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CORONARY HEART DISEASE MORTALITY AND LONG-TERM EXPOSURE TO AMBIENT PARTICULATE AIR POLLUTANTS IN ELDERLY NONSMOKING CALIFORNIA RESIDENTS

By

Lie Hong Chen

A Dissertation in Partial Fulfillment of the Requirements for the

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P.O. Box 1346
Ann Arbor, MI 48106-1346

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Synnove M.F. Knutsen, MD, MPH, PhD
Professor & Chair, Department of Epidemiology & Biostatistics

_____

W. Lawrence Beeson, DrPH, MSPH
Associate Professor, Department of Epidemiology & Biostatistics

_____

Samuel Soret, PhD, MPH
Associate Professor & Chair, Department of Environmental & Occupational Health

ABSTRACT OF DISSERTATION

Coronary Heart Disease Mortality and Long-Term Exposure to Ambient Particulate Air Pollutants in Elderly Nonsmoking California Residents

By

Lie Hong Chen

Doctor of Public Health in Epidemiology

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Synnove M.F. Knutsen, Chair

The purpose of this study is to assess the effect of long-term concentrations of ambient PM on risks of all causes, cardiopulmonary, coronary heart disease (CHD), total cancer, and any mention of nonmalignant respiratory disease (NMRD) mortality.

The health effects of long-term ambient air pollution have been studied with up to 30 years of follow-up in the AHSMOG cohort, a cohort of 6,338 nonsmoking white California adults. Monthly concentrations of ambient air pollutants [particulate matter <10 μm in aerodynamic diameter (PM_{10}), Ozone (O_3), sulfur dioxide (SO_2), nitrogen dioxide (NO_2) or particulate matter <2.5 μm in aerodynamic diameter ($PM_{2.5}$)] were obtained from monitoring stations or airport visibility data (for $PM_{2.5}$) and interpolated to ZIP code centroids of work and residence locations. All participants were asked to complete a detailed lifestyle questionnaire at baseline (1976). Follow-up information on environmental tobacco smoke and other personal sources of air pollution was available

from four subsequent questionnaires from 1977 to 2000.

In the AHSMOG cohort, each increment of 10 $\mu g/m^3$ in PM_{10} in two-pollutant models showed increased risks of fatal NMRD with the relative risk (RR) of 1.13 [95% confidence interval (CI), 1.04-1.22], 1.05 (95% CI, 0.98-1.13) or 1.06 (95% CI, 0.99-1.14) controlling for O_3, NO_2 or SO_2, respectively. Also the RR of cancer mortality for each increment of 30 days/year of PM_{10} in excess of 100 $\mu g/m^3$ was 1.16 (95% CI: 1.03-1.31).

In the AHSMOG airport subcohort (n=3,239), the RR for fatal CHD with each 10 $\mu g/m^3$ increase in $PM_{2.5}$ was 2.00 (95 % CI: 1.51, 2.64) in the two pollutant model with O_3 in females. Corresponding RR's for a 10 $\mu g/m^3$ increases in $PM_{10-2.5}$ and PM_{10} were 1.62 and 1.45, respectively, in all females. No significant associations were found in males.

A positive association with fatal CHD was found with all three PM fractions in females, but not in males. The risk estimates were more significant after adjustment for gaseous pollutants, especially O_3. The risk estimates were the highest for $PM_{2.5}$. Also, increased risks of NMRD and cancer mortality were found with ambient levels of PM_{10} and gases (O_3, or SO_2).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 3 – FIRST PUBLISHED PAPER

CHAPTER 4 – SECOND PUBLISHABLE PAPER

CHAPTER 5 – OTHER FINDINGS

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CHAPTER 1

INTRODUCTION

A. Background and Significance of the Study

Interest in the cardiovascular effects of particulate air pollution has increased dramatically in the past decade. Since the early reports of increased cardiopulmonary deaths following serious air pollution episodes (Logan, 1953), epidemiologic evidence has shown that increased daily cardiovascular morbidity and mortality were associated with acute exposure to particulate air pollution (Dominici, Peng, Zeger, White, & Samet, 2007; Pope, et al., 2006; Samet, Dominici, Curriero, Coursac, & Zeger, 2000; Zanobetti, Schwartz, & Dockery, 2000). Fine particulate matter with diameter less than 2.5 μm ($PM_{2.5}$) was found to be one of these most important particulate pollutants. Chronic exposure to the ambient particulate matter (PM) (Abbey, et al., 1999; Dockery, et al., 1993; McDonnell, Nishino-Ishikawa, Petersen, Chen, & Abbey, 2000; Pope, et al., 2002; Pope, Burnett, et al., 2004; Pope, et al., 1995), black smoke (Hoek, Brunekreef, Goldbohm, Fischer, & van den Brandt, 2002), and nitrogen oxides was found to increase risks of cardiopulmonary, non-cancer respiratory and respiratory cancer deaths (Hoek, et al., 2002; Nafstad, et al., 2004).

Although increased concentrations of particulate air pollution might increase risk of morbidity and mortality, not all groups of people respond to PM exposure in the same way (Burnett, et al., 2000; Goldberg, et al., 2000; Goldberg, Burnett, Yale, Valois, & Brook, 2006; Kwon, Cho, Nyberg, & Pershagen, 2001; Mann, et al., 2002; Peters, Dockery, Muller, & Mittleman, 2001; Sunyer & Basagana, 2001; Ulirsch, et al., 2007;

Zanobetti & Schwartz, 2001, 2002; Zanobetti, Schwartz, & Gold, 2000). People with chronic obstructive pulmonary disorder (Sunyer & Basagana, 2001), conduction disorder (Mann, et al., 2002; Zanobetti, Schwartz, & Gold, 2000), congestive heart failure (Goldberg, et al., 2003; Kwon, et al., 2001; Mann, et al., 2002), diabetes (Zanobetti & Schwartz, 2001, 2002; Zanobetti, Schwartz, & Gold, 2000), and myocardial infarction (Peters, et al., 2001) were found to be at greater risk of adverse events associated with air pollution, especially with PM. They were more susceptible to the short term effects of air pollution, particularly in individuals with systemic diseases (Goldberg, et al., 2001). The identification of susceptible subgroups at risk would provide information regarding mechanisms and also help them to reduce exposure rates to PM.

This study has built upon previous findings from the AHSMOG study with special focus on particles (PM_{10}, and $PM_{2.5}$) and coronary heart disease (CHD) mortality. However, the AHSMOG data on $PM_{2.5}$ have only been collected in the airport subcohort which used airport traffic controllers' visibility data at 9 selected airports in California. Previous analysis had been addressing the effects of $PM_{2.5}$ on cardiopulmonary mortality only through 1992. The $PM_{2.5}$ data were available on only 57% of the cohort, which gave the study less power for statistical analysis. To solve these problems, our proposed study was based on current AHSMOG data and continued to collect data from the AHSMOG cohort. We focused more on the association between respirable particles (PM_{10}, and $PM_{2.5}$) and CHD mortality. The association between particulate pollution and CHD mortality in sensitive subgroups was also included. We also extend the follow-up time to 22 years and more which helped to produce more information and offered the study more statistical power from the previous follow-up of this cohort. The purpose of this study

was to assess the effects of long-term ambient PM on risks of mortality for all-causes, cardiopulmonary, CHD, total cancer, and any mention of nonmalignant respiratory disease (NMRD). Our results will be useful for public policy makers to set the right policy to protect these high risk populations, and also, for persons to protect themselves appropriately from the harmful effects of air pollutants.

B. Specific Aims

- To study the association between CHD mortality and all-cause mortality and long-term ambient exposure to particulate matter with diameter < 10 μm (PM_{10}) and gaseous pollutants (O_3, NO_2, SO_2) in the AHSMOG cohort.
- To study the association between CHD mortality and all-cause mortality and long-term ambient exposure to particulates (PM_{10}, $PM_{2.5,}$ and $PM_{10-2.5}$) and gaseous air pollutants in the AHSMOG airport subcohort.
- To study the association between CHD mortality and long-term ambient exposure to PM_{10} and gaseous pollutants (O_3, NO_2, SO_2) in sensitive subgroup (elderly, those with cardiovascular disease, pulmonary respiratory disease, diabetes, and past smokes) in the AHSMOG cohort.

C. Research Questions

- What is the association between ambient air pollutant ($PM_{10,}$ O_3, $NO_{2,}$ or SO_2) and CHD mortality as well as all-cause mortality in the AHSMOG cohort?
- What is the association between ambient particulate air pollutant (PM_{10}), adjusting for gases (O_3, NO_2 or $SO_{2,}$) and CHD mortality and all-cause mortality in the AHSMOG cohort?

- What is the association between ambient air pollutant (PM_{10}, $PM_{10-2.5,}$ $PM_{2.5,}$ O_3, $NO_{2,}$ or SO_2) and CHD mortality in the AHSMOG airport subcohort?
- What is the association between ambient particulate air pollutants (PM_{10}, $PM_{10-2.5,}$ or $PM_{2.5}$), adjusting for gases (O_3, NO_2 or SO_2,) and CHD mortality in the AHSMOG airport subcohort?
- What is the association between ambient air pollutant (PM_{10}, O_3, NO_2 or SO_2) and CHD mortality in sensitive subgroup (age, CHD, diabetes, COPD and smoking) in the AHSMOG cohort?
- What is the association between ambient air pollutant (PM_{10}), adjusting for gases (O_3, NO_2 or SO_2,) and CHD mortality in sensitive subgroup (age, CHD, diabetes, COPD and smoking) in the AHSMOG cohort?

CHAPTER 2

REVIEW OF THE LITERATURE

A. Overview

Cardiovascular disease (CVD) is the leading cause of both death and disability in the U.S. In 2006, CVD claimed 831,272 lives in the U.S., nearly as many as all other diseases combined (American Heart Association, 2010). There are many risk factors that can cause CVD. After individual modifiable cardiovascular risk factors such as diet, drugs, exercise, weight management, and smoking including environmental tobacco smoking (ETS) or secondhand smoke exposure, air pollutants have continued to be reported as a major contributing factor to CVD. More evidence has suggested that ambient air pollution can increase CVD morbidity and mortality.

This is not only the case for CVD. Early studies reported that serious air pollution episodes (Logan, 1953; Nemery, Hoet, & Nemmar, 2001; Schrenk, 1950) were associated with a wide range of health end points, including worsening of respiratory lung function and respiratory symptoms which lead to increase hospitalization and mortality. These results were confirmed by studies both within the United States and abroad (Dominici, McDermott, Zeger, & Samet, 2003; Samet, et al., 2000; Zanobetti, Schwartz, & Dockery, 2000). Increased risks of cardiopulmonary disease (CPD), non-cancer respiratory and respiratory cancer deaths were also found to be associated with chronic exposure to ambient particulate matter (PM) (Abbey, et al., 1999; Dockery, et al., 1993; Jerrett, et al., 2005; McDonnell, et al., 2000; Pope, Burnett, et al., 2004; Pope, et al., 1995), black smoke (BS) (Filleul, et al., 2005; Hoek, et al., 2002), and nitrogen oxides (NO_x) (Hoek, et

al., 2002; Nafstad, et al., 2004). Among these ambient air pollutants, $PM_{2.5}$ has been found to be positively associated with mortality for all-cause (McDonnell, et al., 2000; Pope, et al., 2002), CPD (Pope, et al., 2002), ischemic heart disease (IHD) (Pope, Burnett, et al., 2004), and respiratory or lung cancer in the US and Europe (McDonnell, et al., 2000; Miller, et al., 2007; Pope, et al., 2002; Pope, Burnett, et al., 2004).

The risk of mortality and morbidity increases with increased concentrations of ambient particulate air pollution. However, not all groups of people respond to PM exposure in the same way (Brook, Jerrett, Brook, Bard, & Finkelstein, 2008; Goldberg, et al., 2006; Kwon, et al., 2001; Mann, et al., 2002; Peters, et al., 2001; Peters, et al., 2005; Sunyer, et al., 2003; Sunyer, et al., 2000; Ulrich, et al., 2002). Several studies have reported that people with chronic obstructive pulmonary disorder (COPD) (Sunyer, et al., 2000), conduction disorder (Kwon, et al., 2001; Mann, et al., 2002; Zanobetti, Schwartz, & Gold, 2000), congestive heart failure (CHF) (Goldberg, et al., 2003; Kwon, et al., 2001; Mann, et al., 2002), diabetes (Brook, et al., 2008; Goldberg, et al., 2006; Zanobetti & Schwartz, 2001, 2002; Zanobetti, Schwartz, & Gold, 2000), and myocardial infarction (Peters, et al., 2001; Peters, et al., 2005) were at greater risk of adverse events associated with air pollution. Individuals with systemic diseases such as cardiac disease and diabetes are susceptible to the short term effects of air pollution (Goldberg, et al., 2006). The effect of air pollutants seems to be stronger in certain subgroups of the population. Unfortunately, female gender and elderly have frequently been identified as populations with higher risk (Felber Dietrich, Ackermann-Liebrich, et al., 2008; Felber Dietrich, Gemperli, et al., 2008; Fischer, Hoek, Brunekreef, Verhoeff, & van Wijnen, 2003).

Recent epidemiological studies have demonstrated a consistent increased risk for

cardiovascular events in relation to both short- and long-term exposure to ambient particulate matter. Possible mechanistic pathways include enhanced coagulation/ thrombosis (Peters, Dockery, Heinrich, & Wichmann, 1997), a propensity for arrhythmias (Peters, et al., 2000), acute arterial vasoconstriction(Kunzli, et al., 2005), systemic inflammatory responses (Pope, 2001), and chronic progression of atherosclerosis. However, the exact mechanisms are still unclear. The purpose of this literature review is to assess and evaluate current scientific evidence on the association between the short term and long term exposure to ambient air pollutants and cardiovascular mortality.

B. Characteristic of Particulate Matter

Air pollution is the contamination of air by anthropogenic and biogenic discharge of harmful substances. There are seven National Ambient Air Quality Standards (NAAQS) criteria air pollutants (e.g. PM_{10}, $PM_{2.5}$, O_3, NO_2, SO_2, CO, Pb) which have been regulated by EPA since the Clean Air Act passed in 1970 (Gerard, 2005). These pollutants can harm both human health and the environment. Of these pollutants, particle pollution and ground-level ozone are the most widespread health threats. Particulate air pollution, also known as PM, is a mixture of solids and liquid droplets. It includes acids, organic and inorganic chemicals, metals, and soil or dust particles. It is a mixture of contaminants from a wide range of sources and could be characterized into primary and secondary particles. The primary particles are emitted directly into the air (e.g. from exhaust stacks and tailpipes and other ground-level activities as well as from biogenic sources such as vegetation, undomesticated animals and microbes albeit the later tends to be gaseous in nature). The secondary particles are formed in the atmosphere from

condensation of vaporized materials or from the byproducts of the oxidation of gases. The toxicity of the particles greatly depends on their aerodynamic properties.

Total suspended particles (TSPs) in the ambient air include large particles (>10 μm in aerodynamic diameter), inhalable particles, coarse particles, fine particles, and ultrafine particles. Size-selective sampling of PM refers to collecting particles below, above, or within a specified aerodynamic size range. It is usually selected to have special relevance to inhalation and deposition, sources, or toxicity (Chow, 1995). Inhalable particles are defined as PM less than 10 μm aerodynamic diameter (PM_{10}) and are easily deposited in the respiratory system. Coarse particles ($PM_{10-2.5}$) are often indicated by mass concentrations of particles greater than 2.5 μm and less than 10 μm. Fine particles are defined as aerodynamic diameter less than 2.5 μm ($PM_{2.5}$). Ultrafine particles ($PM_{0.1)}$ are typically defined as particles with an aerodynamic diameter less than 0.1 μm. There has been increased interest lately in ultrafine particles because they serve as a primary source of fine particle exposure. Ultrafine particles are more likely than larger particles to translocate from the lungs to the systemic system and thus to other parts of the body (Oberdorster, Oberdorster, & Oberdorster, 2005). The nanoparticles within $PM_{0.1}$ are very short-lived and are largely found within only a few hundred meters of their sources (e.g. near roadways). Nonetheless, certain aspects of $PM_{0.1}$ may implicate them as a cause of human diseases as they are an important component of $PM_{2.5}$ (Nogueira, 2009).

The health effects of particulate matter are significant for short-term and long-term exposures, particularly those containing several metals and silicate-derived constituents that can be cytotoxic to lung cells. Particle size is very important in terms of air pollution and health (Osornio-Vargas, et al., 2003). In 1979, the U.S. National

Research Council said that measuring particles by weight, without regard to particle size, had "little utility for judging effects" (National Research Council National Academy of Sciences, 1979). Fine particulates predominate in the particle mixes around most U.S. cities. PM_{10} can get into the large upper airways just below the throat where they are caught and removed (by coughing and spitting or by swallowing). $PM_{2.5}$ can penetrate the deepest (alveolar) portions of the lungs. If these particles are soluble in water, they can pass directly into the alveolar capillaries and become systemic via the vascular system or, if they are not, they are retained in the deep lungs for long periods. About 60% of PM_{10} particles (by weight) have a diameter of 2.5μm or less, which may constitute major harm to human health (Dockery & Pope, 1994). The study of fine particles and their effects on human health has been under way in earnest since the mid 1970s.

C. Short-Term Exposure and Health Effects

1. Early Episodes

Air pollution episode studies are the earliest and most methodologically simple epidemiological studies. The mortality and morbidity are compared before, during and after pollution episodes. The air pollution disasters in the Meuse valley in Belgium in 1930 (Nemery, et al., 2001), Donora in Pennsylvania in 1948 (Schrenk, 1950), and London in England in 1952 (Logan, 1953) demonstrated that extremely high levels of particulate-based smog could produce large increases in the daily mortality rate (Table 2.1). An excellent example was seen in the Greater London area in 1952, when the daily mortality was substantially increased after unmeasured accumulation of air pollutants in the area increased rapidly (Logan, 1953). It was believed that both respiratory and

cardiovascular diseases leading to medical care or death were associated with exposures to elevated levels of particulate and/or sulfur oxide air pollution before, during, and after the episode (Jelinkova & Branis, 2001; Wichmann, et al., 1989). A recent study showed that the pollution level during the London smog was 5-19 times above current regulatory standards (Bell & Davis, 2001), and such exposure might cause respiratory and sudden cardiac mortality in vulnerable populations (Mage & Donner, 1995). Later studies on daily air pollution and daily mortality have found that such associations can occur at much lower concentrations of air pollution than those in London in the 1950s and in Philadelphia, Santa Clara, St. Louis, Utah valley, Detroit, and eastern Tennessee in the 1970s and 1980s, respectively (Dockery, Schwartz, & Spengler, 1992; Pope, Schwartz, & Ransom, 1992; Schwartz, 1991; Schwartz & Dockery, 1992). These results suggested that lower mortality effects were seen with less extreme pollution (Table 2.2).

2. Hospital Admissions

By the early 1990s, several studies had evaluated acute morbidity effects of particulate pollution by examining the short-term temporal associations between particulate air pollution and hospital admissions, clinical visits, or other measures of restricted activity due to CVD (Burnett, Cakmak, Brook, & Krewski, 1997; Burnett, et al., 1995; Le Tertre, Medina, et al., 2002; Schwartz, 1997, 1999; Schwartz & Morris, 1995; Zanobetti, Schwartz, & Dockery, 2000). These studies did not rely on extreme pollution episodes as earlier studies but evaluated changes in daily event counts associated with daily changes in air pollution at relatively low, more common levels of pollution. Exposure to environmental air pollutants was suggested as a major cause of

Table 2.1 Selected Episode Studies

Studies	Health Endpoint	Summary of Findings
Meuse Valley Fog, Meuse Valley, Belgium, 1930 (Nemery, et al., 2001) b	Respiratory symptoms	Severe respiratory symptoms and deaths (deaths >60).
Killer fog, Donora, PA, 1948 (Schrenk, 1950)	Fatal CRD	Increased mortality and morbidity in hospitals (CRD death=20 and hospitalized=7,000) in 13,000 population within 14 hrs.
London fog, London, England, 1952 (Logan, 1953)	Fatal CVD	80-90% of excess deaths due to respiratory and/or CVD following London's lethal smog in the winter.
New York, 1966 (Glasser & Greenburg, 1971; Glasser, Greenburg, & Field, 1967)	Fatal heart disease	Significant increase fatal total and heart disease (Heart disease death/day=91.7, total death/day=261.3)
Smog Episode, West Germany, 1985 (Wichmann, et al., 1989)	Fatal CVD & hospital admission	Increased mortality and morbidity in hospitals. The effects were more pronounced for CVD than for respiratory diseases
Winter Smog Episodes, Czech Republic, 1982, 85, 87 & 93 (Jelinkova & Branis, 2001)	Fatal CVD	Significant associations of CVD mortality with SPM & SO_2; Significant association between mortality & SPM found in women under 65.

Abbreviation: CHF=Congestive heart failure; CVA=Cerebrovascular accident; CVD=Cardiovascular disease; CVS=Cardiac and/or respiratory; RD=Cardiorespiratory disease; DSR=Dysrhythmia; IHD=Ischemic heart disease.

Table 2.2 Selected Studies Investigating the Relationship between Short-Term Exposure and Hospital Admission

Studies	Endpoint	Exposure	Summary of Findings
Detroit, Michigan (Schwartz & Morris, 1995)	CVD	PM_{10}	Significant positive association between IHD/CHF mortality and PM_{10} (PM_{10}& IHD: RR=1.02, PM_{10} & CHF: RR=1.02 w IQR of 32 $\mu g/m^3$)
Ontario, Canada (Burnett, et al., 1997; Burnett, et al., 1995)	CVD	Sulfate, NO_2, O_3	Significant positive association between CVD hospital admissions and sulfate, NO_2, and O_3
Tucson, AZ (Schwartz, 1997)	CVD	PM_{10}	A 23 $\mu g/m^3$ increase in PM_{10} was associated with increased 2.75% in CVD mortality
10 US cities (Zanobetti, Schwartz, & Dockery, 2000)	CVD, COPD	PM_{10}	A 10 $\mu g/m^3$ increase in PM_{10} was associated with an increase in hospital admission due to CVD and COPD equal to 1.27% and 2.5%, respectively
Netherlands (Hoek, Fischer, Van Den Brandt, Goldbohm, & Brunekreef, 2001)	CVD, CHF,	PM_{10}, BS, CO, NO_2 SO_2, O_3,	PM_{10}, SO_2, CO & NO_2 response for heart failure, 10% up of CVD
New Zealand (McGowan, Hider, Chacko, & Town, 2002)	CRD	PM_{10}	Each IQR increase in PM_{10} was associated with an increase in 1.26% and 3.37% rise in cardiac and respiratory admissions.
8 European cities (Le Tertre, Quenel, et al., 2002)	CVD	PM_{10}	A 10 $\mu g/m^3$ increase in PM_{10} was associated with an increase in 0.5% for CVD hospital admission

Table 2.2 (continued) Selected Studies Investigating the Relationship between Short-Term Exposure and Hospital Admission

Studies	Endpoint	Exposure	Summary of Findings
14 U.S. cities (Janssen, Schwartz, Zanobetti, & Suh, 2002)	CVD	PM_{10}	Air conditioning and proportion of especially traffic-related particles significantly modify the effect of PM_{10} on CVD hospital admission
7 European areas (Sunyer, et al., 2003)	IHD	PM_{10}, SO_2	The increase IHD admissions were significant associated for particles in older. RR of PM_{10} & IHD was 1.3 %,
13 Japanese cities (Omori, Fujimoto, Yoshimura, Nitta, & Ono, 2003)	CVD, Resp	SPM	A positive association between CVD and SPM. RR of CVD and SPM with10 $\mu g/m^3$ increment was 1.01.
204 US urban counties (Dominici, et al., 2006)	CVD, Resp	$PM_{2.5}$	Positive association between CVD and $PM_{2.5}$ was observed. The largest increase of heart failure in 1.28% was associated with in same-day 10 $\mu g/m^3$ increase in $PM_{2.5}$.
6 French cities (Host, et al., 2008)	IHD, Resp	PM_{10}, $PM_{2.5}$, $PM_{2.5-10}$	Positive associations between PM and Resp were observed, Significance association was observed between $PM_{2.5-10}$ and CVD, IHD (RR=6.4%).
119 US urban communities (Peng, et al., 2009)	CVD, Resp	$PM_{2.5}$	An IQR increase in PM2.5(EC) was associated with a 0.80%, 1.01% increasec in risk of same-day CVD and Resp admissions, respectively

Table 2.2 (continued) Selected Studies Investigating the Relationship between Short-Term Exposure and Hospital Admission

Studies	Endpoint	Exposure	Summary of Findings
Roma, Italy (Belleudi, et al., 2010)	CHF, COPD	PM_{10}, $PM_{2.5}$, $PM_{2.5-10}$	A 2.3-2.4% increase in CHF was associated with an immediate and delayed impact of $PM_{2.5}$, 1.6% increase in COPD. The effects were stronger in the elderly and during the winter.

Abbreviation: CHF=Congestive heart failure; CVA=Cerebrovascular accident; CVD=Cardiovascular disease; CVS=Cardiac and respiratory; CRD=Cardiac or respiratory disease; DSR=Dysrhythmia; IHD=Ischemic heart disease; Resp=Respiratory; SPM=Suspended particulate matter.

an increase in hospital admissions for CVD (Ballester, et al., 2006; Burnett, Smith-Doiron, Stieb, Cakmak, & Brook, 1999; Dominici, et al., 2006; Lanki, et al., 2006; Le Tertre, Medina, et al., 2002; Maheswaran, et al., 2005; von Klot, et al., 2005; Wellenius, Schwartz, & Mittleman, 2005; Zanobetti & Schwartz, 2006; Zeka, Zanobetti, & Schwartz, 2005).

Regarding the specific end point of myocardial infarction (MI), however, there were inconsistent findings in some of the single city or community studies. D'Ippoliti et al. (2003) analyzed hospital admissions for first episode of MI in Rome between January 1995 and June 1997 by using a case cross-over analysis. They found a positive association of MI with total suspended PM during the warm period of the year. The association tended to be stronger among people older than 74 years of age and people who had heart conduction disorders. Another case cross-over study in the greater Boston area carried out by Peters et al. (2001) has demonstrated a similar finding but the risk was related to increased concentration of $PM_{2.5.}$ They found that even temporary exposure after just a few hours to high concentrations of $PM_{2.5}$ increased the risk of MI in this high-risk population of MI patients. Significant associations between cardiac disease admission and particulate pollution were also observed in several studies outside the US, such as seven European areas and Ontario, Canada (Burnett, et al., 1997; Burnett, et al., 1995; McGowan, et al., 2002; Sunyer, et al., 2003). In contrast, Sullivan et al. (2003) observed a slight effect of fine PM on onset of MI by using outpatient data with members of a health organization in western Washington State between 1985 and 1994. However, there was no association when the data were stratified for those with and without heart disease. Mann et al. (2002) conducted a Poisson regression analysis of 19,460 hospital

admissions for acute MI among southern California Kaiser Permanente members over an 8-year study period. The discharge diagnose was used to classify each admission. No effect of daily PM_{10} was observed with acute MI. These diverse results might be a result from the different diagnostic criteria, methodology, and possibly the population difference.

Some recent multicity studies have confirmed that an increase of 10 $\mu g/m^3$ in ambient PM_{10} levels result in an increased risk of hospitalization for MI with same day exposure (Ballester, et al., 2006; Lanki, et al., 2006; Maheswaran, et al., 2005; von Klot, et al., 2005; Zanobetti & Schwartz, 2005). PM_{10} is associated with overall hospital admissions for cardiovascular disease in these studies. Most of these studies suggested that an elevated PM_{10} on the day of admission, or 1 or 2 days earlier before admission was typically associated with increased number of hospital admission and clinic visits for cardiac diseases (Burnett, et al., 1997; Burnett, et al., 1995; Janssen, et al., 2002; Le Tertre, Medina, et al., 2002; Zanobetti, Schwartz, & Dockery, 2000). Some studies found that the adjustment for co-pollutants tended to substantially reduce the effect of particles. Opinions range from the perspective that the PM_{10} effect may be entirely the result of co-pollutants and that PM_{10} is simply a surrogate for these pollutants(Moolgavkar, 2000) to the assertion at the other extreme that the PM_{10} effect is independent of co-pollutants (Schwartz, 1999).

There are a few studies on the short term effect of $PM_{2.5}$ (Dominici, et al., 2006; Peng, et al., 2009). Burnett and co-workers suggested that $PM_{2.5}$ might have a greater effect than PM_{10} on combined CVD admissions (Burnett, et al., 1999). The ratio of the

$PM_{2.5}$ effect to the PM_{10} effect was ranged from 0.7 to 1.7. They also found that the effect for the coarse fraction of PM ($PM_{10-2.5}$) was greater than that for PM_{10} alone.

Small differences in geographic locations and pollution characteristics within a single city have been shown to be stronger determinants of CV risk than those found for inter-city differences. The national study done by Dominici et al. (2006) is an example of a multicity study to represent regional difference. It included 204 US urban counties (minimum population of 200,000 in each county) with 11.5 million Medicare enrollees (aged 65 years and older) living an average of 5.9 miles from a $PM_{2.5}$ monitor. This study found that short-term increases in hospital admission rates were associated with $PM_{2.5}$ for all of the health outcomes except injuries. The strongest association was for heart failure, which had a 1.28% (95% confidence interval (CI), 0.78%-1.78%) increased risk per 10 $\mu g/m^3$ increase in same-day $PM_{2.5}$. Other multicity studies indicated that CVD admissions are most strongly related to PM in the Northeast, Midwest and Southern U.S. regions, whereas exposure in Northwestern U.S. regions may not be associated with any excess risk (Peng, et al., 2009; Zanobetti, Schwartz, & Dockery, 2000).

3. CVD Mortality

In 1996, Thurston reviewed time-series studies on PM_{10} mortality to provide a common basis for an evaluation of the PM_{10} and CVD mortality association (Thurston, 1996). The studies confirmed that acute pollution-mortality association could occur at routine ambient levels. Their effects extend below the present United States air quality standards, especially for susceptible subpopulations. Furthermore, results of recent PM_{10} studies are consistent with the hypothesis noted in past studies that PM is a causal agent in the mortality impacts of air pollution (Dominici, et al., 2006; Zanobetti &

Schwartz, 2006). Although the relative risk (RR) of mortality increased monotonically with particulate concentrations in most studies, RR for PM_{10} mortality was found to vary across studies which may be secondary to differences in PM_{10} composition and the PM_{10} averaging period employed in the analysis. This variation may also be due to differences in whether other pollutants were considered simultaneously in the mortality- PM_{10} model (Janssen, et al., 2002) (Table 2.3).

Until the late 1990s, most studies were single-city daily time series mortality studies. Because there was no clearly defined or uniform criteria for selecting study cities, a fundamental concern regarding PM-mortality estimation from published single city studies is the potential for city selection and publication bias. The multicity studies are designed to address concerns about city selection bias, publication bias, and influence of co-pollutants. The National Morbidity, Mortality, and Air Pollution Study (NMMAPS) was one of the largest multicity studies using daily time series analyses (Stylianou & Nicolich, 2009). The magnitude of this effect was highly variable and depended on the specific disease category being considered, the time lag used in the analysis, and the role of co-pollutants (Analitis, et al., 2006; Stylianou & Nicolich, 2009; Wong, Vichit-Vadakan, Kan, & Qian, 2008; Zanobetti & Schwartz, 2009). Based on the evidence from these studies, ambient PM levels are consistently associated with the increased risk of death from all causes, cardiovascular and respiratory illnesses. With respect to the choice of time lags used in the analysis, selection of the time lag with the maximum effect could result in an overestimation of the true effect size (Table 2.3).

Table 2.3 Selected Studies Investigating the Relationship between Short-Term Exposure and Mortality

Studies	Endpoint	Exposure	Summary of Findings
St. Louis & Eastern Tennessee (Dockery, et al., 1992)	Total	PM_{10}, $PM_{2.5}$	16-17% increase in total mortality was associated with PM_{10}. Weaker Positive associations were found with $PM_{2.5}$
Provo/Orem, UT (Pope, et al., 1992)	CVD	PM_{10}	A 16% increase in CVD deaths was associated with 5-day moving avg. of PM_{10}
Detroit Philadelphia, PA (Schwartz, 1991; Schwartz & Dockery, 1992)	Total CVD	TSP	A 10% increase in total/CVD mortality was associated with TSP.
Philadelphia, PA (Moolgavkar, Luebeck, Hall, & Anderson, 1995)	Total	TSP, O_3, SO_2, NO_2,	Mean current and previous days' levels of TSP, SO_2, and O_3 had statistically significant effects on total mortality; with increases in mortality of 1% for TSP and SO_2, and of 2% for O_3.
Greater London (Anderson, Ponce de Leon, Bland, Bower, & Strachan, 1996)	CVD	O_3, SO_2, NO_2,BS	Significant associated in CVD mortality and daily O_3 was observed.
Philadelphia, PA (Kelsall, Samet, Zeger, & Xu, 1997)	Total	TSP, SO_2, O_3	Statistically significant effects on total mortality and daily TSP, SO_2, O_3 equal to increases in mortality of 1% for TSP and SO_2, and of 2% for O_3.

Table 2.3 (Continued) Selected Studies Investigating the Relationship between Short-Term Exposure and Mortality

Studies	Endpoint	Exposure	Summary of Findings
Helsinki, Finland (Ponka, Savela, & Virtanen, 1998)	CVD	PM_{10}	A 4.1 % increased in CVD mortality was associated with a 10 $\mu g/m^3$ increase $PM_{10.}$
10 large European cities (Zmirou, et al., 1998)	CVD, Resp	SO_2, NO_2, BS	Significant positive associations between CVD/Resp and SO_2, NO_2, BS were observed. The greatest increase was 1.06 (1.02-1.10) in CVD with 8 hr O_3, in western but not central European cities.
Bangkok, Thailand (B. Ostro, Chestnut, Vichit-Vadakan, & Laixuthai, 1999)	CVD	PM_{10}	1-2% increased CVD mortality was associated with a 10 $\mu g/m_3$ increase $PM_{10.}$
Coachella Valley, CA (B. D. Ostro, Broadwin, & Lipsett, 2000)	Total, CVD	PM_{10}, $PM_{10-2.5}$, $Pm_{2.5}$,	Significant effects of $PM_{2.5}$ and total mortality were observed, with 2% increase in $PM_{10}/PM_{10-2.5}$ and CVD mortality.
Mainly 20 largest US cities (Samet, et al., 2000)	CVD	PM_{10}, O_3, SO_2, NO_2	A 10-$\mu g/m^3$ increase PM_{10} was associated with 0.68% (95 % CI: 0.20, 1.16) increased in CVD and Resp, and 0.51% (95% CI: 0.07, 0.93) increased in total deaths.
90 large US cities, NMMAPS (Dominici, et al., 2003)	Total, CPD	PM_{10}	A 10 $\mu g/m^3$ increase PM_{10} was associated with a increase 0.21% for total and 0.31% for CPD.
90 large US cities, NMMAPS (Dominici, McDermott, Daniels, Zeger, & Samet, 2005)	Total, CVD, Resp	PM_{10}	Positive association between Total, CVD, Resp and PM_{10} equal to 0.41%, 0.38, and 0.50.

