1994. *N Engl J Med* 2000; 343:1742-9.

2. Analitis A, Katsouyanni K, Dimakopoulou K, Samoli E, Nikoloulopoulos AK, Petasakis Y, Touloumi G, Schwartz J, Anderson HR, Cambra K, Forastiere F, Zmirou D, Vonk JM, Clancy L, Kriz B, Bobvos J, Pekkanen J. Short-term effects of ambient particles on cardiovascular and respiratory mortality. *Epidemiology* 2006 17:230-3.

3. Le Tertre A, Medina S, Samoli E, et al. Short-term effects of particulate air pollution on cardiovascular diseases in eight European cities. *J Epidemiol Community Health* 2002; 56:773-779.

4. Laden F, Neas LM, Dockery DW, et al. Association of fine particulate matter from different sources with daily mortality in six U.S. cities. Environ Health Perspect. 2000; 108:941-947.

5. Lanki T, de Hartog JJ, Heinrich J, Hoek G, Janssen NAH, Peters A, Stölzel M, Timonen KL, Vallius M, Vanninen E, Pekkanen J. Can we identify sources of fine particles responsible for exercise-induced ischemia on days with elevated air pollution? The ULTRA study. *Environ Health Perspect* 2006;114:655-60.

6. Pagan I, Costa DL, McGee JK, Richards JH, Dye JA. 2003. Metals mimic airway epithelial injury induced by in vitro exposure to Utah Valley ambient particulate matter extracts. *J Toxicol Environ Health A* 2003; 66:1087-1112.

7. Bonvallot V, Baeza-Squiban A, Baulig A, Brulant S, Boland S, Muzeau F, et al. Organic compounds from diesel exhaust particles elicit a proinflammatory response in human airway epithelial cells and induce cytochrome p450 1A1 expression. *Am J Respir Cell Mol Biol* 2001; 25:515-521.

8. Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, et al. Air pollution and cardiovascular disease: a statement for health care professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. *Circulation* 2004; 109:2655-2671.

9. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. *Eur Heart J* 1996;17:354-81.

10. La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet* 1998; 351:478-484.

11. Nolan J, Batin PD, Andrews R, Lindsay SJ, Brooksby P, Mullen M, Baig W, Flapan AD, Cowley A, Prescott RJ, Neilson JM, Fox KA. Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). *Circulation* 1998; 98:1510-1516.

12. Liao D, Duan Y, Whitsel EA, et al. Association of higher levels of ambient criteria pollutants with impaired cardiac autonomic control: A population-based study. *Am J Epidemiol* 2004;159:768-77.

13. Lipsett MJ, Tsai FC, Roger L, Woo M, Ostro BD. Coarse particles and heart rate variability among older adults with coronary artery disease in the Coachella Valley, California. *Environ Health Perspect* 2006; 114:1215-20.

14. Holguin F, Tellez-Rojo MM, Hernandez M, et al. Air pollution and heart rate variability among the elderly in Mexico city. *Epidemiology* 2003;14:521-7.

15. Schwartz J, Litonjua A, Suh H, Verrier M, Zanobetti A, Syring M, Nearing B, Verrier R, Stone P, MacCallum G, Speizer FE, Gold DR. Traffic related pollution and heart rate variability in a panel of elderly subjects. *Thorax* 2005; 60:455-61.

16. Timonen KL, Vanninen E, de Hartog J, Ibald-Mulli A, Brunekreef B, Gold DR, Heinrich J, Hoek G, Lanki T, Peters A, Tarkiainen T, Kreyling W, Pekkanen J. Effects of ultrafine and fine particulate and gaseous air pollution on cardiac autonomic control in subjects with coronary artery disease. The ULTRA study. *J Expo Sci Environ Epidemiol* 2006; 16:332-341.

17. Park SK, O'Neill MS, Vokonas PS, Sparrow D, Schwartz J. Effects of air pollution on heart rate variability: the VA normative aging study. *Environ Health Perspect* 2005;113:304-9.

18. Wheeler A, Zanobetti A, Gold DR, Schwartz J, Stone P, Suh HH. The relationship between ambient air pollution and heart rate variability differs for individuals with heart and pulmonary disease. *Environ Health Perspect* 2006;114:560-566.

19. Pekkanen J, Timonen KL, Tiittanen P, et al. ULTRA: Exposure and risk assessment for fine and ultrafine particles in ambient air. Study manual and data book. *Publications of National Public Health Institute* 2000. Available at http://www.ktl.fi/ultra.

20. Brunekreef B, Janssen NAH, de Hartog JJ, Oldenwening M, Meliefste K, Hoek G, Lanki T, Timonen KL, Vallius M, Pekkanen J, van Grieken R. Personal, indoor, and outdoor exposures to $PM_{2.5}$ and its components for groups of cardiovascular patients in Amsterdam and Helsinki. *Res Rep Health Eff Inst* 2005; 127:1-70; discussion 71-79.

21. Tarkiainen TH, Timonen KL, Tiittanen P, Hartikainen JE, Pekkanen J, Hoek G, Ibald-Mulli A, Vanninen EJ. Stability over time of short-term heart rate variability. *Clin Auton Res* 2005;15:394-399.