Table 2.3 (continued) Selected Studies Investigating the Relationship between Short-Term Exposure and Mortality

Studies	Endpoint	Exposure	Summary of Findings
22 European cities, APHENA (Samoli, et al., 2005)	Total, CVD, Resp	PM_{10}, BS	A 10 $\mu g/m^3$ increase PM_{10} was associated with 0.2-0.6% increase in total, CVD, and Resp cross all ages of cities.
Laden et al., 2006 (Laden, Schwartz, Speizer, & Dockery, 2006)	All cause, IHD COPD	$PM_{2.5}$	$PM_{2.5}$ from mobile sources accounted for a 3.4% (1.7-5.2%) increase in daily mortality.
29 European cities, APHEA2 (Analitis, et al., 2006)	CVD, Resp	PM_{10}, BS	An increase of 0.58-0.84% in CVD/ Resp was associated with PM_{10} /BS.
48 US cities (Medina-Ramon & Schwartz, 2008)	Total	O_3	A 10 ppb increase of O_3 was associated with 0.53-1.10% increase in total mortality, and, Greatest increase was with 1.10% (0.44% to 1.77%) in aged 65 years.
5 Asia cities - PAPA (Wong, et al., 2008)	Total, CVD, Resp	PM_{10}, O_3, SO_2, NO_2	Significant and stronger effects of CVD and PM_{10}, O_3, NO_2 were observed, compare to all cause. Variations between cities were observed.
9 US cities-NMMAPS (Stylianou & Nicolich, 2009)	Total, CVD, Resp	PM_{10}, O_3, SO_2, NO_2	Positive association between total /Resp mortality and PM_{10}, O_3 was observed in different cities.
112 US cities (Zanobetti & Schwartz, 2009)	Total, CVD, MI, stroke, Resp	PM_{10}, $PM_{2.5}$, $PM_{10\text{-}2.5}$	Increase in 0.98%, 0.85%, 1.18%, 1.78% and 1.68% in total, CVD, MI, stroke, and respiratory with $PM_{2.5}$ was observed. Risks in $PM_{2,5}$ was higher than in PM_{10}

Abbreviation: BS=Black smoke; CHF=Congestive heart failure; CVA=Cerebrovascular accident; CVD=Cardiovascular disease; CVS=Cardiac and respiratory; CRD=Cardiac or respiratory disease; DSR=Dysrhythmia; IHD=Ischemic heart disease; Resp=Respiratory; SPM=Suspended particulate matter

The cities involved in the following analyses varied from 20 U.S. cities (Daniels, Dominici, Samet, & Zeger, 2000; Samet, et al., 2000) to 100 cities (Peng, Dominici, Pastor-Barriuso, Zeger, & Samet, 2005). The evidence from these studies was very consistent and showed that the ambient levels of fine particulate matter were associated with the risk of death from all causes and cardiovascular disease although the PM-mortality effect estimates were somewhat sensitive to various modeling and city selection choices. Excess risk estimates are presented in Table 2.3. Because the NMMAPS analysis included many cities with substantially different levels of co-pollutants, the influence of co-pollutants could be directly evaluated. The PM mortality effect was not attributable to any of the co-pollutants studied (NO_2, CO, SO_2, or O_3). A parallel research effort, the Air Pollution and Health - A European Approach (APHEA) project, examined the short-term PM-mortality effects in multiple European cities. Initially, this research effort analyzed daily mortality data from 15 European cities (five from Central Eastern Europe) using a common protocol (Katsouyanni, et al., 1996). Daily mortality was found to be significantly associated with ambient PM and sulfur oxide concentrations, although the effect estimates were sensitive to approaches in controlling for long-term time trends and seasonality (Samoli, et al., 2005). A continuation and extension of the APHEA project, often referred to the APHEA-2, included analyses of daily mortality and pollution data from 29 European cities (Katsouyanni, et al., 2001). APHEA-2 also found that ambient PM air pollution was significantly associated with daily mortality counts. Mortality associations with PM were also observed for nine French cities (Le Tertre, Quenel, et al., 2002) and three Australian cities (Simpson, et al., 2005). Asian multicity studies have reported daily mortality associations with measures of ambient PM. A study

of seven major Korean cities (Lee, et al., 2000) was one of these studies. It suggested that SO_2 may have functioned better as a surrogate for $PM_{2.5}$ in Korea's ambient air than TSP. Mortality associations were observed with TSP, as well as with SO_2.

Time series studies constitute the majority of short-term exposure studies after the 1990's. The primary statistical approach was formal time series modeling of count data using Poisson regression, allowing a comparison of effect to be estimated on a common scale (Wong, et al., 2008; Zanobetti & Schwartz, 2009). Time series studies have observed effects in various locations and have the advantage over many other designs in that they limit relevant confounders to those that have a temporal correlation with air pollution. It is conceivable that many factors could be associated with exposure to particulate air pollution by virtue of the patients' relationship to weekly schedules, holidays, and other events related to the calendar. The daily time-series studies reported positive associations between ambient particles and cardiovascular mortality (Dominici, et al., 2003; Zanobetti & Schwartz, 2009). The factors associated with acute exacerbation of cardiovascular disease generally involve those that place acute stress on the heart or increase the coagulability of the blood. They can include short-term variations in diet, compliance with medications, exertion, physical stress, infections, and acute psychological stress. Despite substantial variations in all of the potential confounding factors, the quantitative relationship between particles and daily mortality were essentially the same.

Over time, increasingly rigorous modeling techniques have been used in attempts to better estimate pollution-mortality associations while controlling for other time-dependent covariables that serve as potential confounders. By the mid-to-late 1990s,

generalized additive models (GAMs) using nonparametric smoothing were being applied in these time series studies. GAMs allowed for relatively flexible fitting of seasonality and long-term time trends, as well as nonlinear associations with weather variables, such as temperature and relative humidity (RH). Subsequent re-analyses were conducted on many of the potentially affected studies using more rigorous convergence criteria or using alternative parametric smoothing approaches (Dominici, McDermott, Zeger, & Samet, 2002). APHEA-2 was one of the studies that were re-analyzed using GAM with strict convergent criteria or parametric smoothing approaches. However, this re-analyses did not substantially alter the estimated PM-mortality effects and subsequent analysis of APHEA-2 data found PM-mortality effects for both cardiovascular and respiratory mortality (Analitis, et al., 2006). Also, Burnett et al. (2000) analyzed daily mortality counts and various measures of air pollution in eight of Canada's largest cities using GAM modeling and reported statistically significant PM-mortality associations. A reanalysis of these data was conducted using strict GAM convergence criteria. Although it was somewhat diminished, statistically significant $PM_{2.5}$ mortality associations remained.

The case-crossover design is another methodological innovation (Maclure, 1991). Rather than using time series analysis, the case-crossover design is an adaptation of the common retrospective case-control design. Basically, exposures at the time of death (case period) are matched with one or more periods when the death did not occur (control periods), and potential excess risks are estimated using conditional logistic regression. Deceased individuals essentially serve as their own controls. The case-crossover study design has been applied to studying mortality effects of daily changes in particulate air

pollution (Pope, 1999). By carefully and strategically choosing control periods, this approach restructures the analysis such that day of week, seasonality, and long-term time trends are controlled for by design rather than by statistical modeling. Because this approach focuses on individual deaths rather than death counts in a population, it facilitates evaluation of individual-level effect modification or susceptibility. The case-crossover design has some drawbacks. The results can be sensitive to the selection of control periods, especially when clear time trends exist. Also, relative to the time series approach, the case-crossover approach has lower statistical power largely because of the loss of information from control periods not included in the analysis (Janes, Sheppard, & Lumley, 2005) (Table 2.3).

D. Long-Term Exposure and Health Effects

Prospective cohort studies are useful complements to time-series studies. This study design uses individual health records with survival lifetimes or hazard rates adjusted for individual risk factors. It typically evaluates human health impacts of long-term PM exposures indexed by community-level measurement. Cohort studies are capable of capturing the entirety of the temporal–risk relationship during the years of follow-up. On the other hand, it remains entirely possible that a portion of the CV risk conveyed by long-term PM exposure is also explained by chronic adverse health effects superimposed upon the acute health effects.

Since the 1970's, three main prospective studies have been conducted in the United States to assess long-term health effects of ambient air pollution in adults [Adventist Health Study on the Health Effects of Smog (AHSMOG) (Abbey, et al., 1999), the American Cancer Society (ACS) study (Pope, et al., 1995), and the Six Cities Study

(Dockery, et al., 1993)]. Associations with PM, especially fine particulates ($PM_{2.5}$) have been found for all-cause mortality, CPD mortality, and respiratory/lung cancer mortality in the ACS, Six Cities, and AHSMOG studies. The ACS study showed that the mortality is attributable to ischemic heart disease (IHD), dysrhythmias, heart failure, and cardiac arrest (Pope, et al., 2002; Pope, Burnett, et al., 2004). The AHSMOG study has also shown positive associations, although not always significant, between PM_{10} and all natural cause mortality and CPD mortality in males, but not in females (Abbey, et al., 1999). For fatal lung cancer and any mention of nonmalignant respiratory disease, a positive association was found with PM_{10} in both genders (Abbey, et al., 1999). Prominent early studies of long-term exposure to air pollution also found an increased risk of mortality associated with long-term exposure to fine particulates. More recently these key studies have shown an association between adverse health outcomes and chronic particulate exposure, even as particulate levels have decreased over time (Pope, et al., 2009) (Table 2.4).

The Harvard Six Cities study by Dockery et al. (1993) evaluated the effects of long-term pollution exposure over 14-16 years in a prospective follow-up of 8,111 adults living in six US cities. Exposure was defined by city specific average air pollution during the follow-up period, ignoring the year-to-year fluctuations. The ACS study by Pope et al. (1995) has linked individual risk factor data from the American Cancer Society Cancer Prevention Study II (CPS-II) with national ambient air pollution data. The study included over 500,000 adults who lived in up to151 different US metropolitan areas and who were followed prospectively for 8 years. Both studies controlled for individual differences in age, sex, cigarette smoking, and other risk factors. Both reported a positive association

Table 2.4 Selected Studies Investigating the Relationship between Long-Term Exposure and Health Effects

Studies	Endpoint	Exposure	Subjects	Summary of Findings
Harvard Six Cities (Dockery, et al., 1993; Krewski, et al., 2003)	Mortality: All cause, CPD Lung cancer	TSP, SO_2, O_3; $PM_{2.5}$, 1979-1985	8111 adults at six US cities, 14-16 yrs follow-up. Age range (25-74) yrs	Positive association with CPD & lung cancer, not other causes combined together was observed. The association was most strong with fine particles.
Harvard Six Cities, extended analysis (Laden, et al., 2006)	Mortality: All cause, CVD, and lung cancer	$PM_{2.5}$	8,096 Whites, 1,364 deaths (1974-89) & 1,368 deaths (1990-98)	Total, CVD, and lung cancer mortality were positively associated with $PM_{2.5}$ concentrations. Improved overall mortality was associated with decreased mean $PM_{2.5}$ between periods.
ACS original (Krewski, et al., 2005; Pope, et al., 1995)	Mortality: All cause, CPD Lung cancer	$PM_{2.5}$, 1979-83 $PM_{2.5}$ mean (SD)=18.2 (5.1) $\mu g/m^3$, range (9.0-33.5) $\mu g/m^3$	552.138 (295.223 $PM_{2.5}$ cohort), 50 US metropolitan areas, Mean age 56.6 yrs	Positive association between $PM_{2.5}$ with CPD and lung cancer was observed, both females and males and among smokers and nonsmokers.
ACS extended (Pope, et al., 2002)	Mortality: All cause, CPD Lung cancer	$PM_{2.5}$, 1979-83, 1999-2000, & avg. of above periods	552.138 (295.223 $PM_{2.5}$ cohort), 50 US metropolitan areas, Mean age 56.6 yrs	Positive association between $PM_{2.5}$ and CPD, all cause, lung cancer mortality was observed.

Table 2.4 (continued) Selected Studies Investigating the Relationship between Long-Term Exposure and Health Effects

Studies	Endpoint	Exposure	Subjects	Summary of Findings
ACS extended analysis (Pope, Burnett, et al., 2004)	Mortality: CVD plus diabetes IHD	$PM_{2.5}$, 1979-83, 1999-2000, & avg. of above periods	552.138 (295.223 $PM_{2.5}$ cohort), 50 US metropolitan areas, mean age 56.6 yrs	An increase in $PM_{2.5}$ was associated with 8%-18% increases in CVD mortality.
AHSMOG (Abbey, et al., 1999)	Mortality: ANC, CPD	PM_{10}	6,338 SDAs, AHSMOG cohort	No significant association with CPD mortality and PM_{10} for either sex was observed.
AHSMOG, males (McDonnell, et al., 2000)	ANC, CRC, and LC mortality (1977-1992)	PM_{10}, $PM_{2.5}$, $PM_{2.5-10}$	3,769 SDAs, airport subgroup; 6,338 SDAs, AHSMOG cohort	No significant positive association of PM_{10} with mortality, $PM_{2.5}$ were best explained the relationship, but not $PM_{2.5-10}$ in males.
WU EPRI Veterans cohort (Lipfert, Morris, & Wyzga, 2000)	All cause mortality	PM (TSP, PM_{10}), sulfate, ozone, NO_2, CO, $PM_{2.5}$	90.070 US male veterans; mean age 51.2 yrs.	No increased mortality with increasing levels of PM. TSP show significant responses, PM_{10} show largest positive responses.
ACS Intrametro, Los Angeles (Jerrett, et al., 2005)	All cause, IHD, CPD, Lung, digest cancer	$PM_{2.5}$	Deaths/subjects= 5856/22,905, 1982-2000	The RRs for $PM_{2.5}$ and mortality resulting from IHD and lung cancer deaths were elevated in the range of 1.24-1.6.

Table 2.4 (continued) Selected Studies Investigating the Relationship between Long-Term Exposure and Health Effects

Studies	Endpoint	Exposure	Subjects	Summary of Findings
French PAARC survey (Filleul, et al., 2005)	All causes, lung cancer	TSP, BS, NO_2, NO, 1974-1976	2,533 deaths, 11,753 alive, and 2,619 unknown, 1974-2000, age range 25-59	Consistent patterns for CPD and lung cancer causes were observed.
CA CPS I, 25 CA counties (Enstrom, 2005)	Total mortality,	$PM_{2.5}$	49,975 subjects, 39,846 deaths, 1973-2000, baseline mean age 65 yrs.	No relationship of $PM_{2.5}$ & total mortality was observed, but not rule out a small effect during 1973-1982.
WHI Observational Study (Miller et al. 2007)	Any CVD, CHD death and event	$PM_{2.5}$, 6 yr follow-up	65,893 Postmenopausal women, 36 US metropolitan area, Age 50-79 yrs	Significant association between $PM_{2.5}$ and CVD incidence and death was observed. Exposure differences within cities were associated with the risk of CVD.
NHS, NE (Puett et al. 2008)	Mortality: All cause, CHD, nonfatal MI	PM_{10} (1992-2002)	66,250 US RN, 11 states, 30-55 yr	Increases in PM_{10} were associated with increases in all-cause and CHD mortality.
ACS CPS II, 50 states (Jerrett et al. 2009)	Any cause, CVD CPD, IHD, Resp	O_3 (1977-2000) $PM_{2.5}$ (1999-2000)	Death/subject= 118,777/448,850, 18 yrs follow up	In single-pollutant model, increase $PM_{2.5}$ or O_3 were significant associated with increased in risk of CPD death. In two pollutant models, $PM_{2.5}$ was associated with CVD death.

Table 2.4 (continued) Selected Studies Investigating the Relationship between Long-Term Exposure and Health Effects

Studies	Endpoint	Exposure	Subjects	Summary of Findings
Brisbane, Australia (Wang, Hu, & Tong, 2009)	CRD mortality	O_3, NO_2 or SO_2	824,489 to 958,504, 162 SLAs	Significant association was observed between CRD mortality and SO_2 at the SLA level, not with NO_2 or O_3.
ACS CPS II, (Pope, et al., 2009)	CVD mortality	$PM_{2.5}$	Death/subject= 118,777/448,850, 18 yrs follow up	The exposure-response relationship between CVD mortality and $PM_{2.5}$ was relatively steep at low levels of exposure and flattens out at higher exposures

Abbreviation: ANC=all natural cause CPD=Cardiopulmonary disease; CRC=Underlying or contributing nonmalignant respiratory disease; CRD=Cardiac or respiratory disease; CVD=Cardiovascular disease; IHD=Ischemic heart disease; LC=Lung cancer; Resp=Respiratory; SLA=Statistical local area

between CPD or cardiovascular deaths and long-term exposure to ambient PM. The association was strongest for fine particles, with relative risks (RRs) varying between 1.06 for CPD deaths (Pope, et al., 2002) and 1.12 for CVD deaths (Pope, Burnett, et al., 2004) for each increment of 10 $\mu g/m^3$ of fine particles after adjusting for age, sex, diet indices, and other demographic covariates. When comparing most-polluted areas with least-polluted areas, the RR for CPD death was 1.31 for a difference of 24.5 $\mu g/ m^3$ in the ACS study (Pope, et al., 1995) and 1.37 for a difference of 18.6 $\mu g/ m^3$ in the Six Cities Study (Dockery, et al., 1993).

Recently, Pope et al. reported that long-term ambient PM levels were most strongly associated with mortality attributable to ischemic heart disease, dysrhythmias, heart failure, and cardiac arrest in the CPS-II cohort study (Pope, 2009; Pope, Burnett, et al., 2004). For these cardiovascular causes of death, a 10 $\mu g/m^3$ elevation in $PM_{2.5}$ was associated with 8-18% increases in mortality risk which was comparable to or larger than risks being observed for smokers relative to nonsmokers. Predominant PM mortality associations were with ischemic heart disease, but statistically significant associations were also observed with the combined category of dysrhythmias, heart failure, and cardiac attest. The RRs for each 10 $\mu g/m^3$ increment in of $PM_{2.5}$ was 1.18 (95% CI 1.14-1.23) for IHD (Pope, Burnett, et al., 2004). The extended analysis of the Six Cities study found that lower $PM_{2.5}$ concentrations were also associated with reduced mortality (Laden, et al., 2006). Recent extended analysis of the ACS cancer prevention study (CPS) II reported similar findings (Pope, et al., 2009). It reported that the exposure-response relationship between cardiovascular disease mortality and $PM_{2.5}$ was relatively steep at low levels of exposure and flattened out at higher exposure (Pope, et al., 2009).

In 1977, the Adventist Health Study (AHS) (Beeson, Mills, Phillips, Andress, & Fraser, 1989) launched a sub-cohort study (AHSMOG study) which followed and studied the health effects of long-term ambient air pollution on mortality in 6,338 nonsmoking, white California Seventh-day Adventists during the period from 1977-1998 (Abbey, Moore, Petersen, & Beeson, 1991). A comprehensive lifestyle and diet questionnaire was completed and the cohort was followed with update of residence and workplace location histories during the follow-up period. The monthly averages of ambient air pollutants throughout the study period were assessed according to residence and workplace locations. Exposures to environmental tobacco smoke, dusts and fumes in the workplaces, potential indoor factors such as type of air condition and heating and time spent outdoors were assessed through self-administered questionnaires in 1977, 1987 and again in 1992 and 2000.

During 16 years follow-up from 1977-1992, the AHSMOG study found weak and non-significant positive associations between cardiopulmonary mortality and ambient PM and gaseous pollutants in males (Abbey, et al., 1999) and no associations in females. Likewise, for PM_{10} and CPD mortality, males showed stronger associations than females (Abbey, et al., 1999). Later, the AHSMOG study reported that long-term ambient PM was most strongly associated with mortality attributable to coronary heart disease (CHD) in females who live near airports in California (Chen, et al., 2005). The RR of CHD mortality for each 10 $\mu g/m^3$ increment in $PM_{2.5}$ was 2.00 (95% CI, 1.51–2.64) in the two-pollutant model with O_3.

Recently, other cohort studies (Women's Health Initiative (WHI) (Miller, et al., 2007), Washington University EPRI Veterans Cohort (Lipfert, Perry, et al., 2000),

Nurse's Health Study (NHS) (Puett, et al., 2008)) have reported similar findings of a significant association of long-term ambient PM and all causes and CVD mortality and cardiac event in females, but not males. The WHI observational study (Miller, et al., 2007) enrolled 65,893 postmenopausal women without previous cardiovascular disease, aged 50-79 years old, in 36 U.S. metropolitan areas from 1994 to 1998. With a median follow-up of 6 years, a total of 1816 women had one or more fatal or nonfatal cardiovascular events. Ambient levels of air pollution for each woman were assessed using the monitor located nearest to each woman's residence. The study showed that long-term exposure to fine particulate air pollution was associated with CVD incidence (HR=1.24) and CVD death (HR=1.76) among postmenopausal women. Further, differences in levels of air pollution within individual cities were also found to be associated with the risk of cardiovascular disease. The Nurses' Health Study is another female prospective cohort study of 66,250 women in northeastern US metropolitan areas. During follow-up (1992–2002), 3,785 women died and there were 1,348 fatal and non fatal MIs. The study found that for each 10 $\mu g/m^3$ increase in a 12-month average $PM_{10,}$ there was an association with increased all-cause mortality (16%, 95% CI: 5%, 28%) with fatal CHD mortality (43%, 95% CI: 10%, 86%). Smokers with higher body mass indexes were at greatest risk of fatal CHD (Puett, et al., 2008). In contrast, the national cohort of male U.S. veterans, where all subjects were hypertensive at baseline, found no increased mortality with increasing levels of fine particulates (Lipfert, Perry, et al., 2000).

In Europe, Hoek et al. (2002) reported increased risk of CPD mortality and all-cause mortality with increased concentrations of black smoke and nitrogen dioxide. Nafstad et al. (2004) also found increased risk of non-cancer respiratory mortality and

CPD mortality with increasing levels of NO_x among Norwegian men. These two European cohort studies have both studied traffic-related pollution (Hoek, et al., 2002; Nafstad, et al., 2004). Hoek et al. (2002) found that persons living near a major road had a RR of 1.95 greater risk of CPD death than did others and, that for each increase of 10 $\mu g/m^3$ in black smoke, the RR increased by 34%. Among Norwegian men, Nafstad et al. (2004) found that for each increase of 10 $\mu g/m^3$ in nitrogen oxides (markers of traffic pollution), the risk increased by 8% for fatal IHD and by 16% for respiratory deaths. The French Pollution Atmosphe´rique et Affections Respiratoires Chroniques/Air pollution and chronic respiratory diseases (PAARC) study showed consistent patterns for non-accident mortalities of cardiopulmonary and lung cancer with ambient air pollution. The greatest adjusted risk ratio was found for CPD mortality with increasing levels of NO_2 (Filleul, et al., 2005).

Among the three early long term cohort studies in the US, the AHSMOG study has some significant components that differ from the Harvard Six Cities and ACS studies. All subjects in the AHSMOG cohort have extensive information on lifestyle. They are all non-smokers (although some were past smokers), and have individual residency and work location histories including ZIP code. Therefore, the higher risk estimates from the AHSMOG (compared to the Harvard six city and the ACS studies) could be due to more precise estimates of ambient air pollution and thus, less exposure misclassification. The AHSMOG study is first study that has reported gender specific findings. No other cohort study on the health effects of ambient air pollution reported gender specific risks for CHD mortality at that time. The Harvard six city and ACS studies used cities as their study unit, in which the ACS study did find a slightly higher, although not significant,

risk of cardiopulmonary mortality among nonsmoking females versus males in the most polluted cities compared to the least polluted (RR=1.57 in females vs. 1.24 in males) (Pope, et al., 1995). Neither the Six Cities Study nor some the European studies (Hoek, et al., 2002; Nafstad, et al., 2004) have reported gender specific findings on cardiopulmonary mortality. The Norwegian cohort only included males (Nafstad, et al., 2004) as did the VA cohort mortality study (Lipfert, Perry, et al., 2000).

Prominent early studies of long-term exposure to air pollution, including the Harvard Six Cities Study (Dockery, et al., 1993), the ACS Study (Pope, et al., 1995), and the AHSMOG study (Abbey, et al., 1999), have been limited to finding an increased risk of mortality associated with long-term exposure to particulates with relatively shorter follow-up period. In 2005, the AHSMOG study reported its findings in females. These results opened new avenues in the investigation of the link between air pollution and heart disease in females. Meanwhile, a study investigating the association between ambient pollution and atherosclerosis offered extra evidence supporting the sex-differential findings observed in the AHSMOG study (Chen, et al., 2005). The study used baseline data from two clinical trials conducted in the Los Angeles area. For a contrast of 10 mg/m^3 in ambient $PM_{2.5}$, Carotid intima-media thickness (CIMT) was approximately 4–5% thicker in females, but not males. Recently, WHI (Miller, et al., 2007) and NHS (Puett, et al., 2008) reported findings which were similar to our results in females in AHSMOG study.

Several experimental studies supported the significant findings in females observed in the AHSMOG and other studies. One of the experimental studies of 50 persons (Sorensen, et al., 2003) showed significant positive associations between

personal $PM_{2.5}$ exposure and oxidation products [e.g., plasma, malondialdehyde, red blood cells (RBCs), and hemoglobin concentrations] in females but not in males. The authors suggested that females are possibly more sensitive to airborne pollution than are males because they have fewer RBCs which make them more sensitive to toxicologic influences of air pollutants.

E. Biological Mechanisms

Cardiovascular response to any stress (which may include air pollution) is a consequence of a complex interplay between the autonomic nervous system governing centrally mediated control of the cardiovascular system, a myocardial substrate (current state of the myocardium) altered in the course of disease processes, and myocardial vulnerability leading to arrhythmogenic or ischemic response. Possible mechanisms considered include: (a) effects on the autonomic nervous system (Holguin, et al., 2003; Pope, Hansen, et al., 2004); (b) alterations in ion channel function in myocardial cells; (c) ischemic responses in the myocardium; and (d) inflammatory responses triggering endothelial dysfunction, atherosclerosis, and thrombosis (Peters, et al., 2001; Seaton, et al., 1999).

There are three interesting studies that have evaluated the impact of long-term exposure to PM air pollution and the development and progression of cardiovascular disease. The first one is based on the data from the Third National Health and Nutrition Examination Survey linked with air pollution data. It explored associations between air pollution and blood markers of cardiovascular risk, specifically fibrinogen levels and platelet and white blood cell counts, and found that elevated fibrinogen levels and platelet and white blood cell counts were all associated with exposure to PM_{10} (Schwartz, 2001).

A second study collected lung tissue samples during necropsies of individuals who died because of violent causes and who lived in relatively clean and polluted areas near Sao Paulo, Brazil (Souza, Saldiva, Pope, & Capelozzi, 1998). Individuals who lived in more polluted areas showed histopathologic evidence of subclinical chronic inflammatory lung injury. A third study used data on 798 participants from two clinical trials conducted in the Los Angeles metro area (Kunzli, et al., 2005). $PM_{2.5}$ was associated with increased CIMT, a measure of subclinical atherosclerosis. It found that a cross-sectional contrast in exposure of 10 $\mu g/m^3$ of $PM_{2.5}$ was associated with a 4% increase in CIMT, but only in females. Meanwhile, several other studies on short-term effects showed that ambient PM increased cardiac arrhythmia (Peters, et al., 2000), decreased heart rate variability (Pope, Hansen, et al., 2004), increased the inflammatory response measured by C-reactive protein (CRP) (Riediker, et al., 2004), and increased blood viscosity (Peters, Doring, Wichmann, & Koenig, 1997) as well as other blood markers (e.g., hemoglobin, fibrinogen, platelet counts, white cell counts) (Riediker, et al., 2004). These observed effects provide a mechanism by which chronic exposure to ambient air pollution is associated with risk of CHD.

Various pathophysiological or mechanistic pathways have been explored. None of these pathways have definitively been demonstrated to be the pathway that clearly and directly links exposure of ambient PM pollution to cardiopulmonary morbidity and mortality. In fact, it is unlikely that any single pathway is responsible. There are almost certainly multiple mechanistic pathways with complex interactions and interdependencies, which provide a schema of some hypothetical mechanistic pathways linking PM with cardiopulmonary disease. Potential mechanisms of deleterious effects of air pollution

may involve response of the respiratory system, oxidative stress and inflammation, and autonomic function. The cardiovascular system seems to be the common end point of these pathways. Elevated PM levels have been linked with cardiac events through these pathways, leading to serious ventricular arrhythmias and myocardial infarction (Table 2.5).

1. Oxidative Stress and Inflammation.

Inhalation of PM, especially $PM_{2.5}$, is believed to cause acute pulmonary inflammation and oxidative stress. It might subsequently generate a systemic inflammatory response, leading to the development of cardiovascular diseases. The particles have been shown to enhance calcium influx on contact with macrophages (Ulrich, et al., 2002). Oxidative stress is anticipated at the huge particle surface, which can be augmented by oxidants generated by recruited inflammatory leukocytes. Atheromatous plaques formed in the coronary arteries are major causes of morbidity and death associated with particulate air pollution in epidemiologic studies.

Declines in lung function caused by respiratory diseases and potentially cardiovascular disease are believed to be related to hypoxia (DeMeo, et al., 2004; Pope, Dockery, Kanner, Villegas, & Schwartz, 1999). Evidence of pollution related inflammation has been observed (Souza, et al., 1998; van Eeden, et al., 2001), and several studies have reported declines in lung function associated with elevated particulate. pollution exposures (Chawla & Lavania, 2008; DeMeo, et al., 2004; Forbes, et al., 2009; Pope, Dockery, et al., 1999). Seaton et al. (1999) hypothesized that fine particulate air pollution may provoke alveolar inflammation in individuals aged 60 years and older. The release of potentially harmful cytokines (such as IL-6) and increased

blood coagulability were found to be associated with increased fine particulate levels. However, the study of potential PM related hypoxia on a panel of 90 elderly in Utah Valley did not consistently observe declines in blood oxygen saturation associated with elevated exposures to particulate air pollution (Pope, Dockery, et al., 1999). They found a negative association only in 80 years and older male individuals, which might be secondary to increased blood coagulability as well as inflammation of the bronchioles and alveoli from air pollution. In a cross-sectional study using part of the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Augsburg survey, Peters et al. (1997) compared measurements of plasma viscosity during a severe episode of air pollution in 1985 with those on less polluted days. They observed an increased risk of extreme values of plasma viscosity in both men and women during the 1985 air pollution episode. Among these pollutants, high concentrations of sulfur dioxide, TSP, and carbon monoxide were found to increase plasma viscosity in women and men to different degrees. Thus, altered blood coagulability and inflammatory processes in the lung that induces an acute-phase reaction might therefore be part of the pathological mechanisms linking air pollution to mortality (Table 2.6).

Experimental evidence has not yet been sufficient to demonstrate the causality and pathogenesis of cardiovascular damage induced by particulate matter. In a rat model, exposure duration and dose-dependent myocardial injury were reported in susceptible rat strains (Kodavanti, Schladweiler, et al., 2000), which might be caused by pulmonary hypertension secondary to the changes in heart rate and blood pressure (Cheng, et al., 2003) or increased whole blood viscosity observed in rats exposed to long-term tobacco

Table 2.5 Selected Studies on Effects of Particulate Air Pollution and Autonomic Control of Cardiac Rhythm

Studies	Design & Exposure	Outcome	Summary of Findings
Panel study, 100 subjects with implanted defibrillators (Peters, et al., 2000)	Ambient $PM_{2.5}$, BC, NO_2,	Defibrillator discharge interventions for ventricular tachycardias/ fibrillation	Increased arrhythmias was associated with increase $PM_{2.5}$,BC, and NO_2
Panel study, 88 elderly subjects (Pope, Hansen, et al., 2004)	Ambient $PM_{2.5}$	HRV	A 100 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 35 msec decreased in SDNN and a 42 msec decreased in r-MSSD
Panel study, 34 elderly residents, nursing home (Holguin, et al., 2003)	$PM_{2.5}$ indoor, outdoor nursing home measure	HRV frequency domain	A 5.0% decrease in high-frequency HRV was associated with increase $PM_{2.5}$
Panel study, 9 highway patrol troopers (Riediker, et al., 2004)	$PM_{2.5}$ vehicle exposure	HRV	Increased heart beat cycle length, HF HRV, SDNN was associated with increase in $PM_{2.5}$

Abbreviation: BS=Black smoke; HF=Heart failure; HRV=Heart rate variability; PM=Particulate matter; SDNN=Standard deviation of normal to normal (heart rate).

Table 2.6 Selected Studies on Effects of Particulate Air Pollution and Systemic Inflammation & Thrombosis

Studies	Design & Exposure	Outcome	Summary of Findings
112 volunteers, 2 UK cities (Seaton, et al., 1999)	Ambient $PM_{10,}$ 3-day personal exposure (one-24 hr personal) & city center	Hemoglobin, RBC, WBC, CRP fibrinogen, etc.	An increased in PM_{10} was significant decreased hemoglobin and RBC; Increased CRP & decreased fibrinogen.
NHANES III (Schwartz, 2001)	Ambient PM_{10}, NO_2, SO_2	Fibrinogen, platelet, WBC	RRs of PM_{10} with Fibrinogen and WBC were 1.77 (1.26-2.49), WBC 1.64 (1.17-2.30). Positive associations between $SO_{2,}$ WBC, NO_2 and platelet & fibrinogen were observed.
Cohort in Augsburg, Germany (Peters, et al., 2001; Peters, Doring, et al., 1997)	Ambient TSP, SO_2, CO	CRP	An increased in TSP, SO_2 was increased in CRP, plasma viscosity.
Panel study, 9 North Carolina highway patrol troopers (Riediker, et al., 2004)	$PM_{2.5}$ vehicle exposure	CRP, plasminogen, lymphocytes	A 100 $\mu g/m^3$ increase in $PM_{2.5}$ was associated in increased CRP.

Abbreviation: CRP=C-reactive protein; RBC=Red blood count; TSP=Total suspended particulate; WBC=White blood count.

smoke (Coates & Richardson, 1978). Similar results were observed in dogs (Wellenius, et al., 2003) and guinea pigs (Wright & Churg, 1991). The apparent dissociation of pulmonary hypertension and emphysema suggests that pulmonary hypertension is not only due to destruction of the lung capillary bed, but could be a result of alteration of the structure of small pulmonary arterioles and arteries (Wright & Churg, 1991). The etiology of this process may be smoke-induced inflammation with release of vasoactive substances as well as proteolytic enzymes, leading to change of red cell adhesiveness secondary to the change of lung endothelial cells or erythrocytes. Further studies indicate that the increased expression levels of various synthases [mainly tumor necrosis factor (TNF) -α) and nitric oxide synthase (iNOS)] might quickly increase the free radical NO level (Ulrich, et al., 2002), which possibly could caused endothelial damage in the lung blood vessels by exposure to ambient particulate pollutants. The mechanism of this quick response of gene expression was not clear, but might be related to free radical damage in the cellular and molecular levels. Increased fibrinogen levels of about 20% increased the tissue blood viscosity, which decreased blood flow and caused the cardiovascular and pulmonary diseases with pulmonary inflammation induced by days' exposure of rat to ambient particulate matter (Table 2.7).

2. Autonomic Function

The autonomic nervous system may play an important role in the pathophysiologic pathway between particulate exposure and cardiopulmonary disease. The autonomic nervous system activates changes in blood viscosity as well as heart rate and heart rate variability (HRV), which increases the likelihood of sudden cardiac death (Nolan, et al., 1998). Dysfunction of the autonomic nervous system and ischemic

responses in the myocardium may contribute to the process of CPD associated with PM. In fact, animal studies with artificial ultrafine particles have demonstrated direct penetration of these particles into the blood stream (Gold, et al., 2000; Liao, et al., 1999; Pekkanen, et al., 2002; Pope, Verrier, et al., 1999). The observation of ambient particulate matter in the heart muscle cells and the brain offers direct evidence of diffusion of particles which may lead to such direct toxic effects. A few epidemiological studies have evaluated autonomic nervous system related physiological measures associated with ambient PM although most of these studies have been only exploratory pilot studies. Liao et al. (1999) examined the cardiac autonomic response to daily variations in PM. He found that increased levels of $PM_{2.5}$ were associated with lower cardiac autonomic control, which suggested that there might be a possible mechanistic link between PM and cardiovascular disease mortality.

Particulate air pollution has shown a positive association with HRV in some studies (Pope, et al., 1995; Pope, Verrier, et al., 1999). In addition, particulate air pollution is associated with changes in heart rate variability (Pope, Hansen, et al., 2004; Riediker, et al., 2004). In a controlled human exposure study, changes in heart rate variability were observed with induced changes in concentrated ambient air pollution particles (Devlin, Ghio, Kehrl, Sanders, & Cascio, 2003). Lower HRV was associated with elevated concentrations of fine particulate pollution and the association was stronger for subjects with preexisting cardiovascular conditions while the pollution levels were relatively low during the study periods. These results extend similar findings reported in recent panel studies and suggest potential mechanisms by which particulate matter may

Table 2.7 Selected Experimental Studies

Studies	Endpoint	Exposure	Summary of Findings
Rats (Coates & Richardson, 1978)	Blood viscosity	Tobacco smoke	Significant higher viscosities from the smoke-treated rats were observed.
Guinea pigs (Wright & Churg, 1991)	Pulmonary hypertension	Cigarette smoke	The hemodynamic changes with alteration of the small pulmonary arterioles and arteries structure was observed after exposed to smoke for periods of 1, 3, 6, and 12 months.
Rats (Gordon, Nadziejko, Schlesinger, & Chen, 1998)	Pulmonary hypertension	CAPs	With 3 hours CAPs, neutrophils elevated lymphocytes was decreased with no change in WBC counts. Small, but consistent changes in HR, but not core temperature.
Dog (Godleski, et al., 2000)	HR, HRSD	CAPs	Increased HR, decreased HRSD was observed after exposed two at a time to CAPS for 6 hrs/day on 3 consecutive days.
Rats (Nadziejko, et al., 2004)	Six coagulation parameters (platelet, fibrinogen, plasminogen)	$PM_{2.5}$	No consistent exposure-related effects on any of the end points across the five experiments and no indication of any dose-dependent effects.
Watanabe heritable hyperlipidemic rabbits (Suwa, et al., 2002)	Atherosclerotic lesions	PM_{10}	Caused progression of atherosclerotic lesions toward a more advanced phenotype after exposed to PM_{10} 4 wk (vol fraction 33.3$\pm$4.6%).

Table 2.7 (continued) Selected Experimental Studies

Studies	Endpoint	Exposure	Summary of Findings
Pulmonary hypertension rats (Cheng, et al., 2003)	HR	$PM_{0.1}$	HR decreased (14.9 beats/min at 1st hr ($p<0.01$) and 11.7 beats/min at 2nd hr ($p=0.01$)) and mean blood pressure also decreased (3.3 mmHg at 1st hr ($p<0.01$) & 4.1 mmHg at 2nd hr ($p<0.01$)
Wistar Kyoto rats (Kodavanti, et al., 2003)	Cardiac lesions	EPM	Decreased numbers of granulated mast cells, and multifocal myocardial degeneration, chronic-active inflammation, and fibrosis exposed to oil combustion-derived, EPM (10 mg/m(3) 6 h/day, 1 day/week for 16 weeks)
CD1 mice (Dick, et al., 2003)	Pulmonary inflammation	$PM_{10-2.5}$, $PM_{2.5}$, $PM_{0.1}$	Increased in neutrophil number was associated in increased in 100 µg $PM_{2.5}$/$PM_{0.1}$group. Two fold increase total antioxidant capacity of the lung was associated in decreased the PM-induced cytokine and neutrophil influx up to 50%.
Mongrel dog (Wellenius, et al., 2003)	Myocardial Ischemia	CAPs	Sig. ST segment elevation. No association with heart rate.
Wistar rats (Ulrich, et al., 2002)	Genes expression	PM 2, 4, 7 days exposure	Elevated expression levels of various genes include TNF-alpha, MIP-2, ET-1, iNOS, and ACE in BALF and plasma, possible endothelial damage in the lung blood vessels by exposure to ambient PMs.

Abbreviation: ACE= angiotensin-converting enzyme; BALF= bronchoalveolar lavage fluid; CAPs=concentration ambient particles; ET= endothelin; EPM= Fugitive emission PM; HR=heart rate; HRSD=heart rate standard deviation; iNOS =nitric oxide synthase; MIP= macrophage inflammatory protein; PM=particulate matter; TNF= tumor necrosis factor; WBC=White blood cell.

directly induce adverse cardiovascular events (Peters, et al., 2000). The results are not entirely consistent, especially with measures of the short-term components of HRV. To what degree these inconsistencies across the studies can be explained by differences in ECG monitoring time frames, make-up of subjects, differences in pollution levels, or other differences, needs to be explored (Table 2.8).

Table 2.8 Selected Studies of Female Specific Findings

Studies	Exposure	Outcome	Findings
SAPALDIA cohort, Swiss (n=1,408) (Felber Dietrich, Gemperli, et al., 2008)	Ambient NO_2, $PM_{2.5}$, PM_{10}	CAD (HRV indices)	Significant negative association of 1-yr average of NO_2 with cardio autonomic dysfunction in elderly women was observed.
Two clinical trials, VEAPS, USC, CA (n=798) (Kunzli, et al., 2005)	$PM_{2.5}$ (mean=20.3 $\mu g/m^3$)	CIMT	5.9% (1-11%) increased in CIMT 15.7% (5.7-26.6%) in older women (age>=60 yrs) was observed.
50 students, central Copenhagen (Sorensen, et al., 2003)	4 time measure personal $PM_{2.5}$ and CB	Plasma MDA, RBCs, hemoglobin	3.7% increase in MDA was observed, significant positive association in other oxidation products with $PM_{2.5}$ was observed in females, but not in males.
22 young adults, UNC, Chapel Hill, NC (Kim & Hu, 1998)	Detailed regional disposition of inhaled particles	LDF, VP	Particle deposition characteristics differ in males and females under controlled breathing conditions (deposition in F >M).
The Nurses' Health Study cohort (n=32,046) (Kawachi, et al., 1997)	ETS exposure	IHD incident & fatal	Strong positive association between IHD and ETS was observed.

Abbreviation: CAD=Cardio autonomic dysfunction; CIMT=Carotid intima-media thickness; ETS=Environmental tobacco smoke; HRV=Heart rate variability; LDF=Local deposition fraction; MDA=malondialdehyde; RBC=Red blood count; VP=Volumetric depth.

CHAPTER 3

FIRST PUBLISHED PAPER

The Association between Fatal Coronary Heart Disease and Ambient Particulate Air Pollution - Are Females at Greater Risk?

Lie Hong Chen, Synnove F. Knutsen, David Shavlik, W. Lawrence Beeson, Floyd Petersen, Mark Ghamsary, David Abbey

Department of Epidemiology and Biostatistics, Loma Linda University

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A. Abstract

The purpose of this study was to assess the effect of long-term ambient particulate matter (PM) on risk of fatal coronary heart disease (CHD). A cohort of 3,239 nonsmoking, non-Hispanic white adults was followed for 22 years. Monthly concentrations of ambient air pollutants were obtained from monitoring stations [PM < 10 um in aerodynamic diameter (PM_{10}), Ozone, sulfur dioxide, nitrogen dioxide] or airport visibility data [PM < 2.5 um in aerodynamic diameter ($PM_{2.5}$)] and interpolated to ZIP code centroids of work and residence locations. All participants had completed a detailed lifestyle questionnaire at baseline (1976) and follow-up information on environmental tobacco smoke and other personal sources of air pollution were available from four subsequent questionnaires from 1977 through - 2000. Persons with prevalent CHD, stroke or diabetes at baseline (1976) were excluded and analyses were controlled for a number of potential confounders including lifestyle. In females, the relative risk (RR) for fatal CHD with each 10 $\mu g/m^3$ increase in $PM_{2.5}$ was 1.42 (95% confidence interval (CI): 1.06, 1.90) in the single-pollutant model and 2.00 (95 % CI: 1.51, 2.64) in the two-pollutant model with O_3. Corresponding RR's for a 10 $\mu g/m^3$ increases in $PM_{10-2.5}$ and PM_{10} were 1.62 and 1.45, respectively in all females and 1.85 and 1.52 in postmenopausal females. No associations were found in males. A positive association with fatal CHD was found with all three PM fractions in females, but not in males. The risk estimates were strengthened when adjusting for gaseous pollutants, especially O_3, and were highest for $PM_{2.5}$. These findings could have great implication for policy regulations.

B. Introduction

Since the early reports of increased deaths from cardiopulmonary disease (CPD) after serious air pollution episodes (Logan, 1953; Nemery, Hoet, & Nemmar, 2001), studies both within the United States (US) and abroad have found similar short term effects of air pollution (Dominici, McDermott, Zeger, & Samet, 2003; Samet, Dominici, Curriero, Coursac, & Zeger, 2000; Zanobetti, et al., 2003).

Studies have also found increased risk of CPD, noncancer respiratory and respiratory cancer deaths with chronic exposure to ambient particulate matter (PM) (Abbey, et al., 1999; Dockery, et al., 1993; McDonnell, Nishino-Ishikawa, Petersen, Chen, & Abbey, 2000; Pope, et al., 2002; Pope, Burnett, et al., 2004; Pope, et al., 1995), black smoke (NO_x) (Hoek, Brunekreef, Goldbohm, Fischer, & van den Brandt, 2002), and nitrogen oxides (Hoek, et al., 2002; Nafstad, et al., 2004). Four main prospective studies have been conducted in the United States to assess long-term health effects of ambient air pollution in adults [the Six Cities Study, the American Cancer Society (ACS) study, the Adventist Health Study on the health effects of smog (AHSMOG) and the national cohort of male U.S. veterans]. Associations with fine particulates [PM < 2.5 μm in aerodynamic diameter ($PM_{2.5}$)] have been found for all-cause mortality, CPD mortality, respiratory/lung cancer mortality in the ACS, Six Cities and AHSMOG studies and with mortality attributable to ischemic heart disease (IHD), dysrhythmias, heart failure, and cardiac arrest in the ACS study. The AHSMOG (Abbey, et al., 1999) has also shown positive associations, although not always significant, between PM < 10 μm in aerodynamic diameter (PM_{10}) and all-natural-cause mortality and CPD mortality in males, but not in females. For fatal lung cancer and any mention of nonmalignant respiratory

disease, a positive association was found with PM_{10} in both sexes. The national cohort of male U.S. veterans, where all subjects were hypertensive at baseline, found no increased mortality with increasing levels of fine particulates (Lipfert, et al., 2000). From Europe, Hoek et al. (2002) reported increased risk of CPD mortality and all-cause mortality with increased concentrations of black smoke and nitrogen dioxide, and Nafstad et al. (2004) found increased risk of noncancer respiratory mortality and CPD mortality with increasing levels of NO_x.

Several studies on short term effects have found that ambient PM increases cardiac arrhythmia (Peters, et al., 2000), decreases heart rate variability (Pope, Hansen, et al., 2004), increases the inflammatory response measured by C-reactive protein (CRP) (Riediker, et al., 2004), and increases blood viscosity (Peters, Doring, Wichmann, & Koenig, 1997) as well as other blood markers (e.g., hemoglobin, fibrinogen, platelet counts, white cell counts) (Riediker, et al., 2004). These observed effects would provide a mechanism by which chronic exposure to ambient air pollution is associated with risk of coronary heart disease (CHD).

This study reports on the risk of fatal CHD associated with long-term ambient air pollution in AHSMOG.

C. Materials and Methods

1. Study Population

AHSMOG began in April 1977 by enrolling 6,338 participants from the Adventist Health Study (AHS) (n= 34,198), a large cohort study of the relationship between lifestyle and risk of chronic disease (Beeson, Mills, Phillips, Andress, & Fraser, 1989). To be included in AHSMOG, subjects must be nonsmoking, non-Hispanic whites

≥ 25 years of age at baseline and must have lived ≥ 10 years within 5 miles of their 1976 neighborhood. All subjects satisfying these criteria were selected from three large metropolitan areas in California: San Francisco, South Coast (i.e. Los Angeles and eastward), and San Diego air basins. In addition, a 13% random sample of 862 AHS subjects was selected from the rest of California assuring large variation and wide ranges in concentrations of different ambient air pollutants.

As part of their enrollment in the AHS in 1976, all participants completed a comprehensive questionnaire that included questions on education, anthropometric data, smoking history, dietary habits, exercise patterns, and previous physician-diagnosed chronic diseases (Beeson, et al., 1989). Monthly residence and work location histories were obtained for each subject for the period January 1966 through December 1998 or until date of death or date of last contact, by using mailed questionnaires (1977, 1987, 1992, 2000), tracing by telephone, and interviewing of surrogates (for deceased subjects). Only 29 (< 0.01%) persons were lost to follow-up with respect to vital status, and these were censored at date of last contact for inclusion in risk sets. The follow-up questionnaires contained standardized questions on respiratory symptoms (American Thoracic Society 1995) and questions to ascertain lifestyle and housing characteristics pertinent to relative exposure to ambient air pollutants, as well as occupational exposures to dust and fumes and indoor sources of air pollution, including environmental tobacco smoke (ETS).

Several air pollutants were estimated for study participants using the statewide network of monitoring stations maintained by the California Air Resource Board (CARB) (Abbey, Moore, Petersen, & Beeson, 1991). Since estimated $PM_{2.5}$ measures were not

available on a statewide basis during follow-up, only the 3,769 (2,422 females and 1,347 males) belonging to the airport subcohort (those who lived within an airshed adjacent to one of nine California airports with available visibility measures: Alameda, Bakersfield, Fresno, Long Beach, Los Angeles, Ontario, Sacramento, San Jose, and San Diego) were included in this study. Of these, 530 (n=332 females, n=198 males) were excluded because of a history of CHD, stroke, or diabetes at baseline, leaving 3,239 subjects for analyses.

2. Estimation of Ambient Air Pollution Concentrations

Estimates of monthly ambient concentrations of PM_{10}, ozone, sulfur dioxide, and NO_2 were formed for study participants for 1973-1998 using fixed site monitoring stations maintained by CARB. The detailed methods for estimating ambient air pollutants for study participants are described elsewhere (Abbey, Hwang, Burchette, Vancuren, & Mills, 1995; Abbey, et al., 1991). Briefly, monthly indices of ambient air pollutant concentrations at 348 monitoring stations throughout California were interpolated to geographic ZIP code centroids according to home and work location histories of study participants. These were cumulated and then averaged over time. Interpolations were restricted to ZIP code centroids within 50 km of a monitoring station and were not allowed to cross barriers to airflow or other topographic obstructions > 250 m above the surrounding terrain. Concentrations of PM_{10} prior to 1987 were estimated using site- and season-specific regressions based on total suspended particles (TSP) (Abbey, Hwang, et al., 1995). Since 1987, directly monitored PM_{10} has been used.

Daily estimates of ambient $PM_{2.5}$ concentration were obtained for 11 airsheds from daily measures of visibility collected at the nine California airports for the years

1973-1998 using regression equations relating $PM_{2.5}$ and visibility. Because of wind patterns, Ontario provided three separate airsheds (East, West, Central). Detailed methods for $PM_{2.5}$ estimation has been described previously (Abbey, Ostro, Fraser, Vancuren, & Burchette, 1995). Individual monthly average $PM_{2.5}$ concentrations were calculated as the mean of the daily ambient $PM_{2.5}$ estimates for the airshed in which the participant resided. Any month with $PM_{2.5}$ estimates for > 75% of the days was considered to have valid data.

3. Ascertainment of Deaths

Fatal CHD, defined by codes 410-414 of the *International Classification of Diseases, 9th Revision* (ICD-9) (World Health Organization 1977) as either "definite fatal myocardial infarction" or "other definite fatal CHD" as underlying or immediate cause of death was used to assess fatal CHD.

Deaths were ascertained through 1998 using record linkage with both the California death certificate files and the National Death Index (Centers for Disease Control and Prevention, National Center for Health Statistics, Atlanta, GA). In addition, our tracing procedures, which included church records, were used (Beeson, et al., 1989). Thus, among the airport subcohort free of CHD, stroke and diabetes at baseline, we identified 1,054 total deaths during follow-up. Death certificates were obtained, and a state-certified nosologist, blinded to the exposure status, coded each death certificate according to the ICD-9 codes.

4. Statistical Analysis

Sex-specific comparisons of baseline descriptive information between CHD mortality cases and noncases were made using the Student t-test or chi-square test.

Time-dependent Cox proportional-hazards regression modeling was used to study associations between pollutants ($PM_{2.5}$, $PM_{10-2.5}$, PM_{10}, O_3, SO_2, and NO_2) and CHD mortality with attained age as the time variable (Greenland, 1989). This was further augmented by adding the Sandwich Variance Estimate (Lin, 1994) to adjust for correlated observations within each airshed. All 11 airsheds around the nine airports were included in the model. We also included the airports as dummy variables stratified with the Cox model. Rate ratios were calculated for an increment of 10 $\mu g/m^3$ for each of the particulate pollutants and 10 ppb for each of gaseous pollutants, except SO_2, which was calculated for an increment of 1 ppb. Because measures for most of the pollutants were available only from 1973, we had 4-year monthly averages for these pollutants at baseline in 1977. To standardize the exposure window preceding events, we therefore selected 4-year average as our moving time period of exposure, but excluded the last month before the event to avoid measuring short-term effects. Participants who did not die were censored at end of follow-up or at time of last contact if they were lost to follow-up (394 females, 166 males). The different pollutants were entered into the model as continuous variables.

The basic multivariable model included past cigarette smoking, body mass index (BMI), years of education, and frequency of meat consumption. We added an interaction term between sex and pollutant to this basic model that was significant and therefore, all analyses were sex specific. Additional candidate variables for inclusion in the final model were ETS (years lived or worked with a smoker), total physical activity at baseline, history of hypertension at baseline, exposure to dust/fumes at work, frequency of eating nuts (Fraser, Sabate, Beeson, & Strahan, 1992), number of glasses of water per day

(Chan, Knutsen, Blix, Lee, & Fraser, 2002), time spent outdoors, and hormone replacement therapy (HRT) (female models). In addition, we found that the levels of PM pollutants used in this study have declined from 1973 to 1998 (Figure 3.1), and we therefore included calendar time as a candidate variable to adjust for possible changes in PM composition over time. All candidate variables were entered into the basic multivariable model one at a time to assess their impact on the main effect. Only calendar year changed the relative risks (RRs) > 10% (actually 16 %) and was retained in the final model (Greenland, 1989).

The proportional hazards assumption was checked by examining log [-log(survival)] curves versus the time (attained age) as well as the product term of each respective variable in the final model with the log of the time variable (Greenland, 1989). Each of these interaction terms produced a p-value >0.05 based on the Wald statistic, indicating that the proportional hazards assumptions were not seriously violated. This was supported further by visual inspection.

The same sex-specific, time-dependent multivariable Cox proportional-hazards regression models with and without the Sandwich Variance Estimate, airport dummy variables and stratified analysis were further used to study associations in two-pollutant models for particulates ($PM_{2.5}$, $PM_{10-2.5}$, or PM_{10}) with each of the gases (O_3, SO_2, and NO_2) and CHD mortality. We evaluated the interactions between two individual pollutants for inclusion in the final model based on whether they changed the RRs > 10%. None of the terms met this criterion (Greenland, 1989). All analyses were repeated for postmenopausal females separately.

In addition, we repeated sex-specific analyses using cumulative monthly averages of each particulate pollutant from 1973 to censoring and also for each of the PM fractions using three levels of exposure (≤ 25, >25-38, >38 $\mu g/m^3$) rather than as a continuous variable. We used the SAS statistical package (version 9.1; SAS institute, Cary, NC) for all analyses.

D. Results

During 22-year follow-up (1977-1998), there were155 CHD deaths in females and 95 among males, 23.7 % of all deaths in this group.

Those who died of CHD were older at baseline, had fewer years of education, were more likely to have hypertension and a larger proportion of the females were postmenopausal and of these, fewer had used HRT (Table 3.1). A higher proportion of female non-cases had lived or worked with a smoker (ETS) and non-cases tended to drink more water than cases. The mean concentrations and correlations of pollutants for this airport subcohort from 1973 through the month of censoring are provided in Table 3.2. Frequency histograms of the individual mean ambient concentrations of each of the PM fractions from 1973 to censoring month are given in Figure 3.2. Those in the lowest distribution of $PM_{2.5}$ lived in the airsheds represented by the San Diego, San Jose, Sacramento, and Alameda airports, medium levels were found in Fresno, Los Angeles International, Bakersfield, Long Beach, Ontario West, and Ontario Central while the highest distribution represents Ontario East. Figure 3.1 shows the secular trends in $PM_{10,}$ $PM_{2.5,}$ and O_3 during the study for the East Ontario and San Diego air basins, and for the study population as a whole.

1. Risk of Fatal CHD

All results presented are from the time dependent Cox model without and with the inclusion of the Sandwich Variance Estimate. For females, in age-adjusted single-pollutant models, a positive, but non-significant, relationship was found between each of the three PM fractions and risk of fatal CHD (Table 3.3). This association became stronger in multivariate analyses with $PM_{2.5}$ having the highest estimate with RR of 1.42 [95% confidence interval (CI): 1.11, 1.81] for each increment of 10 $\mu g/m^3$.

In two-pollutant models with O_3 (Table 3.4), the associations with each of the PM fractions became stronger and statistically significant both in age-adjusted and multivariable adjusted models with the strongest relationship for $PM_{2.5}$ [RR=1.99 (95% CI: 1.37, 2.88)]. NO_2 did not change the associations between PM and fatal CHD whereas SO_2 strengthened the association some, but not to the same degree as did O_3. Point estimates remained virtually unchanged both in single- and multi-pollutant models when including the Sandwich Variance Estimate. When airports were included as dummy variables or in stratified analyses, the risk estimates either remained the same or were strengthened. Limiting the analyses to post-menopausal females resulted in small increases in risk estimates.

Using cumulative monthly averages from 1973 to censoring instead of the 4-year moving average, gave similar, but somewhat weaker associations. Using $PM_{2.5}$ estimates as tertiles (Figure 3.3 for females), showed that those exposed to levels greater than 38 $\mu g/m^3$ were 2.3 times more likely to die of CHD than those living in areas where concentrations were less than or equal to 25 $\mu g/m^3$ ($P_{trend=}0.007$). After adjusting for O_3

in two-pollutant models, the risk estimates for $PM_{2.5}$ increased to 2.03 and 5.35, in the medium and highest tertiles respectively ($P_{trend=}0.006$).

No significant associations were found between any of the gaseous pollutants and fatal CHD in either the age-adjusted or multivariable adjusted analyses in single-pollutant or in two-pollutant models with PM. However, the association with NO_2 was elevated for both males and females in single-pollutant models (Table 3.3). In males, no association was found between particulate pollutants and fatal CHD either as continuous or categorical (tertiles) variables in single or two-pollutant models (Tables 3.3 and 3.4).

E. Discussion

Most studies of the association between ambient particulate air pollution and cardiovascular disease (CVD) have been limited to effects of short term increases in PM on hospital admissions for CVD (Zanobetti, Schwartz, & Dockery, 2000) and total mortality (Dominici, et al., 2003; Samet, et al., 2000). Of the particulate pollutants, $PM_{2.5}$ seems to show the strongest association with CVD outcomes (Pope, et al., 2002; Pope, Burnett, et al., 2004).

The Six Cities and the ACS studies have reported a positive association between cardiopulmonary and cardiovascular deaths and longterm exposure to ambient PM. The association was most strong with fine particles with relative risks varying between 1.06 for cardiopulmonary deaths (Pope, et al., 2002) to 1.12 for cardiovascular deaths (Pope, Burnett, et al., 2004) for each increment of 10 $\mu g/m^3$ after adjusting for age, gender, diet and other demographic covariates. When comparing most polluted with least polluted areas, the relative risk for cardiopulmonary death was 1.31 for a difference of 24.5 $\mu g/m^3$ in the ACS study (Pope, et al., 1995) and 1.37 for a difference of 18.6 $\mu g/m^3$ in the Six

Cities study (Dockery, et al., 1993). Pope et al. (2004) reported a somewhat higher risk estimate for mortality from IHD with a RR of 1.18 for an increment of 10 $\mu g/m^3$ and concluded that "predominant PM mortality associations were with ischemic heart disease". The effect of fine particles on cardiopulmonary mortality has not been reported from the AHSMOG study to date. For PM_{10} and cardiopulmonary mortality, no significant relationships were found, but males had higher estimates than females (Abbey, et al., 1999).

Two European cohort studies have both looked at traffic related pollution (Hoek, et al., 2002; Nafstad, et al., 2004). Hoek found that persons living near a major road had a 1.95 greater risk of cardiopulmonary death than others and for each increase of 10 $\mu g/m^3$ in black smoke, the relative risk increased by 34%. Among Norwegian men, Nafstad et al. (2004) found that for each increase of 10 $\mu g/m^3$ in nitrogen oxides (markers of traffic pollution), the risk increased by 8% for fatal IHD and by 16% for respiratory deaths.

We only found significant relationships between ambient PM and fatal CHD in females. To our knowledge, no other cohort study on the health effects of ambient air pollution has reported gender specific risks for CHD mortality. Therefore, we cannot readily compare our findings to others. However, the ACS study did find a slightly higher, although not significant, risk of cardiopulmonary mortality among never smoking females versus males in the most polluted cities compared to the least polluted (RR=1.57 in females vs. 1.24 in males) (Pope, et al., 1995). As far as we have been able to assess, neither the Six Cities Study nor the Dutch study (Hoek, et al., 2002) have reported gender specific findings on cardiopulmonary mortality. The Norwegian cohort only included males (Nafstad, et al., 2004) as did the VA cohort mortality study (Lipfert, et al., 2000).

In a study of short-term effects, Peters et al. (1997) reported a stronger effect of TSP on blood viscosity in females than males during episodes of high air pollution in Augsburg, Germany.

Several experimental studies of pulmonary deposition of inhaled particles in healthy adults showed that particle deposition characteristics differ between males and females under controlled breathing conditions. Kim and Hu found that deposition in females is greater than that in males, and that the deposition was more localized within the lung in females. The authors suggest that regional deposition enhancement in woman may lead to a greater health risk in females than males (Kim & Hu, 1998). This is consistent with the hypothesized mechanism in which the deposition of particles in the lung could elicit inflammatory responses resulting in a systemic signal (Seaton, MacNee, Donaldson, & Godden, 1995).

An experimental study of 50 persons (Sorensen, et al., 2003) showed significant positive associations between personal $PM_{2.5}$ exposure and oxidation products [such as plasma malondialdehyde, red blood cells (RBC), and hemoglobin concentrations] in females, but not in males. The authors suggest that females possibly are more sensitive to airborne pollution than males since they have fewer RBC and thus may be more sensitive to toxicological influences of air pollutants.

A recent study supporting our gender differential findings assessed the relationship between ambient levels of $PM_{2.5}$ at place of residence and degree of intima-media thickness as measured by ultrasound (Kunzli, et al., 2005). In cross-sectional analyses of baseline data from two clinical trials in Los Angeles, they reported that the association was statistically significant among women, but not among men. Also, the

associations were stronger among older persons who had never smoked or who reported using lipid lowering treatment at baseline. The strongest association, however, was found among older women (≥ 60 years of age). These findings corroborate with our findings from the AHSMOG study which is also an older population with mean age at fatal CHD of 67.6 years in men and 72.3 years in women.

Our findings and those of other studies show that particulate air pollution seems to have a stronger effect on fatal CHD than on other fatal cardiopulmonary endpoints. The ACS study found a somewhat higher RR associated with an increase in $PM_{2.5}$ of 10 $\mu g/m^3$ for fatal ischemic heart disease (IHD) [RR=1.18 (95% CI: 1.14-1.23)] (Pope, Burnett, et al., 2004) than what they had previously found for cardiopulmonary mortality [RR= 1.09 (1.03-1.16)] (Pope, et al., 2002). In females, our findings for fatal CHD and PM are stronger than those we have previously reported for cardiopulmonary mortality in the total AHSMOG cohort (Abbey, et al., 1999) and in the airport cohort (McDonnell, et al., 2000). Also, in previous reports we have only found positive associations with cardiopulmonary mortality in males (Abbey, et al., 1999). In extended follow-up of cardiopulmonary mortality in the total AHSMOG cohort through 1998 using the same models as previously, we continue to find a slightly stronger association in males than in females (unpublished data). However, when we exclude baseline CHD, stroke and diabetes these gender differences disappear and when we limit our analyses to the airport cohort, cardiopulmonary mortality is actually significantly increased in females, but not in males (RR=1.14 vs. 1.02 in males). These findings warrant further study of the effect of PM in sensitive subgroups and in densely populated areas (e.g. airport cohort) versus

less densely populated areas. It also begs the question of whether health effects of air pollution are different in males and females.

Even though we found the strongest association with $PM_{2.5}$, the coarse fraction was also associated with significant risk. Possible explanations for the higher risk estimates for all three PM fractions in our study could be more precise estimates of ambient air pollution and thus less exposure misclassification. The AHSMOG study is the only study with monthly estimates of ambient air pollution for each subject throughout the entire follow-up period. Other reasons could be the homogeneity of the population as discussed under strengths and limitations.

Since different components of air pollution frequently occur together and are highly correlated (Table 3.2), EPA has suggested that the association observed with PM could instead be due to gaseous pollutants (U.S. EPA 1989). We found no significant association between fatal CHD and gaseous pollutants in single or two-pollutant models. However, in two-pollutant models, both O_3 and SO_2 strengthened the relationship between PM and fatal CHD whereas NO_2 had no effect. The modifying effect of O_3 can possibly be explained by findings indicating that lung epithelial permeability increases with exposure to O_3 (Blomberg, et al., 2003) thus making the body more susceptible to intrusion of particulate matter. The proposed mechanisms for the observed cardiovascular effects of particulates have been discussed in detail by Brook et al. (2004) in a statement from the American Heart Association. Several pathways may be involved, but initiation of pulmonary and systemic oxidative stress and inflammation by components of the different PM particles seems to be the most accepted. The resulting cascades of physiologic responses are believed to be able to jointly initiate processes that ultimately

lead to a CHD event. Elevated ambient $PM_{2.5}$ levels have been shown to be associated with cardiac autonomic function (Peters, et al., 2000), heart rate and heart rate variability (Pope, Hansen, et al., 2004), CRP levels (Riediker, et al., 2004), and changes in blood viscosity favoring coagulation (Peters, et al., 1997; Seaton, et al., 1995). Several authors have suggested that risk of CVD may, at least partly, be mediated through increased concentrations of plasma fibrinogen, possibly due to an inflammatory reaction caused by air pollution (Koenig, et al., 1998). Fibrinogen is an important determinant of plasma viscosity, and an independent risk factor for CHD (Koenig, et al., 1998). Numerous animal models corroborate the findings in humans of an effect of PM on heart rate (Chang, et al., 2004), blood viscosity (Coates & Richardson, 1978), and pulmonary inflammation (Wichers, et al., 2004).

These pathways are very similar to those suggested for the effect of cigarette smoking on risk of CHD such as elevated inflammatory markers, especially CRP levels (Panagiotakos, et al., 2004), fibrinogen and white cell counts (Panagiotakos, et al., 2004), blood viscosity (Frohlich, et al., 2003), heart rate (Bolinder & de Faire, 1998), and oxidative stress (Guthikonda, Woods, Sinkey, & Haynes, 2004). Smoking also has been found to trigger acute vasoconstriction and thus the enhanced development of atherosclerosis in the systemic vasculature (Kiechl, et al., 2002). Finally, in studies of the effect of smoking and ETS, Diez-Roux et al. (1995) and Howard et al. (1994) have reported clear effects on intima-media thickness progression over time and on arterial wall stiffness (Mack, Islam, Lee, Selzer, & Hodis, 2003).

1. Strengths and Limitations

Since all subjects in the AHSMOG study are non-smokers, our results are

free from the confounding of active cigarette smoking. We had detailed information about ETS and have been able to adjust for this effect. Any modifying effect of alcohol is also eliminated since virtually everyone was a teetotaler. Since the AHSMOG study has extensive information on lifestyle, we were able to adjust for the effects of a number of such factors including dietary factors found to be associated with CHD in this cohort. This adjustment actually strengthened the associations between PM and fatal CHD in females, but not in males.