22. Janssen NA, de Hartog JJ, Hoek G, Brunegreef B, Lanki T, Timonen KL, Pekkanen J. Personal exposure to fine particulate matter in elderly subjects: relation between personal, indoor and outdoor concentrations. *J Air & Waste Manage Assoc* 2000;50:1133-1143.

23. Janssen NAH, Lanki T, Hoek G, Vallius M, de Hartog JJ, Van Grieken R, Pekkanen J, Brunekreef B. Associations between ambient, personal, and indoor exposure to fine particulate matter constituents in Dutch and Finnish panels of cardiovascular patients. *Occup Environ Med* 2005; 62: 868-877.

24. Vallius M, Janssen NA, Heinrich J, Hoek G, Ruuskanen J, Cyrys J, Van Grieken R, de Hartog JJ, Kreyling WG, Pekkanen J. Sources and elemental composition of ambient $PM_{2.5}$ in three European cities. *Sci Total Environ* 2005;337:147-62.

25. Normand S-L. Meta-analysis: formulating, evaluating, combining, and reporting. *Stat Med* 1999;18:321-59.

26. Gold DR, Litonjua A, Schwartz J, et al. Ambient pollution and heart rate variability. *Circulation* 2000; 101:1267-73.

27. Devlin RB, Ghio AJ, Kehrl H, Sanders G, Cascio W. Elderly humans exposed to concentrated air pollution particles have decreased heart rate variability. *Eur Respir J* 2003;21 Suppl. 40, 76-80.

28. Niemela MJ, Airaksinen KE, Huikuri HV. Effect of beta-blockade on heart rate variability in patients with coronary artery disease. *J Am Coll Cardiol* 1994; 23:1370-1377.

29. Sandrone G, Mortara A, Torzillo D, La Rovere MT, Malliani A, Lombardi F. Effects of beta blockers (atenolol or metoprolol) on heart rate variability after acute myocardial infarction. *Am J Cardiol* 1994; 74:340-345.

30. Kop WJ, Verdino RJ, Gottdiener JS, O'Leary ST, Bairey Merz CN, Krantz DS. Changes in heart rate and heart rate variability before ambulatory ischemic events. *J Am Coll Cardiol* 2001;38:742-9.

31. Kochiadakis GE, Marketou ME, Igoumenidis NE, Simantirakis EN, Parthenakis FI, Manios EG, Vardas PE. Autonomic nervous system activity before and during episodes of myocardial ischemia in patients with stable coronary artery disease during daily life. *Pacing Clin Electrophysiol* 2000; 23:2030-2039.

32. de Bruyne MC, Kors JA, Hoes AW, Klootwijk P, Dekker JM, Hofman A, van Bemmel JH, Grobbee DE. Both decreased and increased heart rate variability on the standard 10-second electrocardiogram predict cardiac mortality in the elderly: the Rotterdam Study. *Am J Epidemiol* 1999;150:1282-8.

33. Riediker M, Cascio WE, Griggs TR, Herbst MC, Bromberg PA, Neas L, Williams RW, Devlin RB. Particulate matter exposure in cars is associated with cardiovascular effects in healthy young men. *Am J Respir Crit Care Med* 2004;169:934-40.

34. Riediker M, Devlin RB, Griggs TR, Herbst MC, Bromberg PA, Williams RW, Cascio WE. Cardiovascular effects in patrol officers are associated with fine particulate matter from brake wear and engine emissions. *Part Fibre Toxicol* 2004; 1:2.

35. Obot CJ, Morandi MT, Beebe TP, et al. Surface components of airborne particulate matter induce macrophage apoptosis through scavenger receptors. *Toxicol Appl Pharmacol* 2002;184:98-106.

36. Soukup JM, Becker S. Human alveolar macrophage responses to air pollution particulates are associated with insoluble components of coarse material, including particulate endotoxin. *Toxicol Appl Pharmacol* 2001;171:20-6.

37. Hetland RB, Cassee FR, Refsnes M, Schwarze PE, Lag M, Boere AJ, Dybing E. Release of inflammatory cytokines, cell toxicity and apoptosis in epithelial lung cells after exposure to ambient air particles of different size fractions. *Toxicol In Vitro* 2004;18:203-12.

38. Lipsett MJ, Tsai FC, Roger L, Woo M, Ostro BD. Coarse particles and heart rate variability among older adults with coronary artery disease in the Coachella Valley, California. *Environ Health Perspect* 2006;114:1215-20.

39. von Klot S, Peters A, Aalto P, Bellander T, Berglind N, D'Ippoliti D, Elosua R, Hörmann A, Kulmala M, Lanki T, Löwel H, Pekkanen J, Picciotto S, Sunyer J, Forastiere F for the HEAPSS Study Group. Ambient air pollution is associated with increased risk of hospital cardiac readmissions of myocardial infarction survivors in European cities. *Circulation* 2005;112:3073-3079.

40. Janssen NAH, Lanki T, Hoek G, Vallius M, de Hartog JJ, Van Grieken R, Pekkanen J, Brunekreef B. Associations between ambient, personal, and indoor exposure to fine particulate matter constituents in Dutch and Finnish panels of cardiovascular patients. *Occup Environ Med* 2005; 62: 868-877.

11 GENERAL DISCUSSION

11.1 Relationships between outdoor, indoor and personal PM$_{2.5}$ and its components

It has been unclear whether PM$_{2.5}$ exposure of elderly persons with compromised health can be reliably estimated using measurements at a central outdoor site. The epidemiological ULTRA study provided an excellent framework to study this in a population subgroup suggested to be especially susceptible to particulate air pollution: elderly persons with cardiovascular disease.

We observed reasonably high longitudinal correlations between outdoor levels of PM$_{2.5}$ and personal exposure (Article I). The correlation coefficients for sulphur and absorbance, markers for outdoor and combustion originating PM$_{2.5}$, respectively, were even higher (Article II). However, correlations between personal and outdoor concentrations were rather low for Ca, Cu, Si, and Cl. In general, the correlation between indoor and personal measurements was high, an exception was Cu. The outdoor, indoor and personal levels of PM$_{2.5}$ were comparable, but exposures to Ca and Cu were higher than outdoor or indoor concentrations.

The observed high longitudinal correlation between central outdoor levels of PM$_{2.5}$ and measured exposure supports the use of central measurements in time-series studies on the health effects of PM$_{2.5}$ in Amsterdam and Helsinki. In other studies conducted in potentially susceptible subpopulations longitudinal PM$_{2.5}$ correlations have been variable (Ebelt et al. 2000, Sarnat et al. 2000, Williams et al. 2000). The outdoor levels of PM$_{2.5}$ were comparable to personal levels in the present study; this is consistent with some previous studies (Rodes et al. 2001, Liu et al. 2003). However, perhaps more often personal PM$_{2.5}$ concentrations have been higher than outdoor concentrations (Rojas-Bracho et al. 2000).

The present study (Articles VI and VII) and some other recent studies (Jansen et al. 2005, Laden et al. 2000, Schwartz et al. 2005) have observed an association between outdoor particles of combustion origin and cardiorespiratory health. The observed high correlation between outdoor and personal absorbance in our study supports the causality of the association. An expected finding in the present study was the high correlation between outdoor and personal S, as it has no significant indoor sources. In other studies sulphate has been used instead of sulphur as an indicator for outdoor originating PM. We have observed a high correlation between S and sulphate (Brunekreef et al. 2005). A method has been suggested for the calculation of outdoor

originating personal PM$_{2.5}$ concentrations based on sulphate concentrations (Wilson and Brauer 2006).

According to our quality control measures, the measurement methods for outdoor and personal PM$_{2.5}$ gave comparable results even though flow rates and size-selective inlets were different. The problems with the personal monitoring systems in the beginning of study forced us to abandon a considerable number of measurement days. Our data-base is still larger than in previously published studies.

Our study was conducted among elderly persons with coronary heart disease, but the results can probably be generalized to elderly persons with other chronic health problems that restrict activities of personal living, and with more caution to healthy elderly. There is some evidence from U.S (Liu et al. 2003) suggesting that healthy elderly persons and persons with coronary heart disease have comparable exposures, which are lower than exposures of adults or children.

However, there are some other limitations to generalizability of our results. All study participants were living within a radius of a few kilometres from the fixed outdoor measurement site. In other studies, one central monitoring site is often used to estimate population exposure in much larger areas, even hundreds of square kilometres, resulting in lower personal-outdoor correlations. Our study did not include all seasons. However, the correlations are not likely to change drastically even if summer would be included, because part of the warm season was included anyway (Brunekreef et al. 2005). Further, correlations would probably have been higher rather than lower if summer would have been included, because of increased engagement in outdoor activities and higher air exchange rates due to open windows (Koistinen et al. 2001).

11.2   Factors affecting personal 24-h PM$_{2.5}$ and elemental carbon (absorbance) exposures

After demonstrating that outdoor PM$_{2.5}$ and absorbance concentrations are important determinants of personal exposure (Article I), we evaluated whether there are also other determinants (Article III). For the purpose, all participants of the study filled in questionnaires about time spent in different microenvironments and other exposure characteristics during the 24-h measurement period.

Within-person variation in both PM$_{2.5}$ and absorbance exposures was higher than between-person variation. In addition to outdoor levels, also housing characteristics and personal behaviour affected personal exposure. All the participants were non-smokers, but in Amsterdam there were still enough ETS events to demonstrate the major effect of ETS exposure on both between-person variation and on the 24-h

levels of personal PM$_{2.5}$ and absorbance. Another factor affecting personal PM$_{2.5}$ was cooking. Absorbance exposure was increased especially by traffic related factors: closeness to a major street and time spent in a motor vehicle.

Our study was one of the few studies where various determinants of exposure were evaluated at the same time. In the cross-sectional EXPOLIS study, traffic and air exchange rates were found to determine personal PM$_{2.5}$ exposures in Helsinki amond adult population (Koistinen et al. 2001). Previous studies have often concentrated on one specific determinant at a time, such as cooking, which is a major determinant of several particle fractions (Abt et al. 2000). There have been several studies looking at the effect of traffic related factors on PM$_{2.5}$ exposure (Cyrus et al. 2003, Wichmann et al. 2005). Our study confirmed that absorbance is a better marker for exposure to traffic exhausts than PM$_{2.5}$. Our results also show that use of questionnaires improves estimation of exposure in studies relying on fixed outdoor measurements.