Although we have shown cardiovascular effects of particulate air pollution in this study, we have unknown amounts of measurement error in both the estimated long-term ambient concentrations of pollutants as well as other covariates. One source of measurement error is due to interpolating ambient concentrations (PM_{10}, O_3, NO_2, SO_2) from fixed site monitoring stations to ZIP code centroids of work and home locations of study participants (Abbey, Hwang, et al., 1995; Abbey, et al., 1991). Another source of measurement error is that ambient $PM_{2.5}$ concentration was not measured directly for the duration of this study, but estimated from airport visibility, temperature, and humidity (Abbey, Hwang, et al., 1995). The precision of the $PM_{10\text{-}2.5}$ is unknown as it is calculated as the difference between PM_{10} and $PM_{2.5}$. Use of ambient concentrations rather than measures of personal exposure could be one limitation in this study, but it is unlikely that we have selective bias in the females only. Further, we cannot rule out the possibility that the observed gender difference in effect could be due to measurement error. Males, more than females, reported working more than 5 miles from their residence and thus may have spent more time in heavy traffic (more commutes and longer commuter distances). We

have not been able to take this into consideration when estimating each subject's ambient air pollution levels.

F. Conclusions

In summary, this study found an elevated risk of fatal CHD associated with ambient levels of PM_{10}, $PM_{10-2.5}$ and $PM_{2.5}$ in females, but not in males. The risk estimates were strengthened when adjusting for gaseous pollutants and were highest for $PM_{2.5}$. Our findings are in line with findings by others of an effect of PM on cardiopulmonary mortality, but are of greater magnitude, possibly because the outcome was limited to fatal CHD with better control of confounding factors such as alcohol and tobacco.

Further studies are needed from larger cohorts and/or with longer follow-up to support our findings of a gender differential effect of PM on risk of fatal CHD. Developing more accurate ways to assess an individual's exposure to ambient levels of PM will improve precision of risk estimates. Further, it is important to study whether the effects of air pollution are reversible in a similar manner as that found when smokers stop smoking. The effect of different exceedance frequencies should also be explored as well as the effect of different chemical compositions of PM.

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Table 3.1 Selected Characteristics of Study Population at Baseline

	Male (n=1149)			Female (n=2090)		
Characteristic	Cases (n=95)	Noncases (n=1,054)		Cases (n=155)	Noncases (n=1,935)	
Age (years), mean ±SD	67.6 ±11.5	55.8 ±12.9	**	72.3 ±8.9	56.6 ±13.4	**
Years of education, mean ±SD	13.5 ±3.5	14.6 ±3.2	*	12.6 ±2.8	13.4 ±2.6	**
Never smokers	51 (53.7)	717 (68.0)	*	133 (85.8)	1,655 (85.5)	
BMI at or above median	46 (48.4)	477 (45.3)		76 (49.0)	875 (45.2)	
Meat consumption[a,b]						
<1 wk	40 (42.1)	496 (47.1)		88 (56.8)	913 (47.2)	
>=1 wk	50 (52.6)	516 (49.0)		57 (36.8)	917 (47.4)	
Total exercise						
Low	25 (26.3)	344 (32.6)		67 (43.2)	937 (48.4)	
Moderate and high	70 (73.7)	709 (67.3)		83 (53.5)	990 (51.2)	
History of hypertension	32 (33.7)	171 (16.2)	**	70 (45.2)	444 (22.9)	**
ETS	57 (60.0)	619 (58.7)		77 (49.7)	1,208 (62.5)	*
Nuts[a]						
<=2/mo	29 (30.5)	331 (31.4)		60 (38.7)	684 (35.3)	
1-4/wk	37 (38.9)	428 (40.6)		51 (32.9)	736 (38.0)	
5+/wk	23 (24.2)	255 (24.2)		33 (21.3)	397 (20.5)	
Water[a,c]						
<=2 glasses	6 (6.3)	119 (11.3)		26 (16.8)	351 (18.1)	
3-4 glasses	44 (46.3)	369 (35.0)		49 (31.6)	708 (36.6)	
3-4 glasses	42 (44.2)	546 (51.8)		79 (51.0)	833 (43.0)	
Postmenopausal, no. (%)				138 (89.0)	1,323 (68.4)	**
HRT in postmenopausal females				20 (14.5)	431 (32.6)	**

Abbreviations: SD=Standard deviation; BMI=Body mass index, kg/m^2; ETS=Environmental tobacco smoke; HRT=Hormone replacement therapy.

Note. Value are presented as no.(%) or mean ± SD.

[a]Some columns do not add to 100% because of missing data. [b]Significant at p< 0.01 for females only. [c]Significant at p<0.05 for males only. * p< 0.01, **p< 0.001.

Table 3.2 Descriptive Statistics and Correlations between Long-Term Averages of Pollutants Estimated for Study Participants, 1973 through Month of Censoring, Females and Males Combined (n=3,239)

	PM_{10} ($\mu g/m^3$)	$PM_{2.5}$ ($\mu g/m^3$)	$PM_{10-2.5}$ ($\mu g/m^3$)	O_3 (ppb)	NO_2 (ppb)	SO_2 (ppb)
Mean $\pm$SD	52.6 $\pm$16.9	29.0 $\pm$9.8	25.4 $\pm$8.5	26.2 $\pm$7.3	34.9 $\pm$9.7	4.5$\pm$2.7
PM_{10}	1.00	0.83*	0.91*	0.79*	0.50*	0.36*
$PM_{2.5}$		1.00	0.59*	0.60*	0.25*	0.30*
$PM_{10-2.5}$			1.00	0.75	0.51*	0.35*
O_3				1.00	0.22*	0.11*
NO_2					1.00	0.70*
SO_2						1.00

Abbreviations: SD=Standard deviation.
*p<0.01

Table 3.3 Age-Adjusted and Multivariable Adjusted Relative Risks of Fatal CHD for Specific PM Components. Single-Pollutant Models

		Age Adjusted[a]			Multivariable Adjusted[b]			Multivariable Adjusted[c]			Postmenopausal Females Multivariable Adjusted[c]		
Pollutant	Increment	Cases	RR	95% CI	Cases	RR	95% CI	Cases	RR	95% CI	Cases	RR	95% CI
Females													
PM_{10}	10 ($\mu g/m^3$)	92	1.11	0.98-1.26	92	1.22	1.06-1.40	92	1.22	1.01-1.47	80	1.30	1.08-1.57
$PM_{2.5}$	10 ($\mu g/m^3$)	92	1.19	0.96-1.47	92	1.42	1.11-1.81	92	1.42	1.06-1.90	80	1.49	1.17-1.89
$PM_{10-2.5}$	10 ($\mu g/m^3$)	92	1.20	0.95-1.53	92	1.38	1.07-1.77	92	1.38	0.97-1.95	80	1.61	1.12-2.33
O_3	10 (ppb)	92	0.89	0.67-1.18	92	0.97	0.71-1.32	92	0.97	0.68-1.38	80	1.07	0.73-1.59
NO_2	10 (ppb)	92	1.09	0.88-1.35	92	1.17	0.92-1.49	92	1.17	0.98-1.40	80	1.20	1.01-1.44
SO_2	1 (ppb)	87	0.93	0.87-1.01	87	0.94	0.85-1.04	87	0.94	0.81-1.08	77	0.94	0.80-1.11
Males													
PM_{10}	10 ($\mu g/m^3$)	53	0.95	0.81-1.11	53	0.94	0.80-1.11	53	0.94	0.82-1.08			
$PM_{2.5}$	10 ($\mu g/m^3$)	53	0.89	0.69-1.17	53	0.90	0.67-1.19	53	0.90	0.76-1.05			
$PM_{10-2.5}$	10 ($\mu g/m^3$)	53	0.93	0.68-1.29	53	0.92	0.67-1.28	53	0.92	0.66-1.29			
O_3	10 (ppb)	53	0.87	0.58-1.29	53	0.89	0.59-1.33	53	0.89	0.60-1.30			
NO_2	10 (ppb)	53	1.24	0.94-1.64	53	1.16	0.86-1.56	53	1.16	0.89-1.51			
SO_2	1 (ppb)	51	1.06	0.98-1.14	51	1.02	0.92-1.13	51	1.02	0.94-1.11			

Abbreviations: RR=Relative risk; CI=Confidence interval.

[a]Age adjusted.

[b]Adjusted for smoking status (past vs. never), years of education, BMI (below vs. at or above median), meat consumption (< 1/wk vs. 1+/wk), calendar time.

[c]Model "b" with Sandwich Variance Estimate.

Table 3.4 Age-Adjusted and Multivariable Adjusted Relative Risks of Fatal CHD for Specific PM Components, Two-Pollutant Models

Pollutant		Age Adjusted[a]			Multivariable Adjusted[b]			Multivariable Adjusted[c]			Postmenopausal Females Multivariable Adjusted[c]		
PM	Gas	Cases	RR	95% CI	Cases	RR	95% CI	Cases	RR	95% CI	Cases	RR	95% CI
Females													
PM_{10} +	O_3	92	1.33	1.12-1.59	92	1.45	1.21-1.74	92	1.45	1.31-1.61	80	1.52	1.37-1.69
	NO_2	92	1.11	0.97-1.26	92	1.21	1.05-1.40	92	1.21	1.00-1.46	80	1.29	1.06-1.57
	SO_2	87	1.15	1.02-1.31	87	1.27	1.10-1.47	87	1.27	1.08-1.50	77	1.33	1.11-1.59
$PM_{2.5}$ +	O_3	92	1.61	1.17-2.22	92	1.99	1.37-2.88	92	2.00	1.51-2.64	80	1.95	1.52-2.50
	NO_2	92	1.18	0.95-1.47	92	1.39	1.08-1.80	92	1.40	1.04-1.87	80	1.46	1.13-1.89
	SO_2	87	1.36	1.05-1.74	87	1.50	1.15-1.97	87	1.51	1.17-1.95	77	1.51	1.19-1.92
$PM_{10-2.5}$ +	O_3	92	1.47	1.10-1.96	92	1.62	1.21-2.17	92	1.62	1.31-2.01	80	1.85	1.50-2.29
	NO_2	92	1.19	0.92-1.54	92	1.35	1.03-1.76	92	1.35	0.94-1.94	80	1.59	1.07-2.36
	SO_2	87	1.13	1.03-1.68	87	1.49	1.15-1.93	87	1.49	1.12-1.99	77	1.68	1.20-2.35
Males													
PM_{10} +	O_3	53	0.97	0.78-1.20	53	0.96	0.77-1.19	53	0.96	0.87-1.05			
	NO_2	53	0.90	0.76-1.07	53	0.91	0.76-1.09	53	0.91	0.78-1.07			
	SO_2	51	0.92	0.78-1.09	51	0.93	0.78-1.11	51	0.93	0.78-1.11			
$PM_{2.5}$ +	O_3	53	0.92	0.65-1.29	53	0.91	0.64-1.30	53	0.91	0.78-1.06			
	NO_2	53	0.82	0.61-1.10	53	0.85	0.63-1.15	53	0.85	0.70-1.04			
	SO_2	51	0.86	0.65-1.14	51	0.88	0.65-1.19	51	0.88	0.73-1.07			
$PM_{10-2.5}$ +	O_3	53	1.01	0.67-1.51	53	0.97	0.64-1.46	53	0.97	0.74-1.26			
	NO_2	53	0.86	0.62-1.20	53	0.87	0.62-1.23	53	0.87	0.60-1.26			
	SO_2	51	0.90	0.64-1.27	51	0.89	0.63-1.27	51	0.85	0.55-1.32			

Abbreviations: RR=Rrelative risk; CI=Confidence interval.

[a]Age adjusted with Sandwich Variance Estimate.

[b]Adjusted for smoking status (past vs. never), years of education, BMI (below vs. at or above median), meat consumption (< 1/wk vs. 1+/wk), calendar time.

[c]Model "b" with Sandwich Variance Estimate.

[d]RR was calculated for an increase of 10 $\mu g/m^3$ in concentration of the specific PM components.

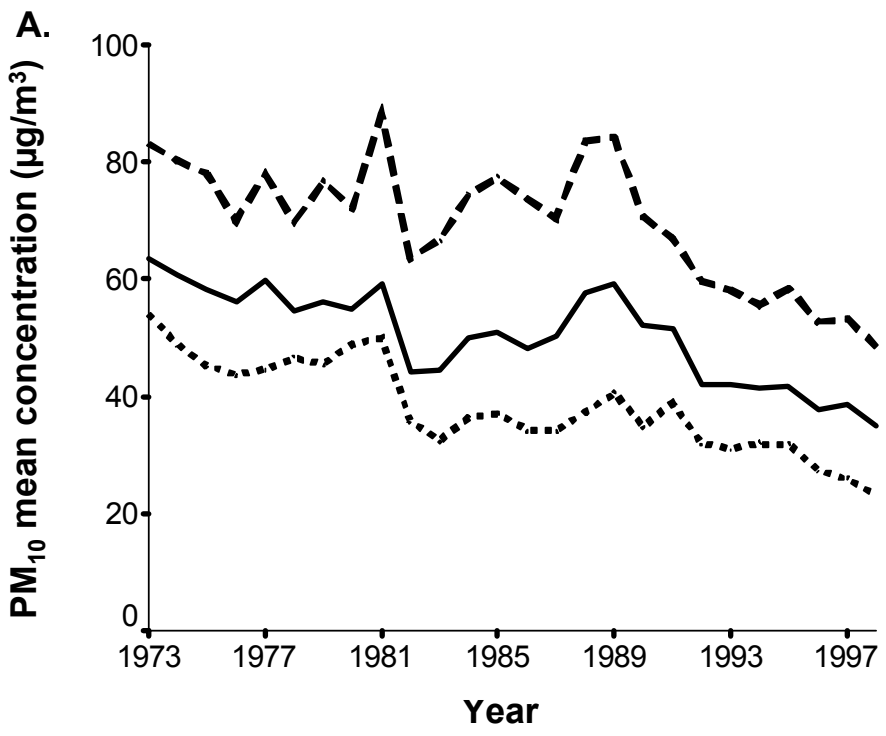

Figure 3.1 Mean Concentration Over Time, $PM_{2.5}$ (A), PM_{10} (B), O_3 (C), 1973-1998. Genders combined A and B: AHSMOG cohort (solid line), East Ontario air basin (dashed line), San Diego air basin (dotted line); C: AHSMOG cohort (solid line), mountain areas (dashed line), coastal areas (dotted line). Note that the vertical scales differ in the three different panels.

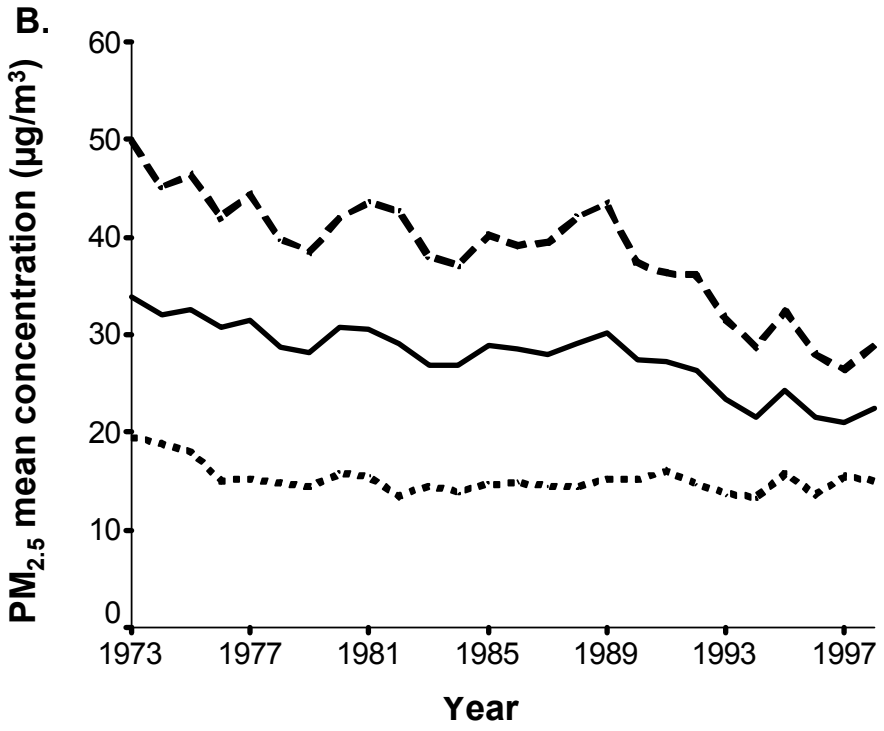

Figure 3.1 (continued) Mean Concentration over Time, $PM_{2.5}$ (A), PM_{10} (B), O_3 (C), 1973-1998. Genders combined A and B: AHSMOG cohort (solid line), East Ontario air basin (dashed line), San Diego air basin (dotted line); C: AHSMOG cohort (solid line), mountain areas (dashed line), coastal areas (dotted line). Note that the vertical scales differ in the three different panels.

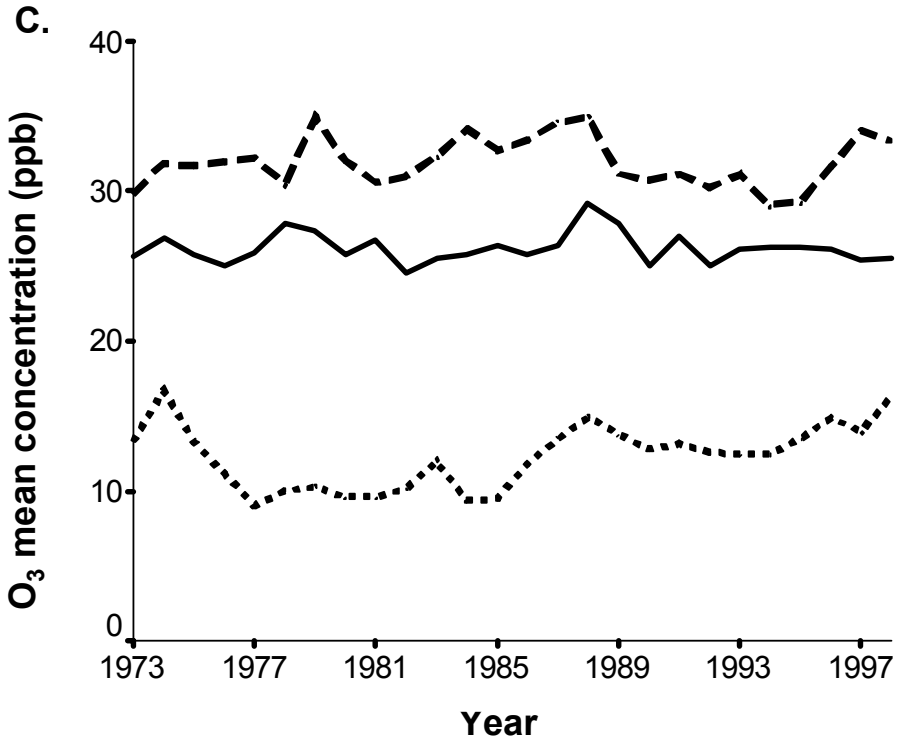

Figure 3.1 (continued) Mean Concentration over Time, $PM_{2.5}$ (A), PM_{10} (B), O_3 (C), 1973-1998. Genders combined A and B: AHSMOG cohort (solid line), East Ontario air basin (dashed line), San Diego air basin (dotted line); C: AHSMOG cohort (solid line), mountain areas (dashed line), coastal areas (dotted line). Note that the vertical scales differ in the three different panels.

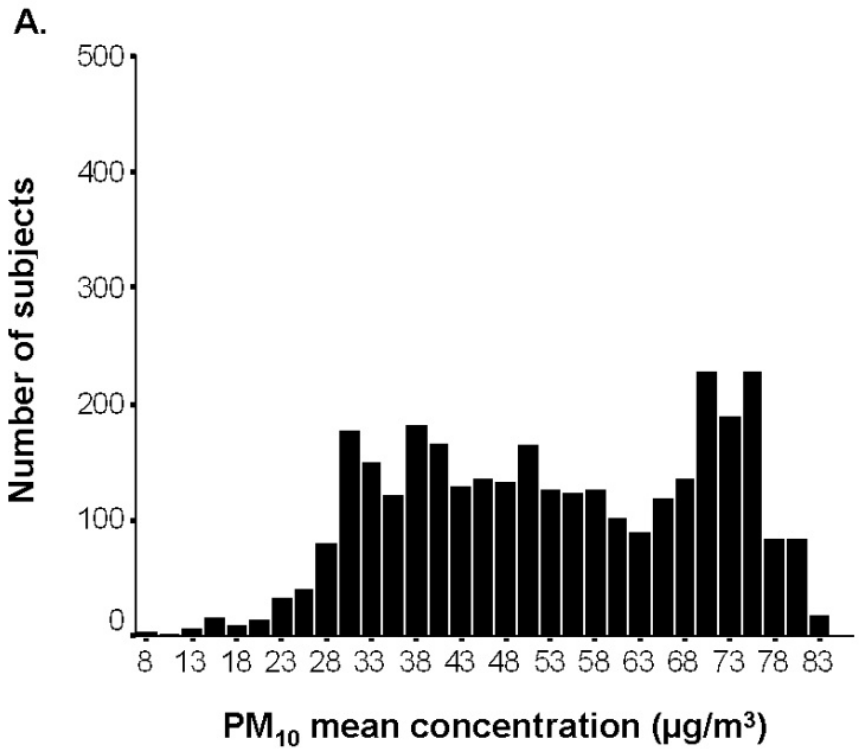

Figure 3.2 Frequency Distribution of Mean Ambient Concentration of PM_{10} (A), $PM_{2,5}$ (B), $PM_{10-2.5}$ (C), 1973 to Censoring Month (n=3,239). Note that the horizontal scales differ in the three different panels.

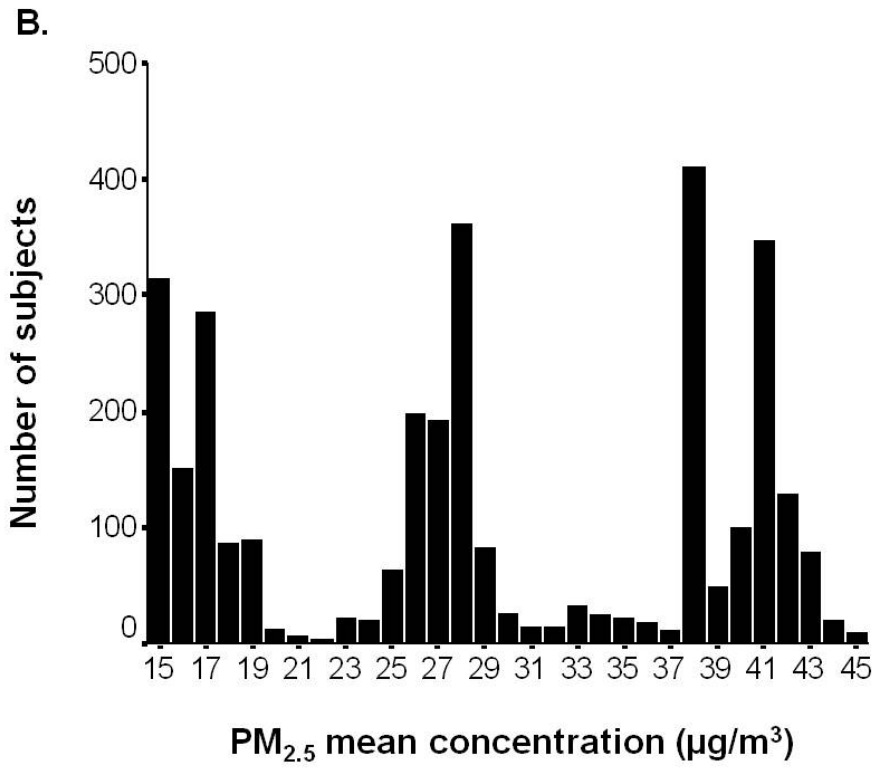

Figure 3.2 (continued) Frequency Distribution of Mean Ambient Concentration of PM_{10} (A), $PM_{2,5}$ (B), $PM_{10\text{-}2.5}$ (C), 1973 to Censoring Month (n=3,239). Note that the horizontal scales differ in the three different panels.

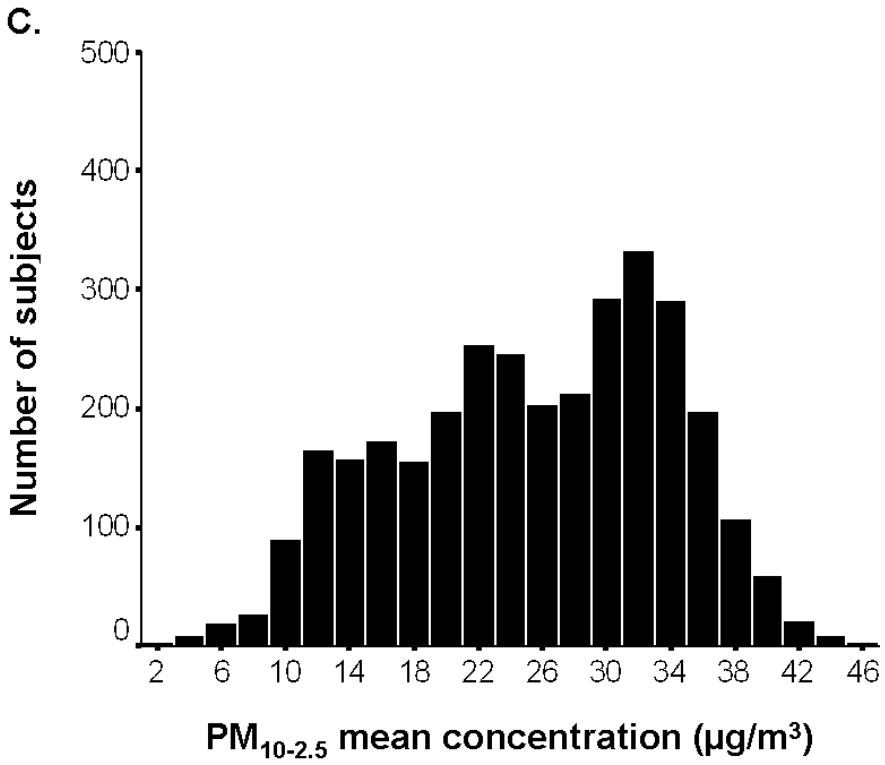

Figure 3.2 (continued) Frequency Distribution of Mean Ambient Concentration of PM_{10} (A), $PM_{2.5}$ (B), $PM_{10\text{-}2.5}$ (C), 1973 to Censoring Month (n=3,239). Note that the horizontal scales differ in the three different panels.

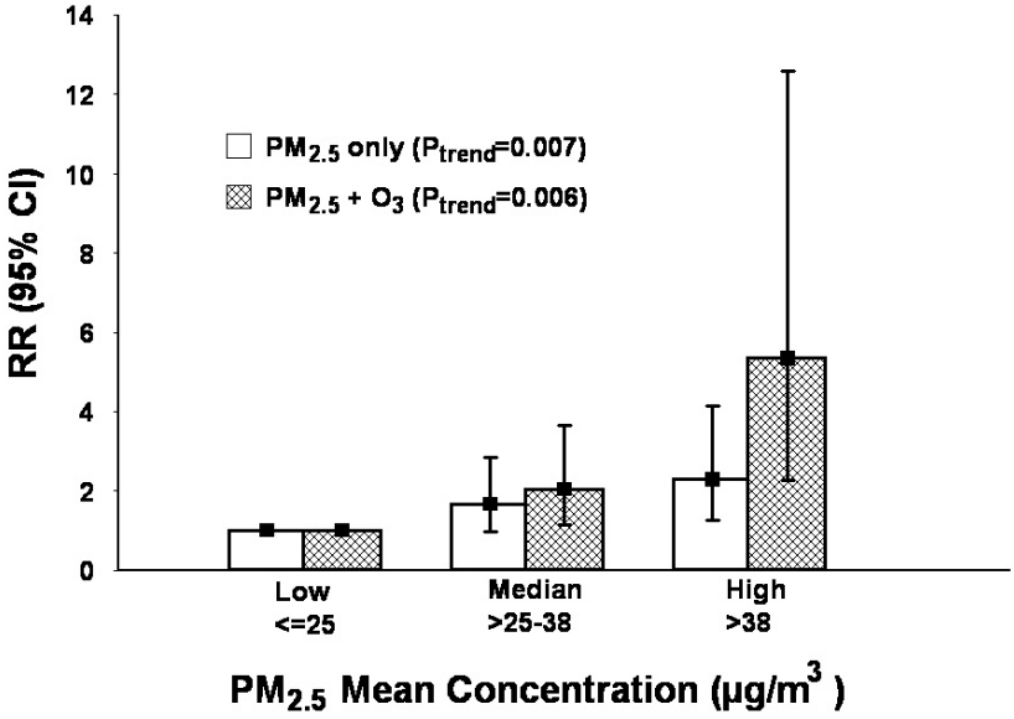

Figure 3.3 Relative Risk of Fatal CHD and Tertiles of $PM_{2.5}$ Mean Concentration in Single and Two-Pollutant Models ($PM_{2.5}$ + O_3). All Females.

CHAPTER 4

SECOND PUBLISHABLE PAPER

The Mortality and Long-Term Exposure to Ambient Air Pollution in Nonsmoking Adults

Lie Hong Chen, Synnove F. Knutsen, W. Lawrence Beeson, Sam Soret, David Shavlik, Mark Ghamsary

Department of Epidemiology and Biostatistics, Loma Linda University, Loma Linda, California, USA

For submission to: Epidemiology

A. Abstract

An increasing number of studies have found elevated risk of all causes of deaths with short- and long-term exposure to ambient particulate matter (PM). The purpose of this study was to assess the effect of long-term ambient PM on mortality in a low risk population.

A cohort of 6,338 nonsmoking, non-Hispanic white adults was followed for almost 30 years. At baseline in 1977, a comprehensive lifestyle questionnaire was completed and the cohort was followed with periodic updates of residence and workplace. Exposure to environmental tobacco smoke (ETS) and other sources of air pollution were assessed through subsequent questionnaires in 1987, 1992, and 2000. Monthly concentrations of ambient air pollutants (PM_{10}, Ozone, SO_2, and NO_2) were obtained from monitoring stations. Air pollution metrics were interpolated to ZIP code centroids of work and residence locations. Time-dependent Cox proportional hazard regressions in single and two-pollutant models were used for analyses over the period of 1973 to time of death or end of study for living subjects. The analyses were controlled for a number of potential confounders including lifestyle.

In two pollutant models, each increment of 10 $\mu g/m^3$ for PM_{10} was associated with an increased risk of fatal nonmalignant respiratory disease (NMRD) controlling for O_3, NO_2 or SO_2 with adjusted relative risk (RR) of 1.13 [95% confidence interval (CI), 1.04-1.22], 1.05 (95% CI, 0.98-1.13) or 1.06 (95% CI, 0.99-1.14), respectively. The highest RR of NMRD of 1.15 (1.03-1.29) was found for PM_{10} after controlling for hours per year in excess of 100 ppb O_3 (O_{3e100})**.** Also, for cancer death, an adjusted RR of 1.16 (95% CI, 1.03-1.31) was observed for each increment of 30 day/year when PM_{10}

exceeded 100 μg/m^3 controlling for O_3.

An increased risk of NMRD mortality was found to be associated with ambient levels of PM_{10}. Also an increased risk of total cancer mortality was found to be associated with ambient levels of PM_{10}. The risk estimates were strengthened when adjusting for gaseous pollutants. These findings could have great implication for policy regulation.

B. Introduction

Short term time series studies have consistently provided evidence for harmful effects of particulate matter (PM) on all-causes mortality of (Dominici, McDermott, Zeger, & Samet, 2003; Samoli, et al., 2005; Wong, Vichit-Vadakan, Kan, & Qian, 2008; Zanobetti & Schwartz, 2009), cardiopulmonary disease (CPD) (Dominici, et al., 2003), and respiratory disease (Samoli, et al., 2005; Zanobetti & Schwartz, 2009) by using timescales from days to months. Many studies have also found increased risks of all-cause mortality as well as deaths from CPD, ischemic heart disease (IHD), respiratory disease and respiratory cancer with chronic exposure to ambient PM (Abbey, et al., 1999; Dockery, et al., 1993; Jerrett, et al., 2005; McDonnell, Nishino-Ishikawa, Petersen, Chen, & Abbey, 2000; Pope, et al., 2004; Pope, et al., 1995), black smoke (BS), and nitrogen oxides (NO_x) (Filleul, et al., 2005; Hoek, Brunekreef, Goldbohm, Fischer, & van den Brandt, 2002; Nafstad, et al., 2004).

The Adventist Health Study on the health effects of smog (AHSMOG) has previously found increases in mortality due to any mention of nonmalignant respiratory disease (NMRD), lung cancer in both genders (Beeson, Abbey, & Knutsen, 1998), all natural cause (ANC) mortality, CPD deaths in males (Abbey, et al., 1999; McDonnell, et al., 2000), and coronary heart disease (CHD) deaths in females (Chen, et al., 2005).

Mortality ascertainment and exposure have recently been updated on the AHSMOG cohort through 2006. The purpose of this study was to assess the association between mortality of all-cause and cause-specific and long term ambient concentrations of PM_{10} and other gaseous air pollutants using 30 years of follow-up.

C. Materials and Methods

1. Study Population

The AHSMOG study began in April 1977 by enrolling 6,338 participants from the larger parent study of California Adventist [Adventist Health Study-1 (AHS-1) (n= 34,198)], a large cohort study of the relationship between lifestyle and risk of chronic disease (Beeson, Mills, Phillips, Andress, & Fraser, 1989). To be included in the AHSMOG study, subjects must be not currently smoking, non-Hispanic white aged 25 years or older at baseline and must have lived 10 years or longer within 5 miles of their 1976 neighborhood. All subjects satisfying these criteria were primarily selected from three large metropolitan air basins in California - San Francisco, South Coast, and San Diego air basins. In addition, a 13% random sample of 862 AHS-1 subjects was selected from the rest of California and these served as a low exposure reference population. This wide geographic spread of study subjects has assured large variation and wide ranges in concentrations of different ambient air pollutants.

As part of their enrollment in the AHS-1 in 1976, all participants completed a comprehensive mailed lifestyle questionnaire which included questions on years of education, anthropometric data, past and current cigarette smoking, current and past dietary habits, exercise patterns, and previous physician diagnosed chronic diseases (Beeson, et al., 1989). As part of the AHSMOG cohort, monthly residence and work

location histories were obtained for each subject for the period January 1966 through December 2000 or until date of death or date of last contact by using mailed questionnaires (1977, 1987, 1992, 2000), tracing by telephone, and interviewing of surrogates (for deceased subjects). Only 29 (< 0.01%) persons were lost to follow-up with respect to vital status and these were censored at date of last contact for purposes of inclusion in risk sets. The follow-up questionnaires contained standardized questions on respiratory symptoms, now included as part of the American Thoracic Society (ATS) questionnaire (American Thoracic Society, 1995), and questions to ascertain lifestyle and housing characteristics pertinent to relative exposure to ambient air pollutants as well as occupational exposures to dust and fumes and indoor sources of air pollution, including environmental tobacco smoke (ETS).