In order to decrease population exposure to harmful, combustion originating particles, more efficient emission control of traffic exhausts is needed. Exposure of susceptible population groups like children and elderly could also be decreased by city planning, e.g. by not locating new day-care or retirement centres in the vicinity of busy roads.

There is still limited information on the determinants of exposure to particles from different sources; in future studies determinants of exposure also to other components of PM$_{2.5}$ than just absorbance could be evaluated.

11.3   Hourly changes in PM$_{2.5}$ exposures: measurement and effects on ST segment depression

It has been suggested that even brief exposures to high PM$_{2.5}$ levels, encountered typically in traffic, are associated with cardiovascular effects (Peters et al. 2001, 2004). In Helsinki, photometers were used to measure personal PM$_{2.5}$ exposure continuously in the ULTRA study. This allowed us to to evaluate whether hourly changes in PM$_{2.5}$ exposure are associated with the occurrence of exercise induced ST segment depression, an indicator for myocardial ischemia (Article V). In a previous paper (Pekkanen et al. 2002), we observed an association between daily outdoor air pollution levels, including PM$_{2.5}$, two days before clinic visit and ST segment depression.

Before taking into use the new continous photometric measurement method, we evaluated its performance and found high correlation between daily photometric and gravimetric PM$_{2.5}$ concentrations (Article IV). Gravimetric method can be

considered as a standard method, and thus our results support the use of photometric measurements in epidemiological studies. We observed an association between personal $PM_{2.5}$ exposures during 4 hours before clinic visits and the occurrence ST segment depressions. Hourly $PM_{2.5}$ concentrations measured at a fixed outdoor site were as strongly associated with ST segment depressions as personal exposures.

The performance of the photometric monitor we used has been evaluated in a number of previous studies, but the devices have been used either without a size-selective inlet or without a pump, i.e. as a passive monitor. Both modifications (the $PM_{2.5}$ inlet and the pump) that we did to the photometer probably helped us to obtain a correlation between the photometric and gravimetric method that was higher than in previous studies (Howard-Reed et al. 2000, Quintana et al. 2000). Active sampling has been found to increase considerably the performance of the photometer (Wu et al. 2005). The importance of cyclone has been less clear as the sensor of the photometer has a maximum response to particles around 1 µm. What was lacking in our study was a method to control the effect of relative humidity. It has been shown in other studies that relative humidity affects measurements of $PM_{2.5}$ that are based on light scattering (Day et al. 2000). We found only a 22% increase in $PM_{2.5}$ in association with high relative humidity. However, we were able to evaluate the effect of humidity on the $PM_{2.5}$ concentrations only indirectly, and the estimate is probably unrealistically low.

There is only one earlier study on the immediate effects of particulate air pollution on ST segment depressions. In the study by Gold et al. (2005), the strongest association was observed between 5-hrs lagged outdoor 1-h black carbon concentration (roughly equivalent to absorbance) and the end-point. It is possible that the high effect estimate at the single hourly lag was a chance finding, but estimates for the other hours were also positive during 12-hrs before the recording of ST segment depression. In controlled human exposure studies (Devlin et al. 2003; Urch et al. 2005), two hours of exposure to concentrated ambient particles (CAPs) has been enough to raise blood pressure and to decrease heart rate variability. This suggests that an immediate component might be involved in several types of responses, which have been evaluated in earlier epidemiological studies almost solely using daily data. Our finding of both an immediate (Article V) and a delayed (Pekkanen et al. 2002) response is in agreement with a study by Peters et al. (2001), where outdoor PM levels of the previous couple of hours and of the previous day were both associated with myocardial infarction. However, other studies have not been able to replicate the result of an immediate effect of $PM_{2.5}$ on MI (Peters et al. 2005, Sullivan et al. 2005).

There has been a lack of suitable measurement methods to estimate short-term changes in $PM_{2.5}$ exposure in field studies. Our results show that photometers can be

used for the purpose, although with some limitations. This opens new possibilities to study the health effects of short peak PM exposures, which are typically experienced e.g. while commuting. Exposure to ultrafine particles while bicycling in traffic has been associated with increased DNA oxidation (Vinzents et al. 2005).The effects of exposure to $PM_{2.5}$ and ultrafine particles in traffic should be compared to find out, whether particle size or composition is the most important determinant of toxicity of traffic exhaust.

In our study the main limitation was the low number of ST events. First of all, there were so few ST segment depressions in Amsterdam and Erfurt that analyses were possible only in Helsinki. The lack of ST events in the two centres was mainly due to low heart rate during exercise test with bicycle ergometer; this was in turn mostly attributable to the fact that the study was conducted in the community setting and the field workers were very cautious in performing the tests among coronary patients. Because of the caution, there were a lot of visits without an exercise test also in Helsinki. On the other hand, the effect of subjective decisions was minimized in the processing of ECG recordings: all processing was conducted in one core laboratory (Kuopio University Hospital), and the classification of the QRS complexes was done automatically (Pekkanen et al. 2002). Trained research assistants interactively edited the predetermined classification only when necessary.

The main problem in the use of photometers in other than indoor working environments, for which they are originally designed for, is caused by high relative humidity outdoors. Several solutions have been proposed, e.g. heating of the inlet and installing dryers (Quintana et al. 2000), but these solutions are not possible for 24-hr measurements which are typical in community studies. In future studies real-time measurements of relative humidity with personal data loggers should be conducted; this would allow for the humidity correction of photometric readings afterwards.

11.4 Associations of source-specific $PM_{2.5}$ with cardiovascular health

The association between fine particle mass and cardiovascular health has been established in epidemiological studies. However, it is unclear which particle sources are responsible for the effect. Thus, we compared the effects of fine particles from different sources on cardiovascular health using risk of ST segment depression (Article VI) and heart rate variability (Article VII) as end-points.

We found particles originating from local traffic to be most strongly associated with the occurrence of ST segment depressions per 1 $\mu g/m^3$ change in concentration, but when calculating the effect per interquartile change in concentration, the effect of long-range transported particles was comparable. Of the individual components of

PM$_{2.5}$, absorbance was most strongly associated with ST segment depression. Heart rate variability was also associated both with traffic (and other local combustion) originating PM$_{2.5}$ and long-range transported PM$_{2.5}$. Also the indicators for the two sources, absorbance and sulphur, were associated with HRV. The effects of total and source-specific PM$_{2.5}$ were strongest among persons not having daily beta-blocker medication. Personal PM$_{2.5}$ exposures or indoor levels during the 24-h preceding clinic visit were not associated with HRV.

The observed association between absorbance and ST segment depressions suggests that combustion originating constituents are mainly responsible for the effects of PM$_{2.5}$ on myocardial ischemia. In city-environments traffic is the main source of primary combustion particles; especially exhausts from diesel vehicles affect outdoor concentrations of absorbance (Gray and Cass 1998). The results for heart rate variability confirmed the role of traffic-related and long-range transported particles. Routine outdoor measurements of elemental carbon (e.g. with aethalometers) are recommended to faciliate further investigations on the cardiovascular effects of combustion originating primary particles.

Our previously published results on the effects of PM$_{2.5}$ on HRV were heterogeneous between the three study centres (Timonen et al. 2006). The present study shows that at least part of the heterogeneity was due to differences in particle composition. We did not find evidence of harmful effects of soil derived particles on cardiovascular health.

There are only few earlier studies comparing the relative effects of PM from different sources on health, and in all these studies combustion originating particles have been associated with the studied end-point (Laden et al. 2000, Tsai et al. 2000, Mar et al. 2000). There are more studies comparing the effects of PM$_{2.5}$ and its combustion originating fraction, and in most of them primary combustion particles have been more strongly associated with health than the particle mass (Jansen et al. 2005, Schwartz et al. 2005). Because in time-series studies the misclassification of exposure is larger for soil originating constituents of PM$_{2.5}$ than for combustion originating PM$_{2.5}$ fraction (Article II), an absence of effect of crustal PM$_{2.5}$ on the indicators of cardiovascular health in the present study does not rule out the possibility of an effect. A recent review article emphasized that the potential of coarse particles, mainly originating from soil, to induce harmful health effects is not yet known (Brunekreef and Forsberg 2005)

An important finding in the HRV study concerned the effect of beta-blocker medication: those not on medication experienced greater decrease in HRV due to particulate air pollution. We have earlier observed similar modifying effect of beta-blockers for the occurrence of ST segment depressions (Pekkanen et al. 2002). It

should be noted that differentitation between effect modification by medication use and by chronic diseases is difficult. In any case, our results urge to take into account medication use in future epidemiological studies. Unfortunately, in register based studies information on medication is often not available

11.5 The use of personal measurements to estimate effects of outdoor PM$_{2.5}$ on health

Not many epidemiological studies have included personal measurements of PM$_{2.5}$ exposure, not even panel studies, although it is clear that PM$_{2.5}$ concentrations at a central outdoor site are never perfect proxies of personal exposure to PM$_{2.5}$ of outdoor origin, and even less so for total PM$_{2.5}$. An obvious reason for the lack of personal measurements is the high cost.

In a study by Brauer et al. (2001), the comparison of the effect estimates of personal and outdoor PM$_{2.5}$ was difficult, because the effects of particles on cardiopulmonary health were generally weak. However, the authors concluded that personal measurements were not more strongly associated with health than outdoor measurements. The comparison of the effects of personal and outdoor PM$_{2.5}$ and absorbance on HRV in our study (Article VII) was also hampered by the lack of an effect at 0-day lag. Another study that included personal measurements of PM$_{2.5}$ also found no association between average exposure during the 24-hrs before clinic visit and HRV (Dales et al. 2004). Outdoor PM$_{2.5}$ concentrations were not reported.

It should be noted that the use of 24-h averaging time for personal measurements may have concealed an immediate, transient effect of PM$_{2.5}$ on HRV in our study. As an example, just two hour exposure to environmental tobacco smoke has been associated with a rapid decrease in HRV (Pope et al. 2001). Effects of very short-term exposures to PM$_{2.5}$ on HRV can be addressed in the future using photometric data from Helsinki.