2. Estimation of Ambient Air Pollution Concentrations.

Estimates of monthly ambient concentrations of PM less than 10 μm in aerodynamic diameter (PM_{10}), number of days of PM_{10} concentrations above 100 $\mu g/m^3$ per year (PM_{10e100}), ozone (O_3), number of hours of O_3 concentrations above 100 ppb per year (O_{3e100}), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2) were established for study participants for 1973-2000 using fixed site monitoring stations. The detailed methods for estimating ambient air pollutants for study participants have been described elsewhere (Abbey, Hwang, Burchette, Vancuren, & Mills, 1995; Abbey, Mills, Petersen, & Beeson, 1991; Abbey, Ostro, Fraser, Vancuren, & Burchette, 1995). Briefly, monthly indices of ambient air pollutant concentrations at 348 monitoring stations throughout California were assigned to geographic ZIP code centroids using Inverse Distance Weighted (IDW) interpolation according to home and work location histories of study participants. These

were cumulated and then averaged over time. Interpolations were restricted to ZIP code centroids within 50 km of a monitoring station and were not allowed to cross barriers to airflow or other topographic obstructions in excess of 250 m above the surrounding terrain. Concentrations of PM_{10} prior to 1987 were estimated using site- and season-specific regressions based on total suspended particles (TSP) (Abbey, Hwang, et al., 1995). Since 1987, directly monitored PM_{10} has been used. After year 2000, concentration data for PM_{10} and O_3 were further extended to 2006 by implementing spatial interpolation methods in a GIS environment (ArcGIS 9.3, ESRI, Redlands, California) in order to derive exposure estimates for the year 2000 residential locations of subjects. Air pollution exposure estimates derived using the pre-2000, non-GIS methods and those produced through the GIS based interpolation method were compared for the years 1999 -2000 and showed a very high correlation (r=0.95). Thus, the GIS based interpolations were used for assessing exposure to ambient air pollution from 2000 to 2006.

3. Ascertainment of Deaths

Deaths were ascertained through 2006 using record linkage with both the California death certificate files and the National Death Index (NDI). In addition, our tracing procedures also included examination of church records (Beeson, et al., 1989). Each death certificate was coded according to the ICD-9 and ICD-10 codes by a state certified nosologist who was blinded to the exposure status of the subject. Since 1998, the cause of death was obtained from the NDI database. A total of 3,230 deaths (2012 in females and 1218 in males) were identified as having ANC's death (ICD-9: 1-799; ICD-10: A00-R99). Specific causes of death with their ICD-9 and ICD-10 codes used in the

study included : CPD (ICD-9: 401-440 and 460-519; ICD-10: I10-I70 and J00-J98), CHD (ICD-9: 410-414; ICD-10: I20-I25), total cancer (ICD-9: ICD9:140-172, 174-209; ICD-10: C00-C43 and C45-C97), and any mention of NMRD (ICD-9: 460-519; ICD-10: J00-J98) (Table 4.1).

4. Statistical Analysis

Time-dependent Cox proportional-hazards regression modeling was used to study associations between pollutants (PM_{10}, O_3, SO_2, and NO_2) and cause- specific mortality with attained age as the time variable (Greenland, 1989). Measures for most of the pollutants were available only from 1973. To standardize the exposure window preceding the fatal event, a monthly average from1973 to the date of censoring was selected as the time period of exposure for all death categories except cancer, CPD, and CHD mortality. For total cancer mortality, a 3-year lag was used. This lag averaged the pollutant only up to the 3 years prior to the date of censoring because of the expected long latency period between the exposure and incidence of cancer. For CPD and CHD mortality, a 4-year moving average of the ambient air pollutant level for the period directly preceding each age risk set with 1 month lag was used as the exposure variable. The last month before event was excluded to avoid measuring short-term effects. Participants who did not die were censored at the end of follow-up or at the time of last contact if they were lost for follow-up. The different air pollutants were entered into the statistical model as continuous variables.

The basic multivariable model included past pack-years of cigarette smoking, body mass index (BMI), and years of education. Additional candidate variables for inclusion in the final model were selected based on literature search in addition to

specially identified risk factors in this population and included years lived or worked with a smoker (ETS), total physical activity at baseline, history of hypertension at baseline, exposure to dust/fumes at work, frequency of eating nuts (Fraser, Sabate, Beeson, & Strahan, 1992), number of glasses of water per day (Chan, Knutsen, Blix, Lee, & Fraser, 2002), time spent outdoors, frequency of meat consumption (< 1/wk vs. 1+/wk) (Kontogianni, Panagiotakos, Pitsavos, Chrysohoou, & Stefanadis, 2008) and hormone replacement therapy (HRT). These candidate variables were entered into the basic multivariable model one at a time to assess their impact on the main effect. None of the candidate variables changed the RR's for the specific air pollutant more than 10% and were therefore not included in the final model (Greenland, 1989). For any mention of NMRD and total cancer mortality, the basic model also included ETS.

Sensitivity analyses were performed by including individuals in the analysis with these prevalent diseases mentioned above and with the disease in question added to the statistical model as a dichotomous indicator variable for each disease, indicating having that disease (code=1) or not (code=0). The RRs of the air pollutants did not change significantly and tended to be similar or somewhat weaker, but with narrower CI. In addition, we found that the levels of PM pollutants used in this study had declined from 1973 to 2006 (Chen, et al., 2005) and we therefore included a variable for calendar time to adjust for possible changes in PM composition over time.

The proportional hazard assumption was checked by examining log[-log(survival)] curves versus time (attained age) as well as the product term of each respective variable in the final model with the log of the time variable (Greenland, 1989). Each of these interaction terms had a p-value greater than 0.05 based on the Wald statistic, indicating

that the proportional hazards assumption was not seriously violated. This was supported further by visual inspection of the log [-log(survival)] plots.

The same time dependent multivariable Cox proportional hazards regression models were further used to study the associations in two-pollutant models of PM_{10} with each of the gases (O_3, SO_2, and NO_2) for mortality from broad categories of causes. The interactions between two individual pollutants were evaluated for inclusion in the final model based on whether they changed the RR's more than 10% or not. None of the terms met this criterion (Greenland, 1989).

D. Results

A total of 1508 subjects (980 females, 528 males) were excluded in the primary analysis because of a history of CHD, stroke, diabetes, cancer and/or COPD at baseline. These subjects with comorbidities were later added in the sensitivity analyses. Thus, a total of 4,830 subjects (3,080 females, 1,750 males) were included for the primary analyses.

Table 4.1 shows the numbers and percentages of specific deaths by cause categories from 1977 to 2006 in the ostensibly healthy AHSMOG cohort. Compared to our earlier follow-up (Abbey, et al., 1999), the additional 6 years of follow-up resulted in approximately 35% increase in number of deaths in each specific mortality cause category. By the end of 2006, a total of 2,159 deaths occurred from ANC, 1,312 from CPD, 536 from CHD, 404 from cancers and 205 from any mentioned nonmalignant respiratory diseases. Baseline characteristics of the study population are given in Table 4.2. Those who died from ANC were older, less educated, and more likely to have hypertension. A lower proportion of ANC cases ate nuts 1 to 4 times per week and drank

water less than 2 glasses per day compared to the non-cases. A lower proportion of ANC death cases had ETS. The mean concentrations of pollutants (PM_{10}, gaseous) in the AHSMOG cohort (Figure 4.1 to Figure 4.6) and correlation of pollutants from 1973 through the month of censoring are provided in Table 4.3. The correlations of PM_{10} with O_3, especially PM_{10e100} with O_{3e100}, were stronger than those with NO_2 and SO_2.

1. All Natural Cause Mortality

In single-pollutant models, a positive, but non-significant, relationship was found between each increment of 10 $\mu g/m^3$ PM_{10} and risk of ANC mortality (Table 4. 4). This relationship became stronger and borderline significant when mean O_3 concentration was added in two-pollutant models [1.04 (95% confidence interval (CI): 1.00-1.09)]. However, this was not the case for NO_2 and SO_2 (Table 4.5).

2. Cardiopulmonary Disease Mortality

In single-pollutant models, no association was found between PM_{10} and risk of fatal CPD (Table 4.4). The relationship became positive and stronger in two-pollutant models with O_3, but not with the other gaseous pollutants (NO_2, and SO_2). The association between PM_{10} and fatal CPD was the strongest in the two-pollutant model with O_3 e100 [RR of 1.07 (95% CI: 1.00-1.14)] (Table 4.5).

3. Coronary Heart Disease Mortality

In single-pollutant models, a weak positive, but non-significant, relationship was found between each pollutant (PM_{10}, NO_2, and SO_2) and risk of fatal CHD, except for O_3 (Table 4.4). The relationship between PM_{10} and fatal CHD was strengthened when O_3 e100 was added to the model [RR=1.09 (95% CI: 0.98-1.20)]. It was virtually unchanged when O_3 was added to the model. Adding mean O_3

concentration or other gaseous pollutants (NO_2 or SO_2) did not change the effect of PM_{10} and fatal CHD with RR of 1.09 (95% CI: 0.98-1.20) after O_3 e100 was added (Table 4.5).

4. Total Cancer Mortality

In single-pollutant models, a positive, but non-significant, relationship was found between each pollutant (PM_{10}, SO_2, and NO_2) and risk of cancer death, except for O_3 (Table 4.4). The association between PM_{10} and risk of cancer death became stronger and significant in two pollutant models with O_3, but not with O_{3e100} in the model. The strongest relationship in the model was found between PM_{10e100} (adjusted for O_3) and cancer with RR of 1.16 (95% CI: 1.03-1.31) (Table 4.5).

5. Any Mention of Nonmalignant Respiratory Disease Mortality.

In single-pollutant models, a positive and borderline significant relationship was found between PM_{10} and any mention of NMRD deaths as well as for NO_2, and SO_2, but not for O_3 (Table 4.4). However, the relationship with PM_{10} became significant in two-pollutant models [(PM_{10}: RR=1.13 (95%CI: 1.04-1.22) with O_3]; and O_{3e100} [(PM_{10}: RR=1.15 (95%CI: 1.03-1.29) with O_{3e100}] as well as PM_{10} e100 [RR=1.14 (95%CI: 1.02-1.27) with O_3] (Table 4.5).

E. Discussion

With 30 years of AHSMOG cohort follow up, we found that long-term exposure to ambient concentrations of air pollutants (PM_{10}, NO_2, and SO_2) were associated with increased mortality. Relative risks were generally small. Statistically significant associations between PM_{10} exposure and mortality by any mention of nonmalignant respiratory causes and cancer were found after adjusting for O_3 with strongest effect for NMRD controlled for O_{3e100}. Relative risks were also non-significantly increased for

ANC mortality as well as mortality from CPD and CHD. The strongest association was found between PM_{10} and mortality by any mention of nonmalignant respiratory causes controlled for O_{3e100}.

Many long-term studies have found increased risks of all-cause mortality and mortality from broad categories of causes with PM, especially with fine PM ($PM_{2.5}$). Unfortunately, we do not have $PM_{2.5}$ estimates for entire AHSMOG cohort and therefore, we cannot directly compare our results with results published from two US long-term studies – the Harvard Six Cities (Dockery, et al., 1993) and the American Cancer Society (ACS) (Pope, et al., 1995). The Harvard Six Cities Study included 8000 adults living in six US cities with a 14- to 16-year prospective follow-up, representing a wide range of pollution exposure. Although the Six Cities Study reported PM_{10} and other pollutants that we have addressed, their pollutants were limited to six centrally located air pollution monitoring sites. The same estimate was assigned to all participants living in the same community and, therefore, the study had less ability to differentiate between specific pollutants.

The Harvard Six Cities study reported that the RRs for ANC mortality and mean concentrations of PM_{10} were 1.27 for a difference of 28.3 $\mu g/m^3$ when comparing most-polluted with least-polluted areas. This effect is greater than the observed in our study with an effect of 1.04 per increment of 10 $\mu g/m^3$. The Six Cities and the ACS studies have also reported a positive association between deaths of cardiovascular disease and CPD, and long-term exposure to ambient PM, but mostly limited to $PM_{2.5}$. The Washington University-EPRI veterans cohort study (Lipfert, et al., 2000), in which all

subjects were male and hypertensive at baseline, showed no increased mortality with increasing levels of PM including TSP and PM_{10}.

Two European cohort studies have both studied traffic related pollution (Hoek, et al., 2002; Nafstad, et al., 2004). In the Netherlands, a random sample of 5000 subjects was selected from the Netherlands Cohort Study on Diet and Cancer (NLCS) cohort (Beelen, et al., 2008). Recently reported results from NLCS were comparable with ours. RRs were generally small in the full cohort. The RRs for a 10 $\mu g/m^3$ increase in BS were 1.05 (95% CI: 1.00–1.11) for ANC, 1.04 (95% CI: 0.95–1.13) for cardiovascular, 1.03 (95% CI: 0.88–1.20) for lung cancer, and 1.04 (95% CI: 0.97–1.12) for mortality other than cardiovascular, respiratory, or lung cancer. Results were similar for NO_2 (Beelen, et al., 2008). Among Norwegian men, Nafstad et al. (2004) found that for each increase of 10 $\mu g/m^3$ in nitrogen oxides (markers of traffic pollution), the risk increased by 8% for ANC deaths and fatal IHD and by 16% for respiratory disease other than lung cancer deaths.

In another European study PAARC which included 14,284 adults who resided in 24 areas from seven French cities, Filleul et al. (2005) found that for each increase of 10 $\mu g/m^3$ in TSP, the risk was increased by 5% for all non-accident causes of death and by 6% for cardiopulmonary disease death. They also reported an increase in risk of 7% for all non-accident causes of death and of 5% in cardiopulmonary disease deaths for each increase of 10 $\mu g/m^3$ in BS.

Our findings of association between ANC, cardiovascular and CHD mortality and PM_{10} were positive and comparable to other US and European studies. Comparisons of current results with published findings from other long-term studies were limited because

they used estimates of $PM_{2.5}$ and in our study $PM_{2.5}$ is only available in a sub-cohort (n=3,769) of our population, those living near airports in California and thus was not included in our analyses. The ACS study has published results only pertaining to $PM_{2.5}$ and gases (e.g. O_3, SO_4) (Pope, et al., 2004; Pope, et al., 1995). The Harvard Six Cities study addressed all the pollutants but emphasized on association with $PM_{2.5}$ too (Dockery, et al., 1993; Laden, Schwartz, Speizer, & Dockery, 2006). The Washington University-EPRI Veterans cohort study (Lipfert, et al., 2000) was limited only to male and hypertensive subjects. It only had significant findings on O_3 and NO_x. European cohort studies (Filleul, et al., 2005; Hoek, et al., 2002; Nafstad, et al., 2004) mainly studied traffic related pollutants (BS, NO_x).

Compared with previous reports from the AHSMOG study (Abbey, et al., 1999), our study extended the follow-up of mortality using improved analytical techniques. Our results on ANC mortality were in line with previously published findings, but the effect estimates were somewhat weaker. Possible explanations for the weaker effect estimates in the current study could be that we excluded many subjects with prevalent diseases (CHD, stroke, diabetes and cancer) whereas these were included in the previous 15-year follow-up reported by Abbey et al (1999). In our study we used 4-year moving average for CPD and CHD mortality where Abbey used cumulative mean concentration from first month through the month of death and interquartile range (IQR) to calculate RRs. Also, we did gender combined analyses since the interaction term with gender was not significant.

For CPD mortality during 30 years follow-up, there were no gender differences and no effect of PM_{10} or the gaseous pollutants when we excluded subjects with baseline

CHD, stroke and diabetes. Based on our previous findings and other studies, particulate air pollution seems to have a stronger effect on fatal CHD than on other fatal endpoints and a stronger effect was found in females (Chen, et al., 2005). We found a similar trend of increasing risks of mortality of ANC, CPD, and CHD.

Except for mean concentrations of O_3, the levels of air pollutants and pollutant indices declined markedly from 1973 to 2006 in our study. However, the most marked decline was seen sometime after 1992 for PM_{10} (Chen, et al., 2005). Compared to the earlier papers from this study, the lower risk estimates on ANC, CPD, and CHD mortality could be partially due to lower exposure levels during recent years.

The findings from our current study were consistent with NMRD mortality when compared with previous report on gender combined results (Abbey, et al., 1999). The AHSMOG previous analysis reported that PM_{10} showed a significant association with any mention of nonmalignant respiratory mortality. The adjusted RRs of NMRD mortality for the 43 day/year IQR of $PM_{10(100)}$ and 24.08 $\mu g/m^3$ IQR of PM_{10} mean concentration were 1.18 (95% CI: 1.02, 1.36) and 1.16 (95% CI: 0.97, 1.39), respectively. The relationship was significantly and positively related to mortality in males, but not in females. With our improved model and exclusion of prevalent COPD, we found that the relationship was increased in combined gender NMRD mortality. The updated analysis from NLCS-AIR study (Beelen, et al., 2008) showed positive but non-significant association with BS with RRs of 1.22 (95% CI, 0.99-1.50) for a 10 $\mu g/m^3$ increase of PM_{10} for respiratory mortality in the whole cohort. Our data showed a significant positive association for PM_{10}. It was comparable to the NLCS-AIR study.

The elevated risk of total cancer mortality with PM_{10} in our report is consistent with the findings of others. Comparisons of current results with published findings were limited because a few cancer mortality studies used exposure estimates of PM. NO_x is a surrogate for PM estimates. An increased risk of lung cancer with NO_x was reported in Norwegian men (Nafstad, et al., 2004) and also, an increased risk of breast cancer with suspended particulate matters (SPMs) or converted $PM_{2.5}$ was reported in Japanese women (Iwai, Mizuno, Miyasaka, & Mori, 2005). The European NCLS study (Hoek, et al., 2002) reported that the relative risk increased 15% for cancer death excluding CPD and lung cancer with background BS. In a previous AHSMOG report, $PM_{10(e100)}$, $O_{3(e100)}$, and SO_2 were all significantly associated with increased risk of lung cancer mortality in males, but not in females (Abbey, et al., 1999). The adjusted RRs of lung cancer mortality for the 43 day/yr IQR of $PM_{10\,(e100)}$ were 2.38 (95% CI: 1.42, 3.97) in males and 1.08 (95% CI: 0.55, 2.13) in females. The previous study, however, had lower power. In this analysis, we combined all cancer deaths, but lung and breast cancers were main cancers. We found that exceedance frequencies of PM_{10} over 100 $\mu g/m^3$ showed stronger associated with cancer mortality than PM_{10} mean concentrations and this finding is in line with previous AHSMOG reports for genders combined (Abbey, et al., 1999).

The biologic mechanism for how ambient PM pollution can increase cancer risk is still not clear. However, other epidemiological studies suggest that the risk of cancer is increased in humans with long-term occupational exposure to diesel exhaust particles (DEP) (U.S. EPA, 2002). In addition, chronic inhalation of high concentration of DEP is association with lung tumor formation in rats in a dose-related manner (Iwai, et al., 2000). An indirect genotoxicity pathway was identified by chronic inhalation of carbon black

particles in rats. This secondary genotoxicity pathway involved a particle overload situation resulting in inflammation and proliferation of alveolar epithelial cells. Lung inflammation is known to occur only at a high dose (a threshold effect) (Greim, et al., 2001).

Since different components of air pollution frequently occur together and are highly correlated (Table 4.2), EPA has suggested that the association observed with PM could instead be due to gaseous pollutants (U.S. EPA, 1989). Some significant associations were observed between specific mortality causes, especially NMRD mortality, when gaseous pollutants were added one at a time to form two-pollutant models with $PM_{10.}$ The modifying effect of gases could possibly be explained by findings which indicate that lung epithelial permeability increases with exposure to O_3 (Blomberg, et al., 2003), making the body more susceptible to intrusion of particulate matter.

1. Strengths and Limitations

Our study is one of the few long-term cohort studies with detailed information on residence and work history in a nonsmoking cohort. Thus, we were able to assign ambient air pollution levels accordingly. In the Harvard Six Cities study, exposure was assessed over a longer period, but based on only one air monitoring station in each city or residence. In the ACS study individual exposure was assessed by ZIP code of a metropolitan area. In our study, estimation of ambient air pollution concentrations was done through interpolations from fixed monitoring stations to ZIP code centroids of work and home locations of study participants.

Since all subjects in the AHSMOG study were non-current smokers, our results were free from the confounding of active cigarette smoking. We had detailed information

about ETS and past smoking and were able to adjust for these effects as well. Any modifying effect of alcohol was also eliminated since more than 90% never consumed alcohol. Since the AHSMOG study has extensive information on lifestyle, we were able to adjust for the effects of a number of such factors including dietary factors.

Although we have shown significant effects of ambient air pollution on cancer and non-malignant respiratory mortality, we have unknown amounts of measurement error in both the estimated long-term ambient concentrations of pollutants as well as other covariates. One source of measurement error is due to interpolating ambient concentrations (PM_{10}, O_3, NO_2, and SO_2) from fixed site monitoring stations to ZIP code centroids of work and home locations of study participants (Abbey, Hwang, et al., 1995; Abbey, et al., 1991). Use of ambient concentrations rather than measures of personal exposure could be another limitation in this study. The results from the Particle TEAM (PTEAM) study indicated that the personal exposure was poorly correlated with outdoor ambient concentration (Ozkaynak, et al., 1996). We have not been able to take this into consideration when estimating each subject's ambient air pollution levels. These could bias the results toward the null.

F. Conclusions

In summary, this study found an increased risk of any mention of nonmalignant respiratory mortality associated with ambient levels of PM_{10}. Also, an increased risk of total cancer mortality was found to be associated with ambient levels of PM_{10}. The risk estimates were strengthened when adjusting for gaseous pollutants. Our findings are in line with findings by others for the effects of PM on all cause, cancer, and non-cancer respiratory mortality.

Further studies are needed from larger cohorts and with longer follow-up to support our findings. Developing more accurate ways to assess an individual's exposure to ambient levels of PM will improve precision of risk estimates. Furthermore, it is important to study whether the effects of air pollution are reversible in a similar manner as found when smokers stop smoking.

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Table 4.1 Mortality Distribution by Cause of Death[b]

Cause of Death	ICD Code	Totals (n= 4,830)
All nature cause	ICD9: 001-799; ICD-10: A00-R99	2159 (44.7)
Cardiopulmonary	ICD9: 401-440, 460-519; ICD-10: I10-I70 and J00-J98	1312 (27.2)
CHD	ICD9: 410-414; ICD-10: I20-I25	536 (11.1)
Total cancer	ICD9:140-172, 174-209; ICD-10: C00-C43 and C45-C97	404 (8.4)
NMRD	ICD9:460-519; ICD-10: J00-J98	205 (4.2)

Abbrevations: ICD=International classification of diseases.
[a]Number and percentage of death by causes.
[b]AHSMOG cohort with exclusion of prevalence coronary, stroke, diabetes, cancer, COPD, 1977-2006.

Table 4.2 Selected Characteristics at Baseline[b]

Characteristic	ANC deaths (n=2,195)	Non deaths (n=2,635)	Total (n= 4,830)	
Age (years), mean±SD	66.5 ±11.1	49.5±10.8	57.1±13.8	**
Male Gender	830 (37.8)	920 (34.9)	1750 (36.2)	*
Years of education, mean±SD	13.2 ±3.1	14.1±2.6	13.7±2.9	**
BMI[‡] at or above median	1040 (47.4)	1130 (42.9)	2170 (44.9)	**
Pack-years of smoking for past smokers, mean±SD	17.4 ±21.0	13.6 ±16.7	15.3 ±18.8	*
Hours outdoors per week, mean±SD	12.7 ±11.6	12.2 ±10.8	12.2 ±11.2	
Never smokers	1680 (76.5)	2132 (80.9)	3812 (78.9)	
ETS	1178 (53.7)	1724(65.4)	2902 (60.1)	**
OHE	103 (4.7)	94 (3.6)	197 (4.1)	*
History of hypertension	640 (29.2)	408 (15.5)	1048 (21.7)	**
Total exercise				**
Low	790 (36.0)	1168 (44.3)	1958 (40.5)	
Moderate and high	1344 (61.2)	1499 (56.9)	2843 (58.9)	
Meat consumption[a]				*
< 1 wk	1051 (47.9)	1225 (46.5)	2276 (47.1)	
>=1 wk	970 (44.2)	1341 (50.9)	2311 (47.8)	
Use alcoholic beverages	118 (5.4)	256 (9.7)	374 (7.7)	**
Nuts[a]				**
<=2 /mo	667 (30.4)	937 (35.6)	1604 (33.2)	
1-4/wk	823 (37.5)	1108 (42.0)	1931 (40.0)	
5+/wk	526 (24.0)	519 (19.7)	1045 (21.6)	
Water[a]				**
<=2 glasses/day	241 (11.0)	542 (20.6)	783 (16.2)	
3-4 glasses/day	793 (36.1)	989 (37.5)	1782 (36.9)	
5+ glasses/day	1076 (49.0)	1102 (41.8)	2178 (45.1)	

Abbreviations: SD=Standard deviation; BMI=Body mass index=weight (kg)/height $(m)^2$; ETS=Environmental tobacco smoke from 1977 questionnaire; OHE=Occupational exposure to air pollutants for more than 10 years; HRT=Hormone replacement therapy.
Note. Values are presented as no. (%) or mean±SD
[a]Some columns do not add to 100% because of missing data.
[b]AHSMOG cohort with exclusion of prevalence coronary, stroke, diabetes, cancer, COPD.
*<0.05, **<0.001

Table 4.3 Descriptive Statistics and Correlations between Long-Term Averages of Pollutants Estimated for Study Participants, 1973 through Month of Censoring (n=4,830)[a]

	PM_{10} mc ($\mu g/m^3$)	$PM_{10\ e100}$ (day/year)	O_3 mc (ppb)	$O_{3\ e100}$ (hrs/year)	NO_2 mc (ppb)	SO_2 mc (ppb)
Mean ±SD	51.8 ±15.8	62.1 ±64.4	26.8 ±7.1	27.4 ±24.8	36.0 ±12.9	5.2 ±3.1
PM_{10}	1.00	0.88**	0.69**	0.86**	0.54**	0.43**
$PM_{10\ e100}$		1.00	0.62**	0.85**	0.17**	0.14**
O_3			1.00	0.78**	0.21**	0.15**
$O_{3\ e100}$				1.00	0.41**	0.31**
NO_2					1.00	0.80**
SO_2						1.00

Abbreviations: SD=standard deviation; mc=mean concentration; ppb=parts per billion.
[a]AHSMOG cohort with exclusion of prevalence coronary, stroke, diabetes, cancer, COPD.
** $p<0.01$.

Table 4.4 Adjusted Mortality Relative Risks by Cause of Death in Single-Pollutant Models (n=4,830)

Cause of Death	Pollutant	INC[e]	Cases	RR (95% CI)
All natural cause[a]	PM_{10}	10 μg/m^3	1721	1.01 (0.98-1.04)
(1977-2006)	PM_{10} e100	30 day/yr	1721	**1.04 (1.00-1.09)**
	O_3	10 ppb	1721	0.95 (0.89-1.01)
	O_3 e100	100 hr/yr	1721	1.00 (0.98-1.01)
	NO_2	10 ppb	1719	1.02 (0.98-1.06)
	SO_2	1 ppb	1586	**1.01 (1.00-1.03)**
Cardiopulmonary[b]	PM_{10}	10 μg/m^3	973	1.00 (0.96-1.04)
(1977-2006)	PM_{10} e100	30 day/yr	973	0.99 (0.93-1.06)
	O_3	10 ppb	973	0.92 (0.84-1.00)
	O_3 e100	100 hr/yr	973	0.98 (0.96-1.01)
	NO_2	10 ppb	971	0.99 (0.94-1.05)
	SO_2	1 ppb	935	1.01 (0.98-1.04)
CHD[b]	PM_{10}	10 μg/m^3	412	1.02 (0.96-1.08)
(1977-2006)	PM_{10} e100	30 day/yr	412	1.03 (0.93-1.13)
	O_3	10 ppb	412	0.93 (0.82-1.07)
	O_3 e100	100 hr/yr	412	0.99 (0.95-1.03)
	NO_2	10 ppb	412	1.01 (0.94-1.11)
	SO_2	1 ppb	398	1.04 (0.99-1.09)
Total cancer[c]	PM_{10}	10 μg/m^3	341	1.05 (0.98-1.12)
(1977-2006)	PM_{10} e100	30 day/yr	341	1.08 (0.99-1.20)
	O_3	10 ppb	341	0.98 (0.85-1.13)
	O_3 e100	100 hr/yr	341	1.03 (0.99-1.07)
	NO_2	10 ppb	341	1.04 (0.96-1.12)
	SO_2	1 ppb	314	1.01 (0.98-1.05)

Table 4.4 (continued) Adjusted Mortality Relative Risks by Cause of Death in Single- Pollutant Model (n=4,830)

Cause of Death	Pollutant	INC[e]	Cases	RR (95% CI)
Any mention of nonmalignant Respiratory[d] (1977-2006)	PM_{10}	10 μg/m^3	450	**1.06 (1.00-1.12)**
	PM_{10} e100	30 day/yr	450	1.08 (0.99-1.17)
	O_3	10 ppb	450	0.98 (0.86-1.12)
	O_3 e100	100 hr/yr	450	1.01 (0.98-1.04)
	NO_2	10 ppb	449	1.05 (0.98-1.13)
	SO_2	1 ppb	421	1.02 (0.99-1.06)

Abbreviations: RR=Relative risk; CI=Confidence interval.

[a]Adjusted for years of past smoking, years of education, BMI (below vs. at or above median), calendar month and 80% good data flag for PM_{10} & gaseous, with exclusion of prevalent coronary, stroke, diabetes, cancer, COPD, pollution average 1973-censor date.

[b]Adjusted for years of past smoking, years of education, BMI (below vs. at or above median), calendar month and 80% good data flag for PM_{10} & gaseous, with exclusion of prevalent coronary, stroke, diabetes, cancer, COPD, pollution 4-yr average prior to event date.

[c]Adjusted for years of past smoking, years of education, BMI (below vs. at or above median),ETS, calendar month and 80% good data flag for PM_{10} & gaseous, with exclusion of prevalent coronary, stroke, diabetes, cancer, COPD, pollution average 1973-censor date with 3 yrs lag.

[d]Adjusted for years of past smoking, years of education, BMI (below vs. at or above median), ETS, calendar month and 80% good data flag for PM_{10} & gaseous, with exclusion of prevalent coronary, stroke, diabetes, cancer, COPD, pollution average 1973-censor date.

[e]Rate ratios were calculated for an increment of 10 μg/m^3 for each of the particulate pollutants and 10 ppb for each of the gaseous pollutants, except SO_2 which was calculated for an increment of 1 ppb. Also, an increment of 30 days/year was chosen to calculate rate ratios for PM_{10} above 100 μg/m^3 and an increment of 100 hours/year was used to calculate rate ratios for O_3 above 100 ppb.

Table 4.5 Adjusted Mortality Relative Risks by Cause of Death in Two-Pollutant Models (n=4,830)

Cause of Death	Two Pollutants		INC[e]	Cases	RR (95% CI)
All natural cause[a]	$PM_{10} + O_3$	PM_{10}	10 μg/m^3	1721	**1.04 (1.00-1.09)**
(1977-2006)		O_3	10 ppb		**0.89 (0.81-0.97)**
	PM_{10} e100 + O_3	PM_{10} e100	30 day/yr	1721	1.04 (0.98-1.10)
		O_3	10 ppb		**0.91 (0.84-0.99)**
	$PM_{10} + O_3$ e100	PM_{10}	10 μg/m^3	1721	1.04 (0.98-1.10)
		O_3 e100	100 hr/yr		0.98 (0.95-1.01)
	$PM_{10} + NO_2$	PM_{10}	10 μg/m^3	1719	0.99 (0.95-1.02)
		NO_2	10 ppb		1.02 (0.98-1.07)
	$PM_{10} + SO_2$	PM_{10}	10 μg/m^3	1586	1.01 (0.97-1.05)
		SO_2	1 ppb		1.01 (0.99-1.03)
Cardiopulmonary[b]	$PM_{10} + O_3$	PM_{10}	10 μg/m^3	973	1.03 (0.98-1.08)
(1977-2006)		O_3	10 ppb		**0.88 (0.80-0.98)**
	PM_{10} e100 + O_3	PM_{10} e100	30 day/yr	973	1.03 (0.96-1.11)
		O_3	10 ppb		1.01 (0.99-1.04)
	$PM_{10} + O_3$ e100	PM_{10}	10 μg/m^3	973	**1.07 (1.00-1.14)**
		O_3 e100	100 hr/yr		**0.95 (0.91-0.99)**
	$PM_{10} + NO_2$	PM_{10}	10 μg/m^3	971	1.00 (0.95-1.05)
		NO_2	10 ppb		0.99 (0.92-1.06)
	$PM_{10} + SO_2$	PM_{10}	10 μg/m^3	935	1.00 (0.97-1.05)
		SO_2	1 ppb		1.01 (0.98-1.04)
CHD[c]	$PM_{10} + O_3$	PM_{10}	10 μg/m^3	412	1.05 (0.98-1.13)
(1977-2006)		O_3	10 ppb		0.88 (0.75-1.03)
	PM_{10} e100 + O_3	PM_{10} e100	30 day/yr	412	1.07 (0.95-1.19)
		O_3	10 ppb		0.89 (0.77-1.04)
	$PM_{10} + O_3$ e100	PM_{10}	10 μg/m^3	412	1.09 (0.98-1.20)
		O_3 e100	100 hr/yr		0.95 (0.89-1.01)
	$PM_{10} + NO_2$	PM_{10}	10 μg/m^3	412	1.01 (0.94-1.09)
		NO_2	10 ppb		1.01 (0.91-1.12)
	$PM_{10} + SO_2$	PM_{10}	10 μg/m^3	399	1.02 (0.96-1.09)
		SO_2	1 ppb		1.04 (0.99-1.09)

Table 4.5 (continued) Adjusted Mortality Relative Risks by Cause of Death in Two-Pollutant Models (n=4,830)

Cause of Death	Two Pollutants		INC[e]	Cases	RR (95% CI)
Total cancer[c] (1977-2006)	PM_{10} + O_3	PM_{10}	10 μg/m^3	341	**1.10 (1.01-1.21)**
		O_3	10 ppb		0.84 (0.69-1.03)
	PM_{10} e100 + O_3	PM_{10} e100	30 day/yr	341	**1.16 (1.03-1.31)**
		O_3	10 ppb		0.85 (0.71-1.03)
	PM_{10} + O_3 e100	PM_{10}	10 μg/m^3	341	1.00 (0.89-1.13)
		O_3 e100	100 hr/yr		1.03 (0.96-1.10)
	PM_{10} + NO_2	PM_{10}	10 μg/m^3	341	1.04 (0.96-1.12)
		NO_2	10 ppb		1.01 (0.93-1.11)
	PM_{10} + SO_2	PM_{10}	10 μg/m^3	315	1.06 (0.98-1.15)
		SO_2	1 ppb		1.00 (0.97-1.04)
Any mention of nonmalignant respiratory[d] (1977-2006)	PM_{10} + O_3	PM_{10}	10 μg/m^3	450	**1.13 (1.04-1.22)**
		O_3	10 ppb		**0.82 (0.68-0.98)**
	PM_{10} e100 + O_3	PM_{10} e100	30 day/yr	450	**1.14 (1.02-1.27)**
		O_3	10 ppb		0.86 (0.73-1.02)
	PM_{10} + O_3 e100	PM_{10}	10 μg/m^3	450	**1.15 (1.03-1.29)**
		O_3 e100	100 hr/yr		0.95 (0.89-1.01)
	PM_{10} + NO_2	PM_{10}	10 μg/m^3	449	1.05 (0.98-1.13)
		NO_2	10 ppb		1.02 (0.93-1.11)
	PM_{10} + SO_2	PM_{10}	10 μg/m^3	421	1.06 (0.99-1.14)
		SO_2	1 ppb		1.01 (0.97-1.05)

Abbreviations: RR= Relative risk; CI= Confidence interval.