There are some studies, where personal PM$_{2.5}$ concentrations have been more strongly associated with health than outdoor concentrations measured at a central site. In a study by Sørensen et al. (2003), personal PM$_{2.5}$ measurements were associated with plasma protein oxidation, whereas outdoor PM$_{2.5}$ levels were not. In a study by Delfino et al. (2004), photometric personal PM$_{2.5}$ concentrations were more strongly associated with forced expiratory volume than were gravimetric outdoor PM$_{2.5}$ concentrations. However, neither authors reported how far the study subjects lived from the outdoor measurement site. Outdoor PM$_{2.5}$ monitor does not necessarily reflect adequately exposure when study population is spread over a large area; personal measurements of PM$_{2.5}$ indeed may give more precise estimates of air

pollution effects in these situations. However, even when the study area is more limited, the location of the outdoor PM monitor should be carefully selected as it may affect the comparison of different measures of exposure (de Hartog et al. 2005).

In the present study, indoor and personal $PM_{2.5}$, as well as absorbance, correlate highly (Article I). However, indoor measurements do not capture the considerable exposures to combustion particles encountered while in traffic (Article III), so personal measurements should in general be preferred, although they are more of a burden to study subjects. Some studies have used indoor measurements of PM instead of personal ones. In a study by Liao et al. (1999) the effects of indoor $PM_{2.5}$ on HRV did not clearly differ from the effects of outdoor $PM_{2.5}$. In another study (Jansen et al. 2005), indoor $PM_{2.5}$ was more strongly associated with exhaled nitric oxide than outdoor $PM_{2.5}$. In contrast, both indoor and and outdoor absorbance were associated with the outcome, possibly because of fewer indoor sources of absorbance.

In general, the value of personal (and indoor) measurements of $PM_{2.5}$ in time-series studies evaluating the effects of outdoor $PM_{2.5}$ appears limited, due to high correlation of central outdoor $PM_{2.5}$ with personal (and indoor) $PM_{2.5}$, and because of the significant effect of indoor sources on personal (and indoor) $PM_{2.5}$ concentrations. Personal measurements are needed in the evalution of the effects of those $PM_{2.5}$ sources, for which fixed outdoor measurements provide less accurate estimates of exposure, e.g crustal particles (Article II). However, in that specific case personal monitoring could also focus on coarse particles, which are most strongly associated with crustal elements. Continuous personal measurements of $PM_{2.5}$ are valuable for studying the effects of short-term exposures in different microenvironments, for example in traffic. However, time-activity data is required to make full of use of continuous data.

11.6   Conclusions

The main conclusions from the present study are:

- Daily levels of $PM_{2.5}$ and absorbance, a marker for elemental carbon, measured at a central outdoor measurement site can be used as surrogates for personal exposures to PM of outdoor origin in epidemiological time-series studies.

- Personal measurements should be preferred in studies on the health effects of soil particles and of brief exposures to e.g. fresh traffic emissions.

- By collecting questionnaire data on home characteristics and personal behaviour, estimation of personal exposure can be improved in epidemiological studies.

- PM$_{2.5}$ concentrations measured with a new photometric method correlate highly with gravimetric concentrations. The method can be used to evaluate associations between very short-term changes in PM$_{2.5}$ exposure and health. However, personal relative humidity measurements are recommended in order to be able to conduct humidity correction of photometric PM$_{2.5}$ concentrations.

- Even brief exposures to high levels of PM$_{2.5}$ are associated with increased risk of myocardial ischemia among persons with coronary heart disease. It seems that particulate air pollution has both a rapid (within hours) and a more delayed (within days) effect on cardiovascular health. There may be two separate mechanisms of action, but the results need to be confirmed.

- Routine outdoor measurements of elemental carbon (e.g. with aethalometers) are recommended to facilitate studies on the cardiovascular effects of (primary) combustion originating particles.

- The medication use of study subjects should be taken into account in studies evaluating the effects of (source-specific) PM$_{2.5}$ on especially heart rate variability.

- The most harmful sources of PM$_{2.5}$ are emissions from local traffic and long-range transported air pollution.It is unclear, to what extent traffic emissions accounted for the harmful effects of long-range transported particles in our study.

Traffic is a major determinant of both short-term and long-term exposure to (combustion related) PM$_{2.5}$, and traffic also appears to be the source of more potent particles. In order to decrease population exposure to this harmful particle fraction, more efficient emission control of traffic exhausts is needed. Exposure of susceptible population groups like children and elderly could also be decreased by city planning, e.g. by not locating new day-care or retirement centres in the vicinity of busy roads.

11.7 References

Abt E, Suh HH, Allen G, Koutrakis P. Characterization of indoor particle sources: a study conducted in the metropolitan Boston area. Environ Health Persp 2000; 108: 35-44.

Brauer M, Ebelt ST, Fisher TV, Brumm J, Petkau AJ, Vedal S. Exposure of chronic obstructive pulmonary disease patients to particles: respiratory and cardiovascular health effects. J Expo Anal Environ Epidemiol 2001; 11:490-500.

Brunekreef B, Forsberg B. Epidemiological evidence of effects of coarse airborne particles on health. Eur Respir J 2005; 26:309-318.

Brunekreef B, Janssen NA, de Hartog JJ, Oldenwening M, Meliefste K, Hoek G, Lanki T, Timonen KL, Vallius M, Pekkanen J, Van Grieken R. Personal, indoor, and outdoor

exposures to $PM_{2.5}$ and its components for groups of cardiovascular patients in Amsterdam and Helsinki. Res Rep Health Eff Inst 2005: Jan (127): 1-70; discussion 71-79.

Cyrys J, Heinrich J, Hoek G, Meliefste K, Lewne M, Gehring U, Bellander T, Fischer P, van Vliet P, Brauer M, Wichmann HE, Brunekreef B. Comparison between different traffic-related particle indicators: Elemental carbon (EC), PM(2.5) mass, and absorbance. J Expo Anal Environment Epidemiol 2003; 13:134-143.

Dales R on behalf of the Air Pollution-Cardiac Health Research Group. Ambient carbon monoxide may influence heart rate variability in subjects with coronary artery disease. J Occup Environ Med 2004; 46:1217-1221.

Day DE, Malm WC, Kreidenweis SM. Aerosol light scattering measurements as a function of relative humidity. J Air Waste Manage Assoc 2000; 50:701-717.

Delfino RJ, Quintana PJE, Floro J, Gastanaga VM, Samimi BS, Kleinman MT, Liu SL-J, Bufalino C, Wu C-F, McLaren CE. Association of FEV_1 in asthmatic children with personal and microenvironmental exposure to airborne particulate matter. Environ Health Perspect 2004; 112:932-941.

Devlin RB, Ghio AJ, Kehrl H, Sanders G, Cascio W. Elderly humans exposed to concentrated air pollution particles have decreased heart rate variability. Eur Respir J 2003; 21:Suppl. 40, 76-80.

Ebelt ST, Petkau AJ, Vedal S, Fisher T, Brauer M. Exposure of chronic obstructive pulmonary disease patients to particulate matter: relationships between personal and ambient air concentrations. J Air&Waste Manage Assoc 2000: 50: 1081-1094.

de Hartog JJ, Hoek G, Mirme A, Tuch T, Kos GPA, ten Brink H, Brunekreef B, Cyrus J, Heinrich J, Pitz M, Lanki T, Vallius M, Pekkanen J, Kreyling WG. Relationship between different size classes of particulate matter and meteorology in three European cities. J Environ Monit 2005; 7:302-310.

Howard-Reed C, Zufall MJ, Burke JM, Williams RW, Sugss JC, Sheldon LS, Walsh D, Kwok R. Use of continuous nephelometer to measure personal exposure to particulate matter during the U.S. Environmental Protection Agency Baltimore and Fresno panel studies. J Air & Waste Manage Assoc 2000; 50: 1125-1132.

Gold DR, Litonjua AA, Zanobetti A, Coull BA, Schwartz J, MacCallum G, Verried RL, Nearing BD, Canner MJ, Suh H, Stone PH. Air pollution and ST-segment depression in elderly subjects. Environ Health Perspect 2005; 113:883-887.

Gray HA, Cass GR. Source contributios to atmospheric fine carbon particle concentrations. Atmos Environ 1998; 32:3805-3825.

Jansen KL, Larson TV, Koenig JQ, Mar TF, Fields C, Stewart J, Lippmann M. Associations between health effects and particulate matter and black carbon in subjects with respiratory disease. Environ Health Perspect 2005; 113:1741-1746.

Koistinen KJ, Hänninen O, Rotko T, Edwards RD, Moschandreas D, Jantunen M.J. Behavioral and environmental determinants of personal exposures to $PM_{2.5}$ in EXPOLIS - Helsinki, Finland. Atmos Environ 2001: 35: 2473-2481

Laden F, Neas LM, Dockery DW, et al. Association of fine particulate matter from different sources with daily mortality in six U.S. cities. Environ Health Perspect 2000; 108:941-947.

Liao D, Creason J, Shy C, Williams R, Watts R, Zweidinger R. Daily variation of particulate air pollution and poor cardiac autonomic control in the elderly. Environ Health Perspect 1999; 107:521-525.

Liu L-JS, Box M, Kalman D, Kaufman J, Koenig J, Larson T, Lumley T, Sheppard L, Wallace L. Exposure assessment of particulate matter for susceptible populations in Seattle. Environ Health Persp 2003; 111: 909-918.

Mar TF, Norris GA, Koenig JQ, Larson TV. Association between air pollution and mortality in Phoenix, 1995-1997. Environ Health Perspect 2000; 108:347-353.

Pekkanen J, Peters A, Hoek G, Tiittanen P, Brunekreef B, de Hartog J, Heinrich J, Ibald-Mulli A, Kreyling WG, Lanki T, Timonen KL, Vanninen E. Particulate air pollution and risk of ST-segment depression during repeated submaximal exercise tests among subjects with coronary heart disease. The exposure and risk assessment for fine and ultrafine particles in ambient air (ULTRA) study. Circulation 2002; 20:933-8.