[a]Adjusted for years of past smoking, years of education, BMI (below vs. at or above median), calendar month and 80% good data flag for PM_{10} & gaseous, with exclusion of prevalent coronary, stroke, diabetes, cancer, COPD, pollution average 1973-censor date.

[b]Adjusted for years of past smoking, years of education, BMI (below vs. at or above median), calendar month and 80% good data flag for PM_{10} & gaseous, with exclusion of prevalent coronary, stroke, diabetes, cancer, COPD, pollution 4-yr average prior to event date.

[c]Adjusted for years of past smoking, years of education, BMI (below vs. at or above median),ETS, calendar month and 80% good data flag for PM_{10} & gaseous, with exclusion of prevalent coronary, stroke, diabetes, cancer, COPD, pollution average 1973-censor date with 3 yrs lag.

[d]Adjusted for years of past smoking, years of education, BMI (below vs. at or above median), ETS, calendar month and 80% good data flag for PM_{10} & gaseous, with exclusion of prevalent coronary, stroke, diabetes, cancer, COPD, pollution average 1973-censor date.

[e]Rate ratios were calculated for an increment of 10 μg/m^3 for each PM, 10 ppb for each of O_3 or NO_2, and 1 ppb for each of SO_2. Also, an increment of 30 days/year was chosen to calculate rate ratios for PM_{10} e100 and an increment of 100 hours/year was used to calculate rate ratios for O_3 e100.

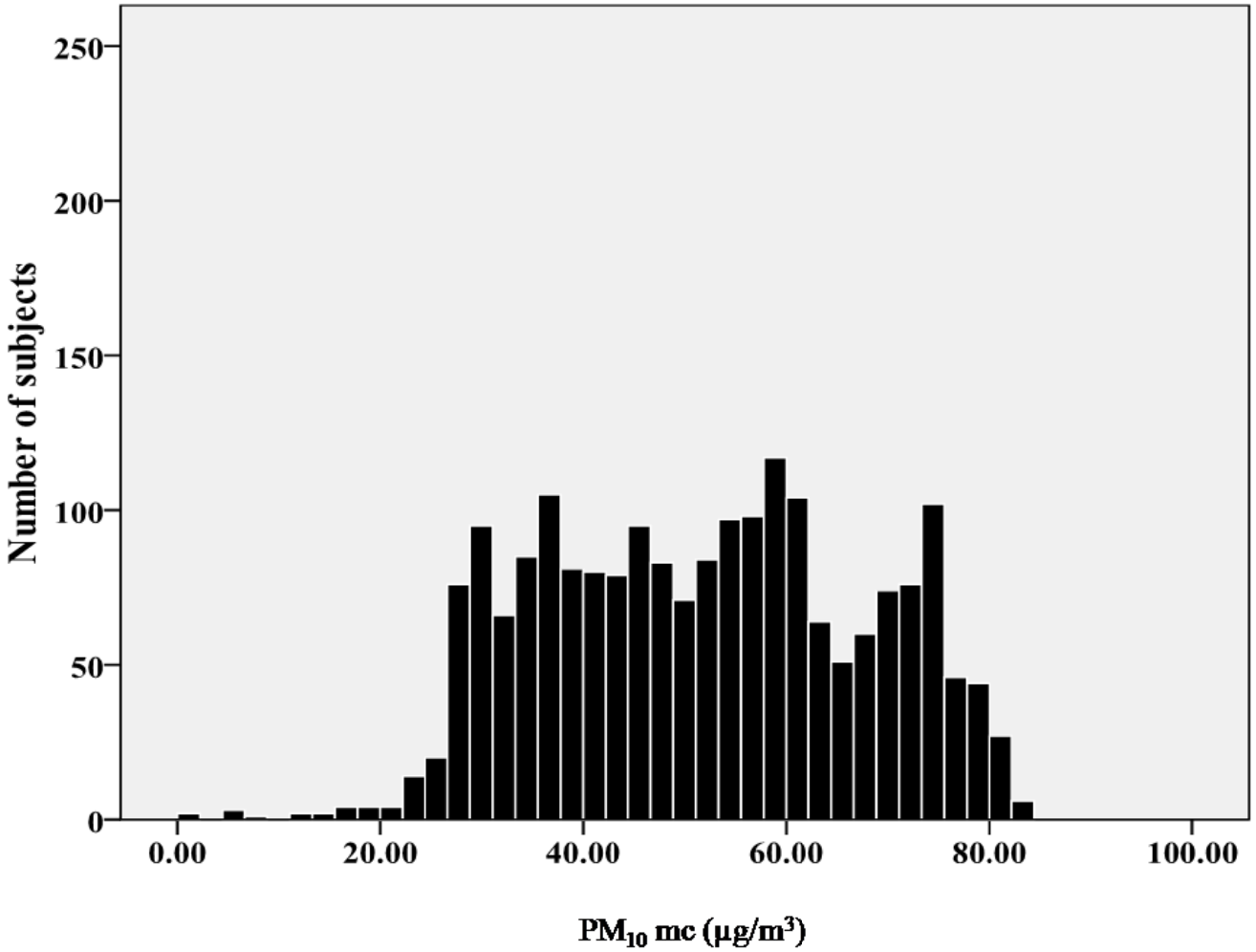

Figure 4.1 Frequency Distribution of Mean Ambient Concentration of PM_{10}, 1973-Censoring Month (n=4,830)

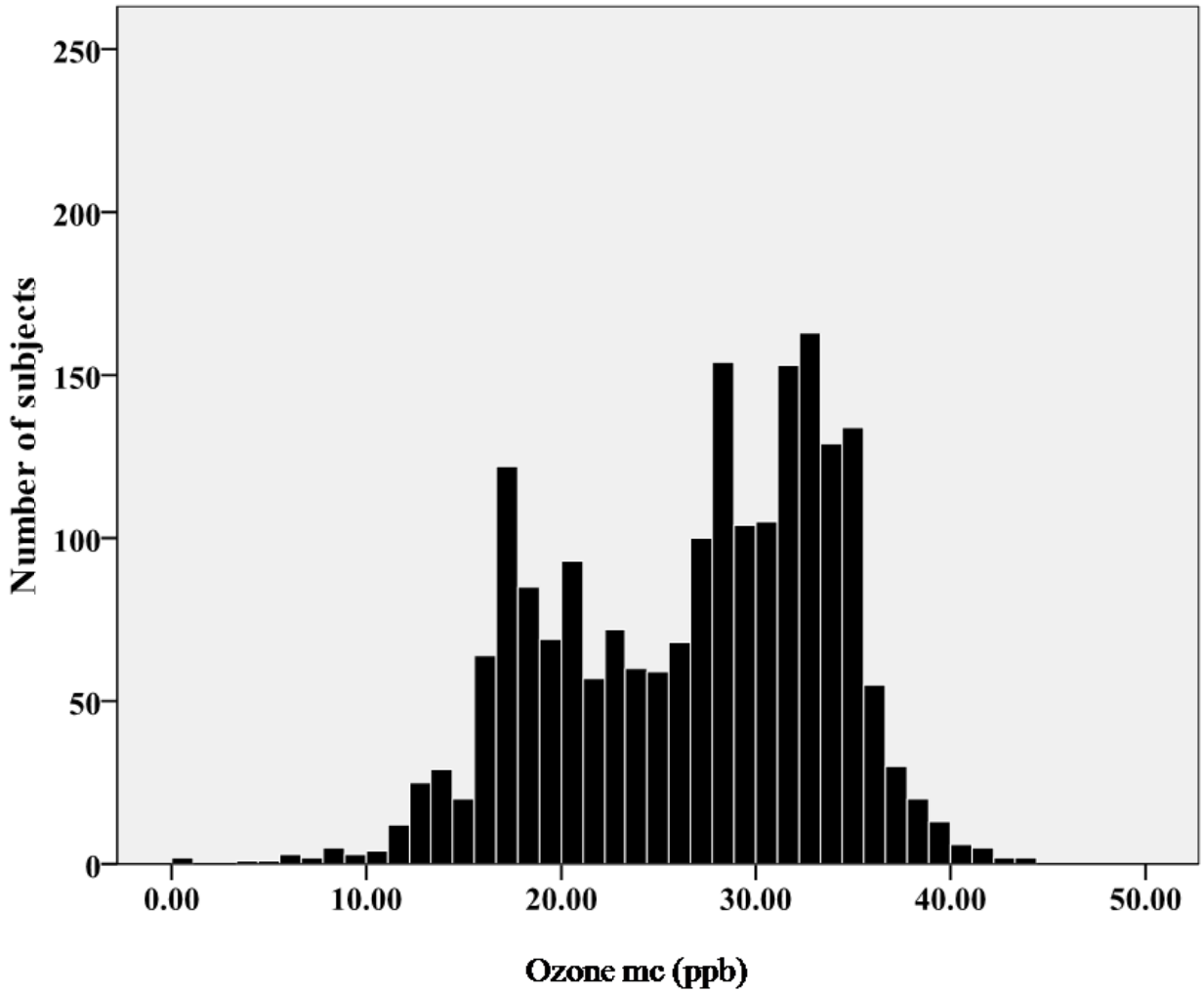

Figure 4.2 Frequency Distribution of Mean Ambient Concentration of O_3, 1973-Censoring Month (n=4,830)

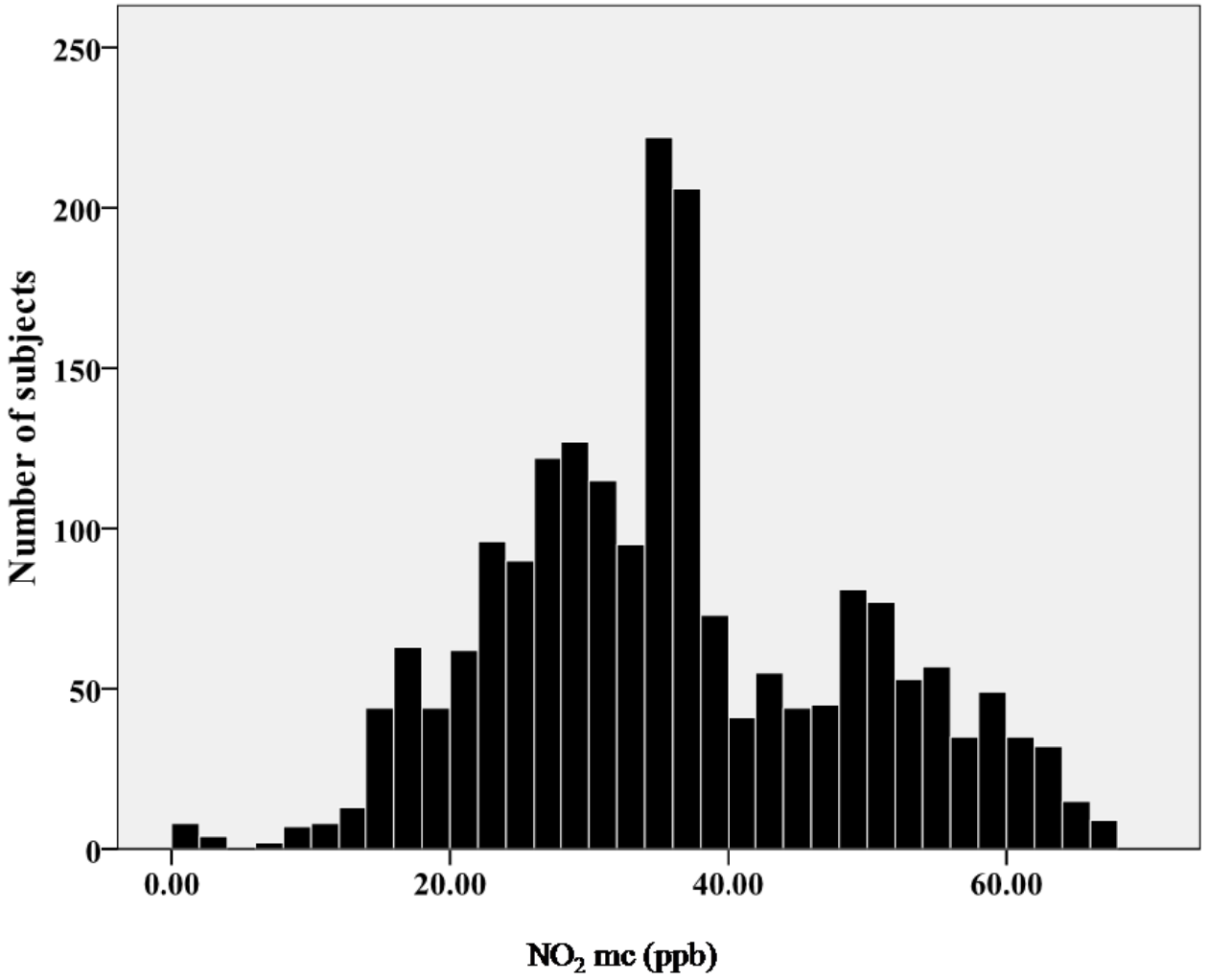

Figure 4.3 Frequency Distribution of Mean Ambient Concentration of NO_2, 1973-Censoring Month (n=4,830)

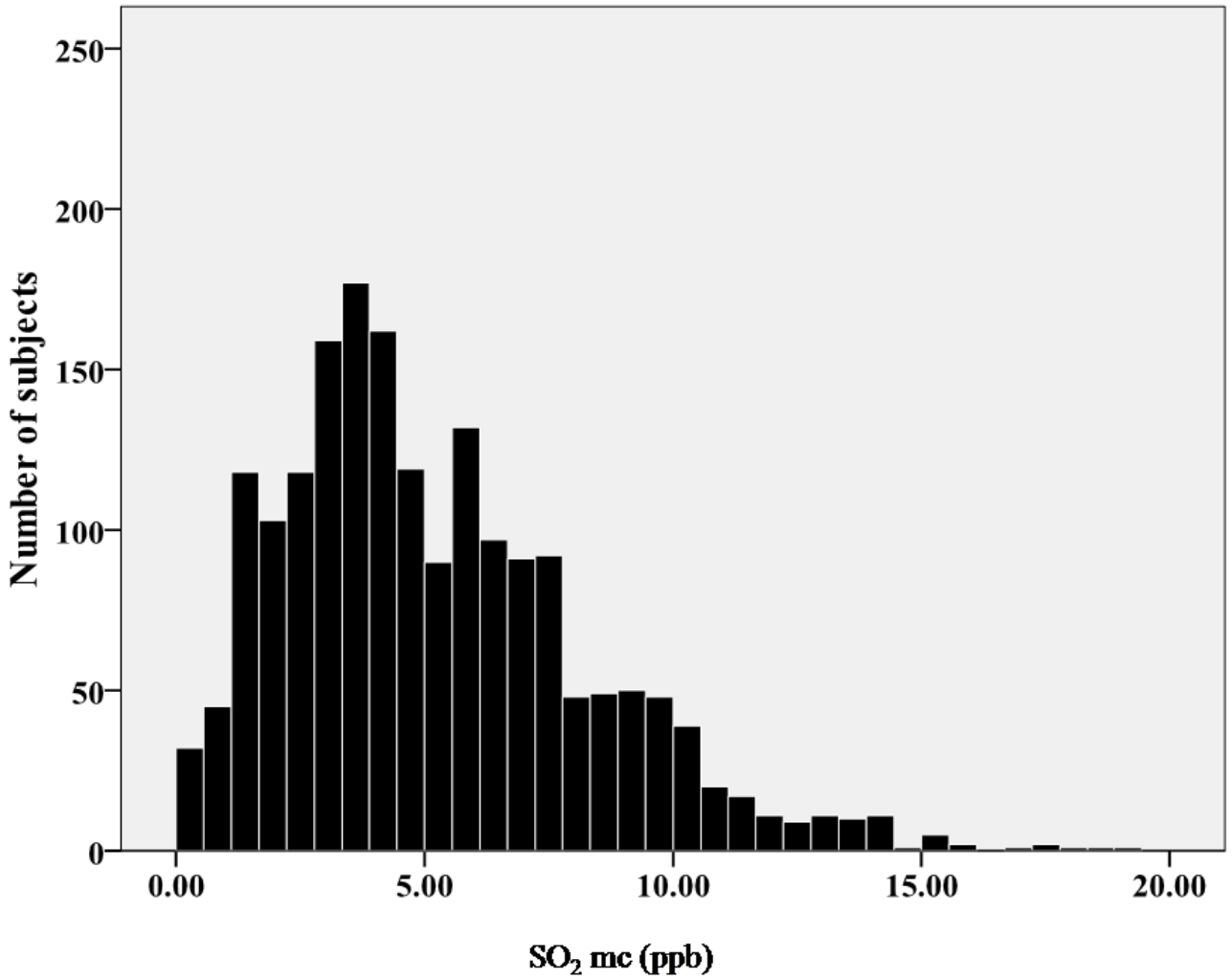

Figure 4.4 Frequency Distribution of Mean Ambient Concentration of SO_2, 1973-Censoring Month (n=4,830)

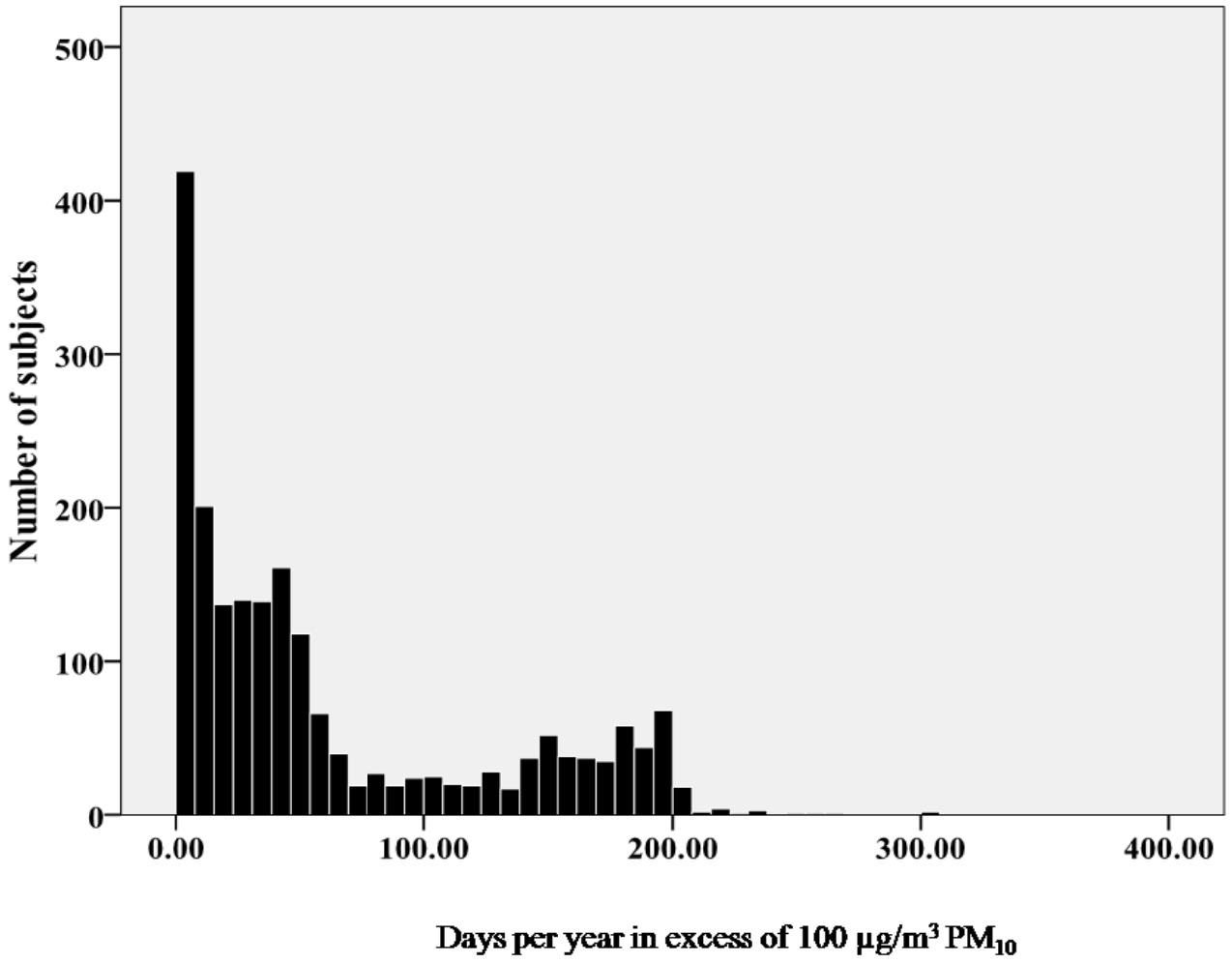

Figure 4.5 Frequency Distribution of Days per Year in Excess of 100 µg/m^3 PM_{10}, 1973-Censoring Month (n=4,830)

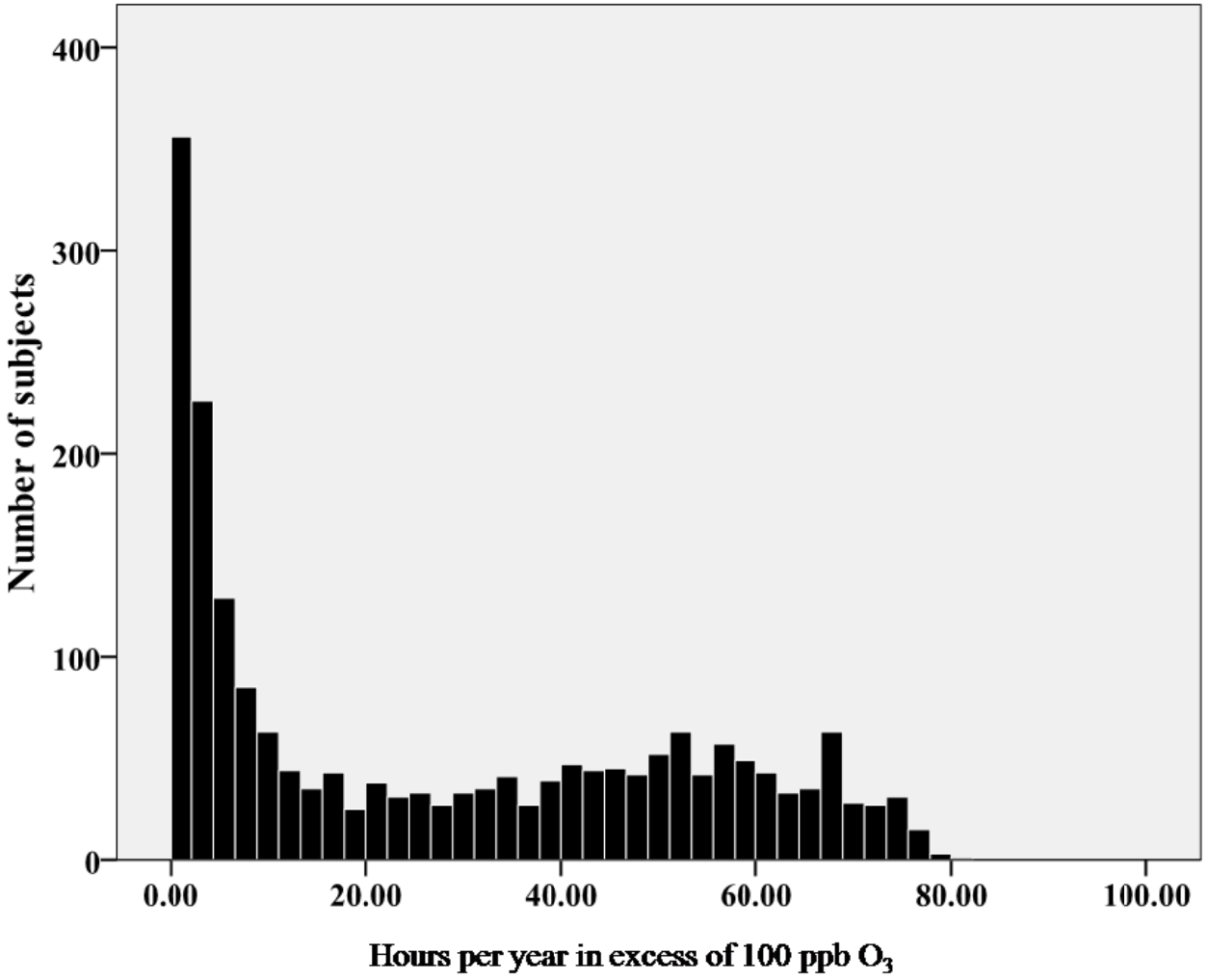

Figure 4.6 Frequency Distribution of Hours per Year in Excess of 100 ppb O_3, 1973-Censoring Month (n=4,830)

CHAPTER 5

OTHER FINDINGS

A. Introduction

The risks of mortality and morbidity are increased with increased concentrations of particulate air pollution. However, not all groups of people respond to ambient particulate matter (PM) in the same way (Goldberg, et al., 2000; Goldberg, et al., 2001; Kwon, et al., 2001; Kwon, Lee, Jee, Lee, & Hwang, 2007; Mann, et al., 2002; Peters, et al., 2001; Sunyer, et al., 2000; Ulirsch, et al., 2007; Zanobetti & Schwartz, 2001, 2002; Zanobetti, Schwartz, & Dockery, 2000)

Several studies have reported that people with chronic obstructive pulmonary disorder (Sunyer, et al., 2000), conduction disorder (Mann, et al., 2002; Zanobetti, Schwartz, & Gold, 2000), congestive heart failure (Goldberg, et al., 2000; Kwon, et al., 2001; Mann, et al., 2002), diabetes (Brook, et al., 2008; Goldberg, et al., 2000; Goldberg, et al., 2006; Zanobetti & Schwartz, 2001, 2002; Zanobetti, Schwartz, & Gold, 2000) and myocardial infarction (Peters, et al., 2001) are at greater risk of adverse events associated with air pollution, especially with particulate matter.

Individuals with systemic disease, such as cardiac disease and diabetes may be susceptible to the short term effects of air pollution (Goldberg, et al., 2001). To identify the susceptible subgroups at risk may provide information regarding mechanisms and could have importance for public health purposes to reduce exposure for certain subgroups. In this study, we have focused on the risk of coronary heart disease (CHD)

deaths associated with long term ambient particulate air pollution in specific susceptible subgroups.

B. Materials and Methods

1. Study Population

The AHSMOG study began in April 1977 by enrolling 6,338 participants from the Adventist Health Study (AHS) (n= 34,198), a large cohort study of the relationship between lifestyle and risk of chronic disease (Beeson, et al., 1989). To be included in the AHSMOG study, subjects must be nonsmoking, non-Hispanic whites aged 25 years or older at baseline and must have lived 10-years or longer within 5 miles of their 1976 neighborhood. All subjects satisfying these criteria were selected from three large metropolitan air basins in California - San Francisco, South Coast, and San Diego air basins. In addition, a 13% random sample of 862 AHS subjects was selected from the rest of California. This wide geographic spread of study subjects has assured large variation and wide ranges in concentrations of different ambient air pollutants.

As part of their enrollment in the AHS in 1976, all participants completed a comprehensive questionnaire which included questions on years of education, anthropometric data, past and current cigarette smoking, current and past dietary habits, exercise patterns, and previous physician diagnosed chronic diseases (Beeson, et al., 1989). Monthly residence and work location histories were obtained for each subject for the period January 1966 through December 1998 or until date of death or date of last contact by using mailed questionnaires (1977, 1987, 1992, 2000), tracing by telephone, and interviewing of surrogates (for deceased subjects). Only 29 (< 0.01%) persons were lost to follow-up with respect to vital status and these were censored at date of last

contact for purposes of inclusion in risk sets. The follow-up questionnaires contained standardized questions on respiratory symptoms, now included as part of the American Thoracic Society (ATS) questionnaire (American Thoracic Society, 1995), and questions to ascertain lifestyle and housing characteristics pertinent to relative exposure to ambient air pollutants as well as occupational exposures to dust and fumes and indoor sources of air pollution, including environmental tobacco smoke (ETS).

2. Definition of Sensitive Groups

Five potential sensitive groups were identified: elderly, those with prevalent CHD, prevalent diabetes, prevalent COPD, and past smokers. The age group included subjects who were 65 years or old at baseline or reached this age anytime during follow-up. The CHD group was defined as those subjects who reported having ever had any heart attack or myocardial infarction (MI), and/or CHD at baseline, ever had a heart attack or myocardial infarction before ’82 from hospital records, or ever had a heart attack or MI on the 1987, and 2000 follow-up questionnaires. The diabetes group was defined as those subjects who reported having diabetes at baseline. The COPD group was defined as those subjects who reported having any symptoms of asthma, bronchial condition, or emphysema on the ’77, ’87, ’92, or 2000 questionnaires. The smoking group was defined as those subjects who reported ever having regularly smoked cigarettes, cigars, or a pipe on the ’76, ’77, ‘87, ‘92, ’93 or 2000 questionnaires. The subjects only contributed to the follow-up from the time they indicated having the disease in the questionnaire.

3. Estimation of Ambient Air Pollution Concentrations

Estimates of monthly ambient concentrations of PM less than 10 μm in diameter (PM_{10}), ozone (O_3), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2) were formed for study participants for 1973-1998 using fixed site monitoring stations maintained by California Air Resources Board (CARB). The detailed methods for estimating ambient air pollutants for study participants are described elsewhere (Abbey, Hwang, Burchette, Vancuren, & Mills, 1995; Abbey, et al., 1991). Briefly, monthly indices of ambient air pollutant concentrations at 348 monitoring stations throughout California were interpolated to geographic ZIP code centroids according to home and work location histories of study participants. These were cumulated and then averaged over time. Interpolations were restricted to ZIP code centroids within 50 km of a monitoring station and were not allowed to cross barriers to airflow or other topographic obstructions in excess of 250 m above the surrounding terrain. Concentrations of PM_{10} prior to 1987 were estimated using site- and season-specific regressions based on total suspended particles (TSP) (Abbey, Hwang, et al., 1995). Since 1987, directly monitored PM_{10} has been used.

4. Ascertainment of Deaths

Fatal CHD, defined by codes 410-414 of the International Classification of Diseases, 9th Revision (ICD-9) (World Health Organization, 1977) as either "definite fatal myocardial infarction" or "other definite fatal CHD" as underlying or immediate cause of death was used to assess fatal CHD.

Deaths were ascertained through 1998 using record linkage with both the

California death certificate files and the National Death Index. In addition, our tracing procedures, which included church records, were used (Beeson, et al., 1989). Death certificates were obtained, and a state-certified nosologist, blinded to the exposure status, coded each death certificate according to the ICD-9 codes.

5. Statistical Analysis

For each sensitive subgroup, gender specific time dependent Cox proportional-hazards regression modeling was used to study associations between pollutants (PM_{10}, O_3, and NO_2, and SO_2) and CHD mortality with attained age as the time variable (Greenland, 1989). Rate ratios were calculated for an increment of 10 $\mu g/m^3$ for each of the particulate pollutants and 10 ppb for each of gaseous pollutants, except SO_2 which was calculated for an increment of 1 ppb. A moving 4-year average of the ambient air pollutant level for the period directly preceding the event with a 1 month lag was used as the exposure variable. Last month before event was excluded to avoid measuring short-term effects. Participants who did not die were censored at the end of the follow-up or at time of last contact if they were lost to follow-up. The different pollutants were entered into the model as continuous variables.

The basic multivariable model included past pack-years of cigarette smoking, body mass index (BMI), and years of education for all the sensitive groups, except the smoker group. Additional candidate variables for inclusion in the final model were ETS (years lived or worked with a smoker), total physical activity at baseline, history of hypertension at baseline, exposure to dust/fumes at work, frequency of eating nuts (Fraser, Sabate, Beeson, & Strahan, 1992), number of glasses of water per day (Chan, Knutsen,

Blix, Lee, & Fraser, 2002), time spent outdoors, frequency of meat consumption (< 1/wk vs. 1+/wk), water and nut consumption, and hormone replacement therapy (HRT). These were entered into the basic multivariable model one at a time to assess their impact on the main effect. None of the candidate variables changed the air pollutant RR's more than 10% and were therefore not included in the final model (Greenland, 1989). The basic multivariable model for the smoking group included past pack-years of cigarette smoking, body mass index (BMI), years of education, and ETS. In addition, we found that the levels of PM pollutants used in this study have declined from 1973 to 1998 (Chen, et al., 2005) and we therefore included calendar time as a candidate variable to adjust for possible changes in PM composition over time.

The proportional hazards assumption was checked by examining Log[-log(survival)] curves versus time as well as the product term of each respective variable in the final model with the log of the time variable (Greenland, 1989). Each of these interaction terms produced a p-value greater than 0.05 based on the Wald statistic, indicating that the proportional hazards assumptions were not seriously violated. This was supported further by visual inspection.

The same gender specific, time dependent multivariable Cox proportional-hazards regression models were further used to study associations in two-pollutant models for PM_{10} with each of the gases (O_3, and NO_2, and SO_2) for mortality from broad categories of causes. The interactions between two individual pollutants were evaluated for inclusion in the final model based on whether they changed the RR's more than 10%. None of the terms met this criterion (Greenland, 1989).

C. Results

Table 5.1 shows the numbers and percentages of gender specific CHD deaths in sensitive subgroups between 1977 and 1998 in the AHSMOG cohort. Until the end of 1998, there were 644 fatal CHD cases (398 males and 246 females). Baseline characteristics of the study population are given in Table 5.2. The mean concentrations of pollutants (PM_{10}, gaseous) in the AHSMOG cohort, as well as the correlation of pollutants from 1973 through the month of censoring are provided in Table 5.3. The correlation of PM_{10} with O_3 was stronger than those with NO_2 and SO_2.

1. Age Group

The adjusted mortality RRs for the single pollutant models (PM_{10}, O_3, NO_2, and SO_2) and for two pollutant models (PM_{10} and gaseous pollutants) are presented in Table 5.4. Covariates included in the models are smoking status, education, BMI, and calendar month. For males, in single pollutant model, the RR for fatal CHD for each increment of 10 $\mu g/m^3$ increase in PM_{10} was 1.07 (95% CI: 0.99-1.17). In two-pollutant models with gaseous pollutants (Table 5.4), no significant association between fatal CHD and PM_{10} was observed. The association was even weaker and showed no statistical significance by comparing it to the single-pollutant model. For females, no significant association was found either in single or two-pollutant models (Table 5.4). In males, the associations among subjects younger than 65 years were similar to those in elderly group. The adjusted mortality RRs was similar but with wide confidence interval. In females, the adjusted mortality RRs are larger with similar wide confidence intervals (Figure 5.1).

Table 5.1 CHD Mortality[a] and Sensitive Groups, 1977-1998 (n=6,338)

Cause of Death	Male		Female		Total	
Group	Total	Cases (%)	Total	Cases (%)	Total	Cases (%)
AHSMOG	2,278	246 (10.8)	4,060	398 (9.8)	6,338	644 (10.2)
Age	1,976	245 (12.4)	3,457	395 (11.4)	5,433	640 (11.8)
CHD	202	104 (51.5)	281	121 (43.1)	483	225 (46.6)
Diabetes	132	29 (22.0)	239	57 (23.8)	371	86 (23.2)
COPD	303	35 (11.6)	608	61 (10.0)	911	96 (10.5)
Smoking	711	84 (11.8)	490	31 (6.3)	1,201	115 (9.6)

Abbreviations: ICD=International classification of diseases.
Note. Age, age 65 years or old during study period; CHD, ever diagnosed having heart attack or coronary heart disease during the study period; Diabetes, reported having diabetes at baseline; COPD, reported having symptoms of asthma, some kind of bronchial condition, or emphysema during follow-up; Past Smoking, reported ever having regularly smoked cigarettes, cigars, or a pipe during study period.
[a]ICD9: 410-414

Table 5.2 Selected Characteristics at Baseline (n=6,338)

Characteristic	Males (n= 2,278)	Females (n= 4,060)	
Age (years), mean±SD	58.5 ± 13.5)	59.2 ±14.2)	
Years of education, mean±SD	14.3 ±3.3)	13.1 ±2.6)	**
Pack-years of past smoking, mean±SD	19.8 ±23.2)	11.3 ±14.7)	**
Hours outdoors per week, mean±SD	17.5 ±13.5)	9.0 ± (8.2)	**
BMI‡ at or above median	1050 (46.1)	1858 (45.8)	
ETS	1292 (56.7)	2498 (61.5)	**
OHE	234 (10.3)	15 (0.4)	**
History of hypertension	474 (20.8)	1149 (28.3)	**
History of cancer	87 (3.8)	291 (7.2)	**
Total exercise			**
Low	687 (29.8)	1885 (46.4)	
Moderate and high	1579 (69.3)	2143 (52.8)	
Meat consumption[a]			
< 1 wk	1032 (45.3)	1901 (46.8)	
>=1 wk	1147 (50.3)	1909 (47.0)	
Nuts[a]			**
<=2 /mo	699 (30.7)	1436 (35.4)	
1-4/wk	914 (40.1)	1516 (37.3)	
5+/wk	561 (24.6)	844 (20.8)	
Water[a]			**
<=2 glasses	278 (12.2)	693 (17.1)	
3-4 glasses	813 (35.7)	1503 (37.0)	
5+ glasses	1139 (50.5)	1780 (43.8)	
Postmenopausal		2897 (71.4)	
HRT in postmenopausal females		850 (29.3)	

Abbreviations: SD=standard deviation; BMI=body mass index=weight (kg)/height $(m)^2$;
ETS=Environmental tobacco smoke from 1977 questionnaire; OHE=Occupational exposure to air pollutants for more than 10 years; HRT=Hormone replacement therapy.
Note. Values are presented as no. (%) or mean±SD
[a]Some columns do not add to 100% because of missing data.
*p-value for t-test or chi-square test <0.05
**p-value for t-test or chi-square test <0.005

Table 5.3 Descriptive Statistics and Correlations between Long-term Averages of Pollutants Estimated for Study Participants, 1973 through Month of Censoring (n=6,338)

	PM_{10} mc ($\mu g/m^3$)	O_3 mc (ppb)	NO_2 mc (ppb)	SO_2 mc (ppb)
Mean (SD)	51.2 (15.3)	26.9 (6.7)	35.6 (12.6)	4.9 (2.9)
PM_{10}	1.00	0.67**	0.55**	0.42**
O_3		1.00	0.19**	0.12**
NO_2			1.00	0.78**
SO_2				1.00

Abbreviations: mc=mean concentration, SD=standard deviation.
** $p<0.01$.

Table 5.4 Risk of CHD Mortality According to 10 μg/m^3 of PM_{10} in the Different Sensitive Subgroups (n=6338)

			Females			Males		
Model	Pollutants		Cases	RR[a]	95% CI	Cases	RR[a]	95% CI
AHSMOG[b]	PM10		321	1.04	0.97-1.11	197	1.08	0.99-1.17
	O_3		321	1.00	0.87-1.16	197	1.18	0.99-1.41
	NO_2		321	1.02	0.94-1.12	197	1.09	0.99-1.21
	SO_2		308	0.97	0.92-1.01	189	1.03	0.98-1.08
	PM_{10}+O_3	PM_{10}	321	1.06	0.98-1.15	197	1.04	0.94-1.15
		O_3		0.93	0.78-1.12		1.12	0.90-1.41
	PM_{10}+NO_2	PM_{10}	321	1.04	0.96-1.13	197	1.05	0.95-1.16
		NO_2		0.99	0.89-1.10		1.06	0.94-1.20
	PM_{10}+SO_2	PM_{10}	308	1.05	0.98-1.13	189	1.06	0.97-1.16
		SO_2		0.96	0.92-1.01		1.02	0.97-1.08
Sensitive Subgroups:								
Age[c]	PM_{10}		310	1.03	0.97-1.11	182	1.07	0.99-1.17
	O_3		310	1.00	0.86-1.16	182	1.16	0.97-1.40
	NO_2		310	1.00	0.92-1.10	182	1.08	0.97-1.20
	SO_2		297	**0.95**	**0.91-1.00**	176	1.03	0.98-1.09
	PM_{10}+O_3	PM_{10}	310	1.05	0.97-1.14	182	1.04	0.94-1.16
		O_3		0.94	0.79-1.13		1.10	0.87-1.39
	PM_{10}+NO_2	PM_{10}	310	1.05	0.96-1.14	182	1.05	0.95-1.17
		NO_2		0.97	0.87-1.08		1.04	0.91-1.18
	PM_{10}+SO_2	PM_{10}	297	1.05	0.98-1.13	176	1.05	0.96-1.15
		SO_2		**0.95**	**0.90-0.99**		1.03	0.97-1.08

Table 5.4 (continued) Risk of CHD Mortality According to 10 μg/m^3 of PM_{10} in the Different Sensitive Subgroups (n=6338)

			Females			Males		
Model	Pollutants		Cases	RR[a]	95% CI	Cases	RR[a]	95% CI
CHD[d]	PM_{10}		97	1.06	0.94-1.21	83	**1.15**	**1.01-1.31**
	O_3		97	1.07	0.81-1.42	83	1.26	0.96-1.66
	NO_2		97	1.10	0.94-1.28	83	1.08	0.92-1.26
	SO_2		95	1.01	0.93-1.08	79	1.04	0.96-1.13
	PM_{10}+O_3	PM_{10}	97	1.06	0.92-1.24	83	1.12	0.95-1.31
		O_3		1.00	0.82-1.39		1.11	0.78-1.57
	PM_{10}+NO_2	PM_{10}	97	1.03	0.88-1.20	83	**1.16**	**1.00-1.35**
		NO_2		1.07	0.89-1.30		0.97	0.80-1.18
	PM_{10}+SO_2	PM_{10}	95	1.02	0.89-1.17	79	**1.16**	**1.01-1.33**
		SO_2		1.00	0.93-1.08		1.03	0.94-1.12
Diabetes[e]	PM_{10}		50	0.99	0.84-1.18	24	**1.50**	**1.15-1.96**
	O_3		50	1.19	0.83-1.72	24	1.60	0.95-2.69
	NO_2		50	1.00	0.80-1.23	24	**1.52**	**1.10-2.08**
	SO_2		48	0.98	0.88-1.09	23	1.00	0.87-1.15
	PM_{10}+O_3	PM_{10}	50	0.91	0.74-1.13	24	**1.54**	**1.08-2.20**
		O_3		1.32	0.86-2.05		0.92	0.42-2.01
	PM_{10}+NO_2	PM_{10}	50	0.99	0.80-1.23	24	1.37	0.99-1.89
		NO_2		1.00	0.77-1.31		1.25	0.85-1.85
	PM_{10}+SO_2	PM_{10}	48	1.00	0.83-1.20	23	**1.52**	**1.17-1.99**
		SO_2		0.98	0.87-1.09		0.91	0.76-1.08

Table 5.4 (continued) Risk of CHD Mortality According to 10 μg/m^3 of PM_{10} in the Different Sensitive Subgroups (n=6338)

			Females			Males		
Model	Pollutants		Case	RR[a]	95% CI	Case	RR[a]	95% CI
COPD[f]	PM_{10}		77	1.11	0.95-1.28	37	1.00	0.82-1.24
	O_3		77	0.93	0.68-1.27	37	1.16	0.74-1.80
	NO_2		77	1.12	0.93-1.36	37	1.05	0.82-1.35
	SO_2		75	1.02	0.92-1.13	37	1.02	0.91-1.15
	PM_{10}+O_3	PM_{10}	77	1.18	0.99-1.41	37	0.96	0.75-1.22
		O_3		0.76	0.52-1.13		1.21	0.73-2.03
	PM_{10}+NO_2	PM_{10}	77	1.08	0.90-1.29	37	0.97	0.75-1.26
		NO_2		1.07	0.85-1.35		1.07	0.79-1.45
	PM_{10}+SO_2	PM_{10}	75	1.10	0.94-1.28	37	0.96	0.77-1.19
		SO_2		1.02	0.91-1.13		1.02	0.91-1.15
Smoking[g]	PM_{10}		33	1.11	0.88-1.40	84	**1.13**	**1.00-1.28**
	O_3		33	0.93	0.60-1.44	84	1.18	0.91-1.53
	NO_2		33	1.09	0.83-1.43	84	1.13	0.96-1.32
	SO_2		32	1.00	0.87-1.14	82	1.00	0.93-1.09
	PM_{10}+O_3	PM_{10}	33	1.17	0.90-1.53	84	1.13	0.97-1.32
		O_3		0.79	0.46-1.35		1.01	0.72-1.41
	PM_{10}+NO_2	PM_{10}	33	1.10	0.82-1.46	84	1.12	0.96-1.30
		NO_2		1.02	0.73-1.44		1.04	0.85-1.27
	PM_{10}+SO_2	PM_{10}	32	1.11	0.88-1.41	82	1.11	0.97-1.26
		SO_2		0.98	0.85-1.13		0.99	0.91-1.07

[a]RR use 10 increment (except for SO_2 the increment is 1 ppb)
[b]AHOSMOG whole group, adjusted for past smoking, education, BMI
[c]Ever 65 years and older during the study, adjusted for past smoking, education, BMI
[d]Ever diagnosed having heart attack or MI, during the study period, and/or CHD at baseline. Adjusted for smoking, education, BMI[e]Ever diagnosed having diabetes at baseline. Adjusted for years of past smoking, years of education, BMI
[f]Reported having symptoms of asthma, some kind of bronchial condition, or emphysema on one of the 4 follow-up questionnaires (‘77, ’87, ’92, ‘2000). Adjusted for years of past smoking, education, BMI
[g]Reported ever regularly smoked on one of the 4 follow-up questionnaires (’76, ‘77, ’87, ’92, ’93, 2000). Adjusted for education, BMI, ETS

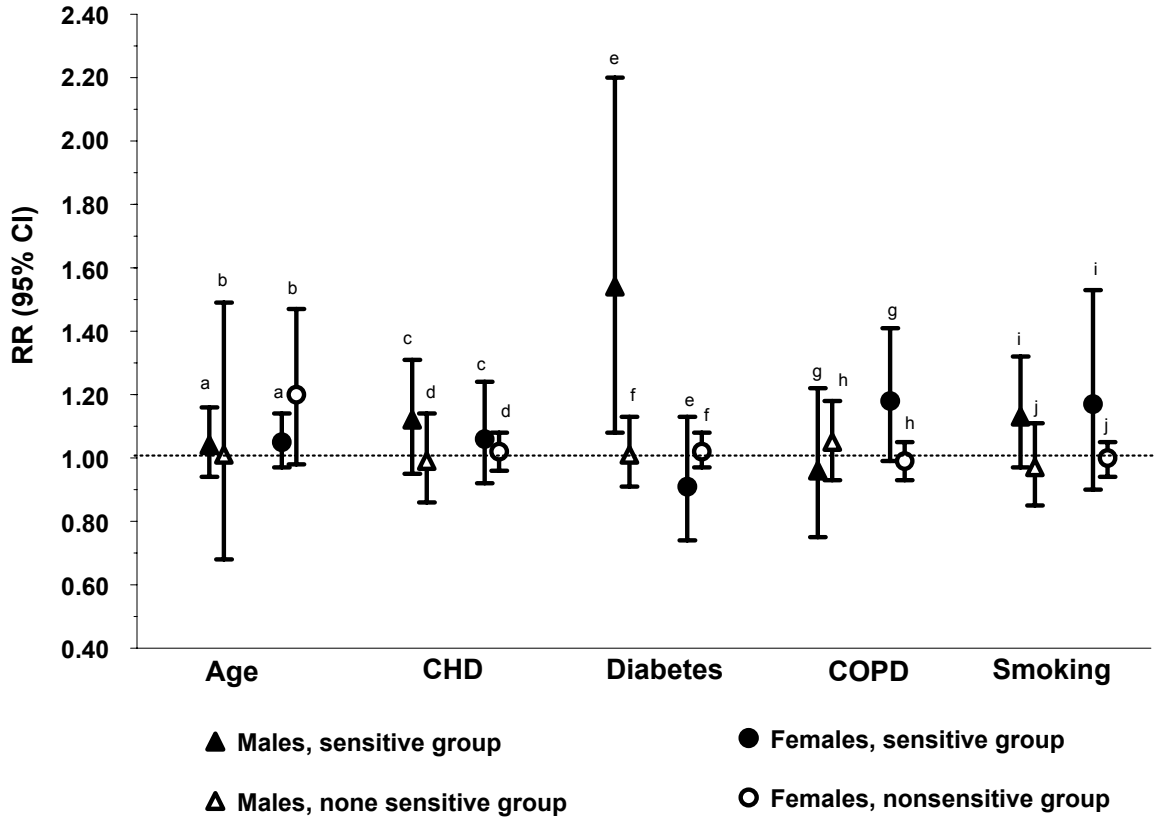

Figure 5.1. Adjusted Relative Risk Ratios and 95% CIs for Fatal CHD and PM_{10} Mean Concentration in Two-Pollutant Models (PM_{10}+ O_3) in Sensitive Groups.

[a]Ever 65 years and older during the study (females=3457, males=1976).
[b]65 years and younger during the study (females=603, males=302).
[c]Ever diagnosed having heart attack or MI, during the study period, and/or CHD at baseline (females=281, males=202).
[d]Never diagnosed having heart attack or MI, during the study period, and/or CHD at baseline (females=3779, males=2076).
[e]Ever diagnosed having diabetes at baseline (females=239, males=132).
[f]Never diagnosed having diabetes at baseline (females=3821, males=2146).
[g]Reported having symptoms of asthma, some kind of bronchial condition, or emphysema on one of the 4 follow-up questionnaires (‘77, ’87, ’92, ‘2000) (females=608, males=303).
[h]Never reported having symptoms of asthma, some kind of bronchial condition, or emphysema on one of the 4 follow-up questionnaires (‘77, ’87, ’92, ‘2000 (females=3452, males=1975).
[i]Report ever regularly smoked on one of the 4 follow-up questionnaires (’76, ‘77, ’87, ’92, ’93, 2000) (females=490, males=711).
[j]Never report regularly smoked on one of the 4 follow-up questionnaires (’76, ‘77, ’87, ’92, ’93, 2000) (females=3570, males=1567).

2. CHD Group

The adjusted mortality RRs for single pollutant models (PM_{10}, O_3, NO_2, and SO_2) and for two pollutant models (PM_{10} and gaseous pollutants) are presented in Table 5.4. Covariates included in the models are smoking status, education, BMI, and calendar month. In single pollutant models, a significant and positive relationship was found with PM_{10} in males, but not in females. For males, in the single pollutant model, the RR of CHD mortality for 10 micrograms/m^3 increase in PM_{10} was 1.15 (95% CI: 1.01-1.31). In two pollutant model with ozone, the association became weaker and was no longer statistically significant [1.12 (95% CI: 0.95-1.31)]. The two pollutant models with other gases, (NO_2 and SO_2), showed a stronger association between CHD mortality and PM_{10}. RRs for 10 micrograms/m^3 increase in PM_{10} with NO_2 was 1.16 (95% CI: 1.00-1.35), and PM_{10} with SO_2 was 1.16 (95% CI: 1.01-1.33) (Table 5.4). With comparison of subjects in CHD group and non-CHD group in the AHSMOG cohort, the adjusted mortality RRs in non-CHD group were slight higher and with narrower CI than those in the CHD group (Figure 5.1).

3. Diabetes Group

The adjusted CHD mortality RRs for single pollutant models (PM_{10}) and for two pollutant models (PM and gaseous pollutants) are presented in Table 5.4. Covariates included in the models are smoking status, education, BMI. In single pollutant models, a positive relationship was found in both genders, but the association was only significant for PM_{10} and fatal CHD in males [RR=1.50 (95% CI: 1.15-1.96)]. The association became stronger after adding gaseous pollutants to the model. The strongest

association was in the model of PM_{10} with Ozone [RR=1.54 (95% CI: 1.08-2.20)] for each increment of 10 μg/m^3 increase in PM_{10} (Table 5.4). The adjusted mortality RRs in non-diabetic group were smaller and with narrower confidence interval (Figure 1). In males, the associations among non-diabetic subjects were weaker when compared them with subjects in diabetic group. In females, the associations among non-diabetic subjects were stronger when compared them with subjects in diabetic group.

4. COPD Group

The adjusted mortality RRs for single pollutant models (PM_{10}, O_3, NO_2, and SO_2) and for two pollutant models (PM_{10} and gaseous pollutants) are presented in Table 5.4. Covariates included in the models are smoking status, education, BMI and calendar month. For both gender, a non-significant positive relationships were found between PM_{10} and CHD mortality in single pollutant models with females showing the strongest association with RR of 1.18 (95% CI: 0.99-1.41) for each 10 micrograms/m^3 increment in PM_{10} in two pollutant model with O_3 (Table 5.4). The adjusted CHD mortality RRs in the non-COPD group were smaller and with relatively narrower confidence interval in both genders when by compared to the COPD subgroup (Figure 5.1).

5. Smoking Group

The adjusted CHD mortality RRs for single pollutant models (PM_{10}, O_3, NO_2, and SO_2) and for two pollutant models (PM_{10} and gaseous pollutants) are presented in Table 5.4. Covariates included in the models are smoking status, education, BMI, ETS and calendar month. For males, a positive relationship was found between PM_{10} and

CHD mortality in the single pollutant model with RR of 1.13 (95% CI: 1.00-1.28) for each 10 $\mu g/m^3$ increment in PM_{10}. For females, the relationship was smaller and not significant for the association between CHD mortality and PM_{10} (Table 5.4). The adjusted CHD mortality RRs among subjects in the never smoking group were slight smaller when compared to those in the ever smoking group in males. In females, the adjusted CHD mortality RRs among subjects in the never smoking group were noticeable smaller when compared to those in the ever smoking group (Figure 5.1).

D. Discussion

Epidemiologic studies have observed a clear and consistent association between high concentrations of ambient PM and negative health effects, but whether there are subgroups of people who are especially susceptible to the health effects of PM is unclear. To identify the sets of individuals who have an enhanced response to ambient PM may suggest specific biologic mechanisms.

In previous analysis of fatal CHD and ambient PM (Chen, et al., 2005), we found an elevated risk of fatal CHD associated with ambient levels of PM_{10}, $PM_{10-2.5}$ and $PM_{2.5}$ in females, but not in males. The risk estimates were strengthened when adjusting for gaseous pollutants and were highest for $PM_{2.5}$. Due to the limited cases in the various subgroups, these analyses have been expanded to the entire AHSMOG. In these analysis, we consistently found similar relationship between PM and fatal CHD in various subgroups.

A general hypothesis proposed by Frank and Tankersley (2002) suggested that persons whose health is failing may be at higher risk for external insults, such as

exposure to ambient air pollution, through the failure of the regulation of physiological set points.

1. Age Group

Studies have reported that persons older than 65 years of age have a somewhat increased risk of death associated with PM (Bateson & Schwartz, 2004; Hong, Lee, Kim, & Kwon, 2002; Saldiva, et al., 1995; Schwartz & Dockery, 1992). The study in Netherland did detail exam of particulate matter relating risk by deciles of age and showed that the risk started to increase at approximately 40 years of age and reaching it maximum for those 75 years of age and older (Fischer, et al., 2003). We also found that risk appeared to increase with age among elderly women, but did not observe such trend among elderly men. Several studies have found that elderly subjects experience significant increase in pulse rate (Pope, Dockery, et al., 1999), decreases in HRV (Devlin, et al., 2003; Liao, et al., 1999), and changes in blood markers, such as CRP (Pope, Hansen, et al., 2004) after exposure to ambient PM. The physiologic importance of these observed changes in HRV is not fully understood, but HRV measures provide quantitative indicators of cardiac autonomic function.

2. CHD Group

Recent epidemiologic studies have shown that persons with preexisting cardiopulmonary conditions are at increased risk for adverse cardiac events associated with ambient PM (Goldberg, et al., 2001; Kwon, et al., 2001; Mann, et al., 2002; Zanobetti, Schwartz, & Gold, 2000).

Bates (1992) suggested that exposure to air pollutants in persons with cardiac disease with myocardial damage may cause acute pulmonary disease, such as bronchiolitis or pneumonia, thereby leading to congestive heart failure. Seaton et al. (1995) suggested that in susceptible individuals, exposure to PM will invoke alveolar inflammation, release inflammatory mediators, exacerbate lung conditions, and increase coagulability of blood, thereby leading to acute episode of cardiovascular disease.

3. Diabetes Group

Frank and Tankerseley (2002) have suggested that among persons with systemic disease (e.g. Diabetes), loss of homeostasis will increase susceptibility to external insults, such as air pollution. We found that risk appeared to increase with increasing PM and gaseous levels among diabetic men, but not among diabetic women. Our findings are consistent with several short term study findings. Hospital admission studies conducted by Zanobetti and Schwartz found stronger associations between increased levels of PM_{10} and hospitalizations for cardiovascular diseases among those with diabetes compared to those without (Schwartz, 2001; Zanobetti & Schwartz, 2001, 2002). These findings may make sense biologically, as persons with diabetes are at risk for a number of cardiovascular and circulatory problems and have some of the same risk factors for these diseases. Individuals with diabetes and cardiovascular diseases are at higher risk. These findings are also consistent with previous observations that inhaled urban particles can cause rapid and sustained elevations of levels of circulating plasma endothelin-1 and endothelin-3 (Bouthillier, et al., 1998; Spieker, Noll, & Luscher, 2001; Thomson, Goegan, Kumarathasan, & Vincent, 2004; Ulrich, et al., 2002; Zouridakis, et

al., 2001). There is some evidence that persons with diabetes have abnormal plasma levels of endothelins and that certain factors may be initiated or activated as a result of hyperglycemia and may lead to endothelin dysfunction (Khan & Chakrabarti, 2003).

4. COPD group

Our study found that the CHD effects of ambient PM were predominant in persons with chronic respiratory symptoms or diseases. Several studies suggest that persons with respiratory illness are at increased risk for cardiovascular effects associated with air pollution (Schwartz, 1994; Zanobetti, Schwartz, & Gold, 2000). A cohort study from Spain found an association between particulate air pollution and all cause mortality in persons with COPD (RR=1.10-1.11) (Sunyer & Basagana, 2001; Sunyer, et al., 2000). A study from Quebec also found significant positive associations across indices of PM among individuals who were classified as having acute lower respiratory diseases (Goldberg, et al., 2001). The magnitude of the risk was substantially greater than that for the general population.

Controlled exposure of animals with chronic bronchitis and control animals to concentrated air particles also demonstrated a potential effect on chronic lung disease in the response to ambient particles (Kodavanti, Mebane, et al., 2000).

5. Smoking Group

We did observe an association with PM_{10} among males who had either been active or passive smokers. However, our data did not support an increased risk of CHD with PM or gaseous pollutants among females who have either been active or passive smokers when compared to non-smokers (either active or passive).

The effect of cigarette smoking on risk of CHD risk factors such as elevated inflammatory markers, especially CRP levels (Panagiotakos, et al., 2004), fibrinogen and white cell counts (Panagiotakos, et al., 2004), blood viscosity (Frohlich, et al., 2003), heart rate (Bolinder & de Faire, 1998), and oxidative stress (Guthikonda, Woods, Sinkey, & Haynes, 2004) are well known. Smoking has also been found to trigger acute vasoconstriction and thus the enhanced development of atherosclerosis in the systemic vasculature (Howard, et al., 1998; Kiechl, et al., 2002). This could potentially explain an elevated risk in cardiovascular outcomes for subjects with both active (Njolstad, Arnesen, & Lund-Larsen, 1996; Prescott, Hippe, Schnohr, Hein, & Vestbo, 1998) and passive (Kawachi, et al., 1997) smoking. It is likely that this effect is so much stronger than the effect of ambient air pollution that it is difficult to assess the effect of air pollution among smokers.

Our data suggest that people with cardiac disease are at no more risk than other subjects for the association of CHD mortality and ambient PM, except PM_{10} and $PM_{10-2.5}$ with O_3. Although there are somewhat significant effects of CHD mortality and PM_{10} and coarse fraction with O_3, there might be some dilution effect since we look at subjects with preexisting cardiac condition.

One hypothesis is that particles trigger the production of inflammatory mediators, which in turn affects pro-coagulants and viscosity (Seaton, et al., 1995). Another hypothesis is that particles affect autonomic function of the heart (Peters, et al., 2000). Both hypotheses are supported by several studies in animals (Watkinson, Campen, & Costa, 1998) and humans (Peters, Doring, et al., 1997; Peters, et al., 2000; Pope, Dockery,

et al., 1999; Pope, Hill, & Villegas, 1999; Schwartz, 2001). Several authors have suggested that risk of CVD may, at least partly, be mediated through increased concentrations of plasma fibrinogen, possibly due to an inflammatory reaction caused by air pollution (Koenig, et al., 1998). Fibrinogen is an important determinant of plasma viscosity, and an independent risk factor for CHD (Koenig, et al., 1998). Numerous animal models corroborate the findings in humans of an effect of PM on heart rate (Chang, et al., 2004), blood viscosity (Coates & Richardson, 1978), and pulmonary inflammation (Wichers, et al., 2004). So persons with specific disease may be more vulnerable to high levels of ambient air pollution.

6. Strengths and Limitations

Our study has 22 year follow up and has extensive information on chronic disease and lifestyle. Thus we were able to adjust for the effects of a number of such factors including dietary factors found to be associated with the outcomes in this cohort. Since each participant had both residence and workplace histories with ZIP code, thus our study have more accurate ambient air pollution estimation for each individual.

Some subjects in our study had more than one specific diagnosis. It may be that people with respiratory disease are at increased risk of death associated with PM, but their risks are increased by their other diagnoses rather than the specific diagnosis of respiratory disease.

Our measures of effect modification had large confidence intervals, especially among the past smoker and ETS groups, because of small number of cases in these subgroups.

Although we have shown some cardiovascular effects of particulate air pollution in some susceptible subjects, we have unknown amounts of measurement error in both the estimated long-term ambient concentrations of pollutants as well as other covariates.

E. Conclusions

Our data suggest that specific subpopulations may be especially sensitive to the effects of PM fractions. In detail, this study found an elevated risk of CHD mortality associated with ambient levels of PM_{10} and gases in diabetic males, but not in females. An elevated risk was found in subjects with past smoking history among males. The risk of higher PM exposure is higher with fatal CHD than other outcomes. Our findings are in line with findings by others of an effect of PM on cardiopulmonary mortality, but most of their findings are based on short term exposure. Further studies are needed from larger cohorts and/or with longer follow-up to support our preliminary findings of a differential effect of PM on risk of CHD mortality among susceptible groups.

CHAPTER 6

SUMMARY AND CONCLUSION

In the AHSMOG cohort, all participants have been followed up for over 30 years. The mortality from all natural cause and specific causes (cardiopulmonary, coronary heart disease (CHD), total cancer, and any mention of nonmalignant respiratory disease (NMRD) were investigated in relation to long-term concentration of PM_{10}, Ozone, NO_3, and SO_2. An increased risk of any mention of NMRD mortality as well as of total cancer mortality was found to be associated with ambient levels of PM_{10}. The risk estimates were strengthened when adjusting for gaseous pollutants.

In the AHSMOG airport sub-cohort, fatal CHD was specifically studied in relation to ambient long-term concentration of particulate matter. The study found an increased risk of fatal CHD associated with ambient levels of PM_{10}, $PM_{10-2.5}$ and $PM_{2.5}$ in females, but not in males. The risk estimates were strengthened when adjusting for gaseous pollutants and were highest for $PM_{2.5}$.

In addition, we found an increased risk of CHD mortality associated with ambient levels of PM_{10} and gaseous pollutants in diabetic males and males with past smoking history, but not in females. The risk is higher for fatal CHD than other outcomes, suggesting that this specific diagnosis may be especially sensitive to the effects of ambient PM fractions.

Our findings are in line with previous results reported by others on the effect of PM on all natural cause, cardiopulmonary, CHD, total cancer, and NMRD mortality. The

findings of fatal CHD in our airport sub-cohort are of greater magnitude than that reported by others. This is possibly due to the fact that we limited our study group to persons living close to airports where PM, including fine PM was measured regularly and the fact that we had better control of confounding factors such as diet, alcohol and tobacco compared to other cohorts.

The effects of air pollution on health, especially CHD are so far not clear. Further studies are needed with larger cohorts, with longer follow-up, and better measures of PM and better control of potential confounders to support our findings. Developing more accurate ways to assess an individual's exposure to ambient levels of PM will improve precision of risk estimates and reduce measurement error.

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APPENDIX A: 1977 AHSMOG Questionnaire

LOMA LINDA UNIVERSITY

LOMA LINDA, CALIFORNIA 92354
(714) 796-7311 EXT. 3717

SCHOOL OF HEALTH
ADVENTIST HEALTH STUDY

Dear Friend:

You are one of a small group selected from all participants in the Adventist Health Study to help in a special substudy. This substudy is sponsored by the Air Resources Board to measure some effects of the type of air you breathe.

We have greatly appreciated your cooperation and efforts in completing the detailed lifestyle questionnaire which is helping us to determine the possible relationship between various aspects of lifestyle and health status. The enclosed questionnaire will supplement this information with some additional questions.

Most other members in your church are receiving only the back page of this questionnaire which is the first of the yearly hospital history forms being sent to all adult SDAs in California. It is extremely important for you to complete this last page because it is our only means of keeping track of the health status of California SDAs. The few minutes necessary to fill in the entire questionnaire will contribute significantly to new knowledge that may save many lives.

By completing this questionnaire NOW, you will save us the expense and effort of having to contact you personally. Please return the completed questionnaire in the enclosed self-addressed envelop. Thank you for your assistance.

Sincerely yours,

Roland L. Phillips, M.D.
Director

RESPIRATORY SYMPTOMS AND RESIDENCE
HISTORY QUESTIONNAIRE

ease answer every question.

COUGH

1. Do you usually cough first thing in the morning?

[ ] Yes
[ ] No

OQ1 - 1040

2. Do you usually cough at other times during the day or night?

[ ] Yes
[ ] No

OQ2 - 1041

3. Do you cough on most days for 3 months or more?

[ ] Yes
[ ] No

OQ3 - 1042

4. For how many years have you had a cough?

[ ] Never
[ ] Less than 1 year
[ ] More than 1 but less than 2 years
[ ] 2-5 years
[ ] More than 5 years

OQ4 - 1043

SPUTUM

5. Do you usually bring up phlegm, sputum, or mucus from your chest first thing in the morning?

[ ] Yes
[ ] No

OQ5 - 1044

6. Do you usually bring up phlegm, sputum, or mucus from your chest at other times during the day or night?

[ ] Yes
[ ] No

OQ6 - 1045

7. Do you bring up phlegm, sputum or mucus from your chest on most days for 3 months of the year or more?

[ ] Yes
[ ] No

OQ7 - 1046

8. For how many years have you raised phlegm, sputum, or mucus from your chest?

[ ] Never
[ ] Less than 1 year
[ ] More than 1 but less than 2 years
[ ] 2-5 years
[ ] More than 5 years

OQ8 - 1047

PLEASE GO TO TOP OF NEXT COLUMN.

1

WHEEZING

9. Does your breathing ever sound wheezy or whistling?

[ ] Yes
[ ] No

OQ9 - 1048

10. Have you ever had attacks of shortness of breath with wheezing?

[ ] Yes
[ ] No

OQ10 - 1049

BREATHLESSNESS

11. Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?

[ ] Yes
[ ] No

OQ11 - 1050

12. Do you get short of breath when walking at a normal pace with other people of your own age on level ground?

[ ] Yes
[ ] No

OQ12 - 1051

RESPIRATORY ILLNESS

13. During the PAST YEAR, how often were you unable to do your usual activities because of illnesses such as chest colds, bronchitis, or pneumonia?

[ ] None
[ ] 1 time
[ ] 2-5 times
[ ] More than 5 times

OQ13 - 1052

14. Do you think you have ever had any of these chest disorders--asthma, any kind of bronchial condition, or emphysema?

[ ] Yes
[ ] No

OQ14 - 1053

15. Has a doctor ever told you that you had asthma, sone kind of bronchial condition, or emphysema?

[ ] No

OQ15 - 1054-55

IF YES, please check [✓] which conditions.