Peters A, Dockery W, Muller JE, Mittleman MA. Increased particulate air pollution and the triggering of myocardial infarction. Circulation 2001; 103:2810-2815.

Peters A, von Klot S, Heier M, Trentinaglia I, Hormann A, Wichmann HE, Lowel H; Cooperative Health Research in the Region of Augsburg Study Group. Exposure to traffic and the onset of myocardial infarction. N Engl J Med 2004; 351:1721-30.

Peters A, von Klot S, Heier M, Trentinaglia I, Hormann A, Wichmann HE, Lowel H; Cooperative Health Research in the Region of Augsburg Study Group. Particulate Air Pollution and Nonfatal Cardiac Events, Part I. Air Pollution, Personal Activities, and Onset of Myocardial Infarction in a Case–Crossover Study. Res Rep Health Eff Inst 2005; 124:7-66; discussion 67-82.

Pope CA III, Eatough DJ, Gold DR, Pang Y, Nielsen KR, Nath P, Verrier RL, Kanner RE. Acute exposure to environmental tobacco smoke and heart rate variability. Environ Health Perspect 2001; 109:711-716.

Quintana PJE, Samimi BS, Kleinman MT, Liu L-J, Soto K, Warner GY, Bufalino C, Valencia J, Francis D, Hovell MH, Delfino R. Evaluation of a real-time passive personal particle monitor in fixed site residential indoor and ambient measurements. J Exposure Anal Environ Epidemiol 2000; 10: 437-445.

Rodes CE, Lawless PA, Evans GF, Sheldon LS, Williams RW, Vette AF, Creason JP, Walsh D. The relationship between personal exposures for elderly populations and indoor and outdoor concentrations for three retirement center scenarios. J Expo Anal Environ Epidemiol 2001; 11:103-115.

Rojas-Bracho, L, Suh, HH, Koutrakis P. Relationship Among Personal, Indoor, and Outdoor Fine and Coarse Particle Concentrations for Individuals with COPD; J. Expo. Anal. Environ. Epidemiol 2000; 10:294-306.

Sarnat JA, Koutrakis P, Suh HH. Assessing the relationship between personal particulate and gaseous exposures of senior citizens living in Baltimore, MD. J Air Waste Manage Assoc 2000; 50:1184-1198.

Schwartz J, Litonjua A, Suh H, Verrier M, Zanobetti A, Syring M, Nearing B, Verrier P, Stone P, MacCallum G, Speizer FE, Gold DR. Traffic related pollution and heart rate variability in a panel of elderly subjects. Thorax 2005; 60:455-461.

Sorensen M, Daneshvar B, Hansen M, Dragsted LO, Hertel O, Knudsen L, Loft S. Personal $PM_{2.5}$ exposure and markers of oxidative stress in blood. Environ Health Perspect 2003; 111:161-165.

Sullivan J, Sheppard L, Schreuder A, Ishikawa N, Siscovick D, Kaufman J. Relation between short-term fine-particulate matter exposure and onset of myocardial infarction. Epidemiology 2005; 16:41-48.

Timonen KL, Vanninen E, de Hartog J, Ibald-Mulli A, Brunekreef B, Gold DR, Heinrich J, Hoek G, Lanki T, Peters A, Tarkiainen T, Kreyling W, Pekkanen J. Effects of ultrafine and fine particulate and gaseous air pollution on cardiac autonomic control in subjects with coronary artery disease. The ULTRA study J Expo Sci Environ Epidemiol 2006; 16:332-341.

Tsai FC, Apte MG, Daisey JM. An exploratory analysis of the relationship between mortality and the chemical composition of airborne particulate matter. Inhal Toxicol 2000; 12:121-35.

Urch B, Silverman F, Corey P, Brook JR, Lukic KZ, Rajagopalan S, Brook RD. Acute blood pressure responses in health adults during controlled air pollution exposures. Environ Health Perspect 2005; 113:1052-1055.

Wichmann J, Janssen NAH, van der Zee S, Brunekreef B. Traffic-related differences in indoor and personal absorption coefficient measurements in Amsterdam, the Netherlands. Atmos Environ 2005: 39: 7384-7392.

Wilson WE, Brauer M. Estimation of ambient and non-ambient components of particulate matter exposure from a personal monitoring panel study. J Expo Sci Environ Epidemiol 2006; 16:264-274.

Vinzents PS, Moller P, Sorensen M, Knudsen LE, Hertel O, Jensen FP, Schibye B, Loft S. Personal exposure to ultrafine particles and oxidative DNA damage. Environ Health Perspect 2005; 113:1485-1490.

Williams R, Suggs J, Creason J, Rodes C, Lawless P, Kwok R, Zweidinger R, Sheldon L. The 1998 Baltimore Particulate Matter Epidemiology-Exposure Study: part 2. Personal exposure assessment associated with an elderly study population. J Expo Anal Environ Epidemiol 2000; 10:533-543.

Wu C-F, Delfino RJ, Floro JN, Samimi BS, Quintana PJE, Kleinman MT, Liu SL-J. Evaluation and quality control of personal nephelometers in indoor, outdoor and personal environments. J Expo Anal Environ Epidemiol 2005; 15:99-110.