[ ] Asthma
[ ] Bronchial condition
[ ] Emphysema

16. How many days per month during the SUMMER (June thru September) are you bothered by stuffy nose or post-nasal drip (i.e. drainage from the back of your nose into your throat)?

1[ ] None
2[ ] 1-5 days
3[ ] 6-10 days
4[ ] 11-20 days
5[ ] 21 days or more

OQ16 - 1056

17. How many days per month during the WINTER (October thru May) are you bothered by stuffy nose or post-nasal drip (i.e. drainage from the back of your nose into your throat)?

1[ ] None
2[ ] 1-5 days
3[ ] 6-10 days
4[ ] 11-20 days
5[ ] 21 days or more

OQ17 - 1057

Have you EVER regularly smoked cigarettes, pipes, or cigars (aside from possibly trying them once or twice)?

	Yes	No		
18.	1[ ]	2[ ]	Cigarettes	OQ18 - 1058
19.	1[ ]	2[ ]	Pipes	OQ19 - 1059
20.	1[ ]	2[ ]	Cigars	OQ20 - 1060

During the PAST YEAR, how many times have you had the following illnesses? (Please heck [✓] the appropriate box for EACH illness.)

21. Head cold (e.g. runny nose, sore throat, etc.) OQ21 - 1061

None 1 2 3 or more
0[ ] 1[ ] 2[ ] 3[ ]

22. Chest cold (acute bronchitis e.g. cough and sputum associated with respiratory infection) OQ22 - 1062

None 1 2 3 or more
0[ ] 1[ ] 2[ ] 3[ ]

23. Pneumonia OQ23 - 1063

None 1 2 3 or more
0[ ] 1[ ] 2[ ] 3[ ]

24. How many times was this pneumonia diagnosed by a physician using a chest x-ray?

None 1 2 3 or more
0[ ] 1[ ] 2[ ] 3[ ]

PLEASE GO TO TOP OF NEXT COLUMN.

RESIDENCE

25. Are you usually away from home for more than 2 weeks during the summer (June thru September)?

1[ ] No
2[ ] Yes

26. IF YES, how long are you usually away?

1[ ] 3-4 weeks
2[ ] 5-6 weeks
3[ ] 7-8 weeks
4[ ] 9 weeks or more

27. How many hours per DAY during the work week do you usually spend driving or riding on CROWDED roadways? (Check the nearest category.)

HRSRDK OQ27 - 1067

1[ ] None
2[ ] Less than 15 minutes
3[ ] 15 minutes to one hour
4[ ] 2 hours
5[ ] 3 hours
6[ ] 4 hours
7[ ] 5 hours
8[ ] 6 hours or more

28. On a typical WEEKEND, how many hours per day do you spend driving or riding on CROWDED roadways? (Check the nearest category.)

HRSRDD OQ28 - 1068

1[ ] None
2[ ] Less than 15 minutes
3[ ] 15-29 minutes
4[ ] 30-59 minutes
5[ ] 1-2 hours
6[ ] 3-4 hours
7[ ] 5-6 hours
8[ ] 6 hours or more

29. How often do you use aerosol sprays (e.g. hair spray, cleaning spray, deodorant, spray paint, etc.)?

1[ ] Daily
2[ ] Several times a week
3[ ] Once a week
4[ ] a few times a month
5[ ] Rarely or never

30. What is your usual or main occupation? (Do not write "retired". If retired or not now working, give your usual occupation when you were working.) 70

Job Title_____

Major duties or responsibilities:

_____

	31. SUMMER (June thru September)	32. REST OF YEAR (October thru May)
How many hours per WEEK, including weekends, do you exercise vigorously or do heavy physical labor (e.g. jogging, tennis, gardening, etc.) in the open air?	1[ ] None 2[ ] 1-7 hours 3[ ] 8-14 hours 4[ ] 15-21 hours 5[ ] 22-28 hours 6[ ] 29-35 hours 7[ ] 36-42 hours 8[ ] More than 42 hours	1[ ] None 2[ ] 1-7 hours 3[ ] 8-14 hours 4[ ] 15-21 hours 5[ ] 22-28 hours 6[ ] 29-35 hours 7[ ] 36-42 hours 8[ ] More than 42 hours
OQ31 - 1072 (HRSEXS)		OQ32 (HRS
	33. SUMMER (June thru September)	34. REST OF YEAR (October thru May)
How many hours per WEEK, including weekends, are you outside of buildings?	1[ ] None 2[ ] 1-7 hours 3[ ] 8-14 hours 4[ ] 15-21 hours 5[ ] 22-28 hours 6[ ] 29-35 hours 7[ ] 36-42 hours 8[ ] More than 42 hours	1[ ] None 2[ ] 1-7 hours 3[ ] 8-14 hours 4[ ] 15-21 hours 5[ ] 22-28 hours 6[ ] 29-35 hours 7[ ] 36-42 hours 8[ ] More than 42 hours
OQ33 - 1074 (HRSOSS)		OQ34 - 1((HRSC

35. Have you ever lived for one year or more with someone who smoked?

0[ ] No
[ ] Yes ------> How many years? (OQ35 - 1076-1077

36. Have you worked in the same room with someone who smoked?

0[ ] No
[ ] Yes ------> How many years? (OQ36 - 1078-1079

37. Have you ever worked where you were exposed much of the time to various types of contaminated air such as chemical fumes, paint fumes, welding, wood or rock dust, etc.

0[ ] No
[ ] Yes ------> How many years? (OQ37 - 1080-1081

1149, 1150-1151

1152, 1153-1154

1155, 1156-1157

USE THESE

IF YES, please list:

38. Type of work 1082 - 1085

39. Type of contamination

If you have worked more than 5 miles from home in the past 10 years, please give the work locations and dates

	Started Job: MONTH	YEAR	Ended Job: MONTH	YEAR	TOWN OF WORK	STATE	ZIP COD PLACE OF W
40.							
41.							
42.							
43.							
44.							
45.							

For each community you have lived in since 1960, please give the information requested below. For large cities, please give the section of the city. If the town was so small that it did not have a post office, give the nearest post office.

Please start with your current place of residence.

	TOWN	STATE	ZIP	Moved to this town MONTH	YEAR
46.					
47.					
48.					
49.					
50.					
51.					

52. For each of the following, please indicate with a [✓] which years you have:

	Never	Prior to 66	1966	67	68	69	70	71	72	73	74	75	76	77
a. Lived in a home with evaporative water cooling.	a[ ]	[ ]	[ ]	[ ]	[ ]	a[ ]	[ ]	[ ]	[ ]	[ ]	a[ ]	[ ]	[ ]	[ ]
b. Lived in a home with refrigerated air-conditioning.	b[ ]	[ ]	[ ]	[ ]	[ ]	b[ ]	[ ]	[ ]	[ ]	[ ]	b[ ]	[ ]	[ ]	[ ]
c. Worked in a building with air-conditioning.	c[ ]	[ ]	[ ]	[ ]	[ ]	c[ ]	[ ]	[ ]	[ ]	[ ]	c[ ]	[ ]	[ ]	[ ]
d. Lived with someone who smoked.	d[ ]	[ ]	[ ]	[ ]	[ ]	d[ ]	[ ]	[ ]	[ ]	[ ]	d[ ]	[ ]	[ ]	[ ]
e. Worked in the same room with someone who smoked.	e[ ]	[ ]	[ ]	[ ]	[ ]	e[ ]	[ ]	[ ]	[ ]	[ ]	e[ ]	[ ]	[ ]	[ ]
f. Worked more than 5 miles from home.	f[ ]	[ ]	[ ]	[ ]	[ ]	f[ ]	[ ]	[ ]	[ ]	[ ]	f[ ]	[ ]	[ ]	[ ]
g. Worked where you were exposed much of the time to various types of contaminated air such as chemical fumes, paint fumes, welding, wood or rock dust, etc.	g[ ] 52	[ ] 53	[ ] 54	[ ] 55	[ ] 56	g[ ] 57	[ ] 58	[ ] 59	[ ] 60	[ ] 61	g[ ] 62	[ ] 63	[ ] 64	[ ] 65

APPENDIX B: 1987 AHSMOG Questionnaire

Loma Linda University

Adventist Health Study
Department of Preventive Medicine
School of Medicine
Loma Linda, CA 92350
714/824-4684

Make sure you are the person named and that **address** and **telephone number** are correct.

See * below if this person is no longer living here.

Dear Friend,

In 1977, you were one of a select group from the Adventist Health Study who participated in a special substudy that was sponsored by the California Air Resources Board. Your response to previous questionnaires has been very much appreciated and the results of this substudy have been widely recognized and used by State and National Agencies. Once again we are seeking your cooperation and assistance in completing the following questionnaire for the follow up of this special substudy.

It is important to the scientific validity of the study that all study participants fill out the questionnaire as close as possible to the same point in time. Please take a few minutes now and complete this questionnaire and mail it in the enclosed stamped, return envelope.

All the information will be kept strictly confidential and will be reported only in statistical summaries of large groups of people. Thank you for **your** important contribution to this research project.

Sincerely yours,

David E. Abbey

David E. Abbey, Ph.D.
Co-director, Adventist Health Study

*
If this person is no longer living at this address, please indicate the person's status and a new address if available or the contact name and address of a close relative and RETURN the **uncompleted** questionnaire in the enclosed envelope.

[ ] This person is deceased

[ ] This person is now living at a new address:

Name of contact person _____

Address _____

_____

A Seventh-day Adventist institution with campuses at La Sierra/Riverside and Loma Linda, California

RESPIRATORY SYMPTOMS AND RESIDENCE HISTORY QUESTIONNAIRE – 1987

INSTRUCTIONS

Please answer EVERY question. For some questions you may not remember the exact detail. If this is the case, then guess as closely as you can.
PLEASE DO NOT LEAVE ANY QUESTIONS BLANK UNLESS ASKED TO SKIP THEM.

Please indicate your answer by placing an X in the appropriate box [ ] or by writing your answer in the space provided.

Check your **name, address** and **telephone number** on the first page adding or correcting address and telephone number if necessary. **Make sure you are the person named on the label.**

1. Please enter today's date ____/____/____ month day year

COUGH

2. Do you usually cough first thing in the morning?

1 [ ] Yes
2 [ ] No — Q2 – 1518

3. Do you usually cough at other times during the day or night?

1 [ ] Yes
2 [ ] No — Q3 – 1519

4. Do you cough on most days for 3 months or more?

1 [ ] Yes
2 [ ] No — Q4 – 1520

5. For how many years have you had a cough?

1 [ ] Never — Q5 – 1521
2 [ ] Less than 1 year
3 [ ] More than 1 but less than 2 years
4 [ ] 2–5 years
5 [ ] More than 5 years

SPUTUM

6. Do you usually bring up phlegm, sputum, or mucus from your chest first thing in the morning?

1 [ ] Yes
2 [ ] No — Q6 – 1522

7. Do you usually bring up phlegm, sputum, or mucus from your chest at other times during the day or night?

1 [ ] Yes
2 [ ] No — Q7 – 1523

8. Do you bring up phlegm, sputum or mucus from your chest on most days for 3 months of the year or more?

1 [ ] Yes
2 [ ] No — Q8 – 1524

9. For how many years have you raised phlegm, sputum, or mucus from your chest?

1 [ ] Never — Q9 – 1525
2 [ ] Less than 1 year
3 [ ] More than 1 but less than 2 years
4 [ ] 2–5 years
5 [ ] More than 5 years

WHEEZING

10. Does your breathing ever sound wheezy or whistling?

1 [ ] Yes
2 [ ] No — Q10 – 1526

11. Does your chest ever sound wheezy or whistling? **(Check No or Yes for each)**

	No	Yes		
Q11a	1 [ ]	2 [ ]	When you have a cold	1527
Q11b	1 [ ]	2 [ ]	Occasionally apart from colds	1528
Q11c	1 [ ]	2 [ ]	Most days or nights	1529

12. Have you ever had attacks of shortness of breath with wheezing?

1 [ ] Yes (continue)
2 [ ] No ⟹ skip to question 15 — Q12 – 1530

PLEASE GO TO TOP OF NEXT COLUMN

PLEASE GO TO TOP OF NEXT PAGE

13. Have you had 2 or more such episodes?

1 [ ] Yes
2 [ ] No
Q13 - 1531

14. Have you ever required medicine or treatment for the(se) attack(s)?

1 [ ] Yes
2 [•] No
Q14 - 1532

BREATHLESSNESS

15. Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?

1 [ ] Yes
2 [ ] No
Q15 - 1533

16. Do you get short of breath when walking at a normal pace with other people of your own age on level ground?

1 [ ] Yes
2 [ ] No
Q16 - 1534

RESPIRATORY ILLNESS

17. During the PAST YEAR, how often were you unable to do your usual activities because of illnesses such as chest colds, bronchitis, or pneumonia?

1 [ ] None
2 [ ] 1 time
3 [ ] 2–5 times
4 [ ] More than 5 times
Q17 - 1535

18. Do you think you have ever had any of these chest disorders--asthma, any kind of bronchial condition, or emphysema?

1 [ ] Yes
2 [ ] No
Q18 - 1536

19. Has a doctor ever told you that you had asthma, some kind of bronchial condition, or emphysema?

1 [ ] No
Q19 - 1537
IF YES, please check [X] which conditions

Q19a 1 [ ] Asthma 1538
Q19b 1 [ ] Bronchial condition 1539
Q19c 1 [ ] Emphysema 1540

PLEASE GO TO TOP OF NEXT COLUMN

THE FOLLOWING QUESTION REQUESTS ADDITIONAL INFORMATION. PLEASE READ IT CAREFULLY. WE NEED TO KNOW IF YOU HAVE HAD THESE AND OTHEI CONDITIONS AND THE AGE OF FIRST DIAGNOSIS.

20. Has a **doctor ever** told you that you had asthma, some kind of bronchial condition, pneumonia, emphysema, or any other serious respiratory condition?

1 [ ] No
Q20 - 1541
IF YES, check all that apply and give age of first diagnosis

1 [ ] Asthma Q20a - 1542
Q20a1 - 1543–44 **age** of first diagnosis
1 [ ] Attacks of bronchitis Q20b - 1545
Q20b1 - 1546–47 **age** of first diagnosis
1 [ ] Chronic bronchitis Q20c - 1548
Q20c1 - 1549–50 **age** of first diagnosis
1 [ ] Pneumonia Q20d - 1551
Q20d1 - 1552–53 **age** of first diagnosis
1 [ ] Emphysema Q20e - 1554
Q20e1 - 1555–56 **age** of first diagnosis
1 [ ] Other (specify) Q20f - 1557
Q20f1 - 1558–59 **age** of first diagnosis

21. Do you currently have asthma that has been confirmed by a doctor?

1 [ ] No
2 [ ] Yes
Q21 - 1560

22. IF YES, are you currently taking medication for asthma?

1 [ ] No
2 [ ] Yes
Q22 - 1561

23. Before starting school (up to 7 years of age) do you think you had more or less than the average number of colds for children your age?

1 [ ] much less
2 [ ] less
3 [ ] about the same
4 [ ] more
5 [ ] much more
Q23 - 1562

PLEASE GO TO TOP OF NEXT PAGE

24. How many **days per month** during the SUMMER (June through September) are you bothered by stuffy nose or post-nasal drip (i.e. drainage from the back of your nose into your throat)?

1 [ ] None
2 [ ] 1–5 days
3 [ ] 6–10 days
4 [ ] 11–20 days
5 [ ] 21 days or more

Q24 – 1563

25. How many **days per month** during the WINTER (October through May) are you bothered by stuffy nose or post-nasal drip (i.e. drainage from the back of your nose into your throat)?

1 [ ] None
2 [ ] 1–5 days
3 [ ] 6–10 days
4 [ ] 11–20 days
5 [ ] 21 days or more

Q25 – 1564

SMOKING HISTORY

26. Have you EVER regularly smoked cigarettes, cigars or a pipe (aside from possibly trying them once or twice?)

1 [ ] No ⟹ skip to question 34
2 [ ] Yes

Q26 – 1565

27. At what age did you first start smoking regularly?

_____ **age in years**

Q27 – 1566–1567

28. Are you currently smoking?

1 [ ] No
2 [ ] Yes ⟹ skip to question 30

Q28 – 1568

29. At what age did you stop smoking?

_____ **age in years**

Q29 – 1569–1570

30. Have you ever regularly smoked cigars?

1 [ ] No
2 [ ] Yes ⟹ **How many years?** Q30a–1572–73

Q30 – 1571

31. Have you ever regularly smoked a pipe?

1 [ ] No
2 [ ] Yes ⟹ **How many years?** Q31a – 1575–76

Q31 – 1574

32. Approximately how many years, **in total**, have you regularly smoked **cigarettes** (not counting the times when you had quit)?

_____ **years**

Q32 – 1577–1578

PLEASE GO TO TOP OF NEXT COLUMN

33. During most of the time that you regularly smoked, how many **cigarettes** did you usually smoke each day?

1 [ ] None
2 [ ] 1–4 per day
3 [ ] 5–14 (1/2 pack) per day
4 [ ] 15–24 (1 pack) per day
5 [ ] 25–34 (1 1/2 packs) per day
6 [ ] 35–44 (2 packs) per day
7 [ ] 45–54 (2 1/2 packs) per day
8 [ ] over 2 1/2 packs per day

Q33 – 1579

CHILDHOOD EXPOSURE TO TOBACCO SMOKE

34. Did your natural mother smoke when she was pregnant with you?

1 [ ] **Definitely NO**
2 [ ] **Don't think so**
3 [ ] **Probably**
4 [ ] **Definitely YES**

Q34 – 1580

35. During **any** time in your life have you EVER **lived** for six months or more with someone who smoked?

1 [ ] No ⟹ skip to question 47
2 [ ] Yes ⟹ continue with question 36

Q35 – 1581

36. When you were a **child or teenager** (up to **18** years), did you ever **live** for six months or more with someone who smoked?

1 [ ] No ⟹ skip to question 41
2 [ ] Yes

Q36 – 1582

37. During what **ages of your childhood** did you **live** for six months or more with someone who smoked? (Check all that apply)

1 [ ] 0–5 years of age — Q37a–1583
1 [ ] 6–12 years of age — Q37b–1584
1 [ ] 13–18 years of age — Q37c–1585

38. During what **ages of your childhood** did your **mother** smoke cigarettes (check all that apply).

1 [ ] Not at all — Q38a – 1586
1 [ ] 0–5 years of age — Q38b – 1587
1 [ ] 6–12 years of age — Q38c – 1588
1 [ ] 13–18 years of age — Q38d – 1589

PLEASE GO TO TOP OF NEXT PAGE

39. During your **CHILDHOOD** (up to **18** years) which of the following persons smoked in your **home** for six months or more? **Check all that apply** and for each person estimate the **total number of years** that you were exposed to their tobacco smoke.

1 [ ] Mother ⟶ _____ **YEARS**
1 [ ] Father ⟶ _____ **YEARS**
1 [ ] Others ⟶ _____ **YEARS**

40. **As a child or teenager,** during the majority of these years that you **lived** with someone who smoked tobacco, how many hours per day **on the average** were you exposed to tobacco smoke?

1 [ ] None
2 [ ] Less than 1 hour per day
3 [ ] 1–2 hours per day
4 [ ] 3–5 hours per day
5 [ ] 6–8 hours per day
6 [ ] 9 or more hours per day

ADULT EXPOSURE TO TOBACCO SMOKE

41. As an **adult** (**19** years of age or over), have you ever **lived** for six months or more with someone who smoked?

1 [ ] No ⟶ skip to question 47
2 [ ] Yes, in the past
3 [ ] Yes, currently

42. What was your age as an **adult** when you **first** lived with someone who smoked?

_____ age in years

43. What was your age as an **adult** when you **last** lived with someone who smoked?

_____ **age in years**

44. During your **ADULT** years (19 years and older), which of the following persons have smoked in your **home** for six months or more? **Check all that apply** and for each person estimate the **total number of years** that you were exposed to their tobacco smoke.

1 [ ] Spouse ⟶ _____ **YEARS**
1 [ ] Others ⟶ _____ **YEARS**

45. **As an adult,** during the majority of these years that you **lived** with someone who smoked tobacco, how many hours per day **on the average** were you exposed to tobacco smoke?

1 [ ] None
2 [ ] Less than 1 hour per day
3 [ ] 1–2 hours per day
4 [ ] 3–5 hours per day
5 [ ] 6–8 hours per day
6 [ ] 9 or more hours per day

46. Are cigarettes **currently** smoked in your home?

1 [ ] No
2 [ ] Yes ⟶ Approximately how many per day?

_____

WORK EXPOSURE TO TOBACCO SMOKE

47. Have you **ever** worked where someone smoked in the same room or enclosed space in which you **worked**?

1 [ ] No ⟶ skip to question 52
2 [ ] Yes, in the past
3 [ ] Yes, currently

48. Approximately how many years **in total** have you ever **worked** where someone smoked in the same room or enclosed space in which you **worked**.

_____ **years**

49. What was your age when you **first** worked with someone who smoked?

_____ **age in years**

50. What was your age when you **last worked** with someone who smoked?

_____ **age in years**

51. During the years that you **worked** where someone smoked tobacco in the same room or enclosed space as you worked, how many hours per day **on the average** were you exposed to tobacco smoke?

1 [ ] None
2 [ ] Less than 1 hour per day
3 [ ] 1–2 hours per day
4 [ ] 3–5 hours per day
5 [ ] 6 or more hours per day

PLEASE GO TO TOP OF NEXT COLUMN

PLEASE GO TO TOP OF NEXT PAGE

52. Please estimate the **total** number of hours per day on the average that you are **CURRENTLY** exposed to someone else's tobacco smoke. Then do the same for exposure **DURING THE LAST TEN YEARS.** (**Include** time in the home, work, in automobiles, public transport and social situations that you are/were exposed to other people's tobacco smoke).

AVERAGE **CURRENT** EXPOSURE

1 [ ] None
2 [ ] Less than 1 hour per day
3 [ ] 1–2 hours per day
4 [ ] 3–5 hours per day
5 [ ] 6–8 hours per day
6 [ ] 9 or more hours per day

AVERAGE **DURING LAST 10 YEARS**

1 [ ] None
2 [ ] less than 1 hour per day
3 [ ] 1–2 hours per day
4 [ ] 3–5 hours per day
5 [ ] 6–8 hours per day
6 [ ] 9 or more hours per day

ACTIVITIES

53. How many **hours per DAY** during the **work week** do you usually spend driving or riding on CROWDED roadways? (Check the nearest category.)

1 [ ] None
2 [ ] Less than 15 minutes
3 [ ] 15 minutes to one hour
4 [ ] 2 hours
5 [ ] 3 hours
6 [ ] 4 hours
7 [ ] 5 hours
8 [ ] 6 hours or more

54. On a typical **WEEKEND**, how many hours **per day** do you spend driving or riding on CROWDED roadways? (Check the nearest category.)

1 [ ] None
2 [ ] Less than 15 minutes
3 [ ] 15–29 minutes
4 [ ] 30–59 minutes
5 [ ] 1–2 hours
6 [ ] 3–4 hours
7 [ ] 5–6 hours
8 [ ] 6 hours or more

55. In total, approximately how many hours **per week** do you usually spend **driving** or **riding** on **any type of roadway**?

1 [ ] Never ride or drive on a weekly basis

_____ **hours per week riding or driving on roadways**

56. How often do you use aerosol sprays (e.g. hair spray, cleaning spray, deodorant, spray paint, etc.)?

1 [ ] Daily
2 [ ] Several times a week
3 [ ] Once a week
4 [ ] A few times a month
5 [ ] Rarely or never

57. How long are you usually away from home during the Summer (**June through September**)?

1 [ ] 2 weeks or less
2 [ ] 3–4 weeks
3 [ ] 5–6 weeks
4 [ ] 7–8 weeks
5 [ ] 9 weeks or more

How many **hours per WEEK**, including weekends, do you exercise vigorously or do heavy physical labor (e.g. jogging, tennis, gardening, etc.) in the open air?

58. **SUMMER**
(June through September)

1 [ ] None
2 [ ] 1–3 hours
3 [ ] 4–7 hours
4 [ ] 8–14 hours
5 [ ] 15–21 hours
6 [ ] 22–28 hours
7 [ ] 29–35 hours
8 [ ] 36–42 hours
9 [ ] More than 42 hours

59. **REST OF YEAR**
(October through May)

1 [ ] None
2 [ ] 1–3 hours
3 [ ] 4–7 hours
4 [ ] 8–14 hours
5 [ ] 15–21 hours
6 [ ] 22–28 hours
7 [ ] 29–35 hours
8 [ ] 36–42 hours
9 [ ] More than 42 hours

PLEASE GO TO TOP OF NEXT COLUMN

PLEASE GO TO TOP OF NEXT PAGE

How many **hours per WEEK**, including weekends, are you outside of buildings?

60. **SUMMER**
(June through September)

1 [ ] None
2 [ ] 1–7 hours
3 [ ] 8–14 hours
4 [ ] 15–21 hours
5 [ ] 22–28 hours
6 [ ] 29–35 hours
7 [ ] 36–42 hours
8 [ ] More than 42 hours

61. **REST OF YEAR**
(October through May)

1 [ ] None
2 [ ] 1–7 hours
3 [ ] 8–14 hours
4 [ ] 15–21 hours
5 [ ] 22–28 hours
6 [ ] 29–35 hours
7 [ ] 36–42 hours
8 [ ] More than 42 hours

62. During your usual daily activities how much time do you usually spend close to any sources of combustion, such as heavy traffic, gas powered equipment, lawn mowers, gas stoves or ranges?

1 [ ] None
2 [ ] Less than 15 minutes
3 [ ] 15–29 minutes
4 [ ] 30–59 minutes
5 [ ] 1–2 hours
6 [ ] 3–4 hours
7 [ ] 5–6 hours
8 [ ] 6 hours or more

EMPLOYMENT

63. What is your current employment status?

1 [ ] Unemployed
2 [ ] Working part time
3 [ ] Working full time
4 [ ] Retired and not working
5 [ ] Retired and working part time
6 [ ] Retired but working full time
→ IF RETIRED, please give date of retirement

____/____
month year

64. What is your **usual** or **main occupation**? (Do **not** write "retired". If retired or not now working, give your usual occupation when you were working.)

Job Title_____

Type of business or industry:

_____

Major duties or responsibilities:

_____

65. How many years have you been employed in this occupation?

_____ **years**

66. Are you currently employed in your **usual** or **main** occupation?

1 [ ] No
2 [ ] Yes → skip to question 68

67. When were you last employed in your **usual** or **main** occupation?

____/____
month year

68. What type of air cooling system do you currently have at your work place?

1 [ ] I am not currently working
2 [ ] None
3 [ ] Evaporative cooler (swamp cooler)
4 [ ] Refrigerating type (air conditioner)
5 [ ] Both

69. **Since March 1977** what type of air cooling system/systems have you had at your place or places of work?

1 [ ] I have not worked since March 1977 → skip to question 73
2 [ ] None
3 [ ] Evaporative cooler (swamp cooler)
4 [ ] Refrigerating type (air conditioner)
5 [ ] Both

PLEASE GO TO TOP OF NEXT COLUMN

PLEASE GO TO TOP OF NEXT PAGE

70. **Since March 1977,** have you changed your **occupation** or your **location** of work?

1 [ ] No
2 [ ] Yes

71. **Since March 1977,** have you worked for 1 month or more at a location **more than 5 miles from home?**

1 [ ] No → skip to question 73
2 [ ] Yes

72. If you have worked **more than 5 miles** from home **since March 1977,** give the work locations and dates.

Started Job: MONTH	Started Job: YEAR	Ended Job: MONTH	Ended Job: YEAR	TOWN OF WORK	STATE	ZIP CODE OF WORK PLACE

73. Have you moved or been away from home for more than one month **since March 1977?**

1 [ ] No → please skip to question 75
2 [ ] Yes, I have moved
3 [ ] Yes, I have been away for more than 1 month.
_____ How many **months?**

74. For each community in which you have lived or stayed for one month or more **since March 1977,** please give the information requested below. For large cities, please give the section of the city. **Please start with your residence in 1977 and work towards the present.**

TOWN	STATE	ZIP	When did you start living in this town? MONTH	YEAR

PLEASE GO TO TOP OF NEXT PAGE

75. Have you **EVER WORKED** (for 3 months or more) where you were exposed much of the time as a **part of your job** to any of the following? If so, write in the approximate number of years you were exposed to each agent and the year when last exposed.

[ ] check here if **no regular** exposure to any of the below

	Number of Years of Exposure	Year when last Exposed	
01	_____	_____	Radiation, X-ray
			DUSTS
02	_____	_____	Sand or rock dust
03	_____	_____	Asbestos
04	_____	_____	Talc, graphite
05	_____	_____	Fiberglass, rock wool
06	_____	_____	Sawdust
07	_____	_____	Metal dust
08	_____	_____	Road, soil dust
			Other **dusts** (specify **dates & dusts**)
	_____	_____	_____
	_____	_____	_____
	_____	_____	_____
			FUMES
15	_____	_____	Paint fumes
16	_____	_____	Formaldehyde
17	_____	_____	Solvents
18	_____	_____	Insecticides
19	_____	_____	Resins or glues
20	_____	_____	Diesel fumes
21	_____	_____	Freon or refrigerants
22	_____	_____	Auto exhaust
23	_____	_____	Solder (or flux) fumes
24	_____	_____	Welding fumes/nitrogen oxides
			Other **fumes** or airborne contaminants (specify **dates & fumes**)
	_____	_____	_____
	_____	_____	_____
	_____	_____	_____

PLEASE GO TO TOP OF NEXT COLUMN

76. Please specify types of jobs or industries where you had the above exposures.

Industries	Job Duties
_____	_____
_____	_____
_____	_____

77. Would you rate your exposures to **dusts** at work (past or present) as

1 [ ] None
2 [ ] Mild
3 [ ] Moderate
4 [ ] Severe

78. Would you rate your exposures to **fumes or airborne contaminants** at work (past or present) as

1 [ ] None
2 [ ] Mild
3 [ ] Moderate
4 [ ] Severe

RESIDENCE

79. How many years have you lived in your present home?

_____ **years**

80. What type of building do you live in?

1 [ ] Single family home detached from any other house
2 [ ] Single family home attached to one or more houses (for example, a townhouse, duplex, triplex)
3 [ ] Mobile home or trailer
4 [ ] Apartment, condominium with more than 3 units.
[ ] Other, please specify_____

81. How old is your residence?

1 [ ] Less than 1 year
2 [ ] 1 year old
3 [ ] 2-3 years old
4 [ ] 4-10 years old
5 [ ] 11 to 20 years old
6 [ ] More than 20 years old

82. What is the size of the living area of your home (in square feet)?

_____ **sq ft**

83. How many **bedrooms** are there in your home?

_____

PLEASE GO TO TOP OF NEXT PAGE

84. How many **bathrooms** are there in your home?

_____

85. Where do you park your car(s) when you are home?

1 [ ] In an attached garage
2 [ ] In an attached carport
3 [ ] Garage or carport detached from your living quarters
4 [ ] In a driveway, next to living quarters
[ ] Other _____

86. What type of air cooling system do you have in your home?

1 [ ] None
2 [ ] Evaporative cooler (swamp cooler)
3 [ ] Refrigerating type (air conditioner)
4 [ ] Both

87. How many years have you had this type of air cooling system in your home?

_____ **years**

88. What type of air cooling system did you have in your home in **March 1977**?

1 [ ] None
2 [ ] Evaporative cooler (swamp cooler)
3 [ ] Refrigerating type (air conditioner)
4 [ ] Both

HEATING AND COOKING

89. How frequently are the following **heating** systems used in your home during the **winter** months? Please check **never** if not used.

	Never	Monthly or less	Weekly	Daily	
01	[ ]	[ ]	[ ]	[ ]	**Gas** forced air furnace
02	[ ]	[ ]	[ ]	[ ]	**Gas** wall furnace
03	[ ]	[ ]	[ ]	[ ]	**Gas** floor furnace
04	[ ]	[ ]	[ ]	[ ]	**Gas** space heater
05	[ ]	[ ]	[ ]	[ ]	**Kerosene** space heater
06	[ ]	[ ]	[ ]	[ ]	**Fireplace**
07	[ ]	[ ]	[ ]	[ ]	**Wood** stove
	[ ]	[ ]	[ ]	[ ]	**Other** (specify)
	1	2	3	4	_____

90. How many months of the year do you heat your home?

_____ **months**

91. How many **YEARS** during your **childhood**, (up to 18 years), were each of the following types of **heating** used in your home? Please check **none** if **never** used.

	None	1–5	6–10	11–15	16+	
1	[ ]	[ ]	[ ]	[ ]	[ ]	**GAS**
2	[ ]	[ ]	[ ]	[ ]	[ ]	**WOOD**
3	[ ]	[ ]	[ ]	[ ]	[ ]	**COAL or OIL**
	[ ]	[ ]	[ ]	[ ]	[ ]	**OTHER** (specify)
	1	2	3	4	5	_____

92. How many **YEARS** during your **adult** life, (19 years and over), have each of the following types of **heating** been used in your home? Please check **none** if **never** used.

	None	1–5	6–10	11–20	21+	
1	[ ]	[ ]	[ ]	[ ]	[ ]	**GAS**
2	[ ]	[ ]	[ ]	[ ]	[ ]	**WOOD**
3	[ ]	[ ]	[ ]	[ ]	[ ]	**COAL or OIL**
	[ ]	[ ]	[ ]	[ ]	[ ]	**OTHER** (specify)
	1	2	3	4	5	_____

93. Have you ever lived in a home with a gas cooking stove?

1 [ ] No ⟹ skip to question 100
2 [ ] Yes, **CURRENTLY**
3 [ ] Yes, **IN THE PAST.**
Year last used
19_____

If you answered CURRENTLY to question 93, answer questions 94–98 for CURRENT use only.

If you answered IN THE PAST to question 93, answer questions 94–98 in terms of PAST USE.

94. How is (was) your gas cooking stove lighted?

1 [ ] Light by hand
2 [ ] Electric ignition
3 [ ] Pilot light ⟹ **how many pilots in range and oven?**

_____

PLEASE GO TO TOP OF NEXT COLUMN

PLEASE GO TO TOP OF NEXT PAGE

95. How often do (did) you use an exhaust fan or range hood when food is (was) being prepared on the stove?

1 [ ] Rarely or never
2 [ ] Occasionally (when kitchen is smoky or for odors)
3 [ ] At least half the time that the stove is on
4 [ ] Always/almost always, whenever stove is on

96. On the average, how many **hours per DAY** is (was) **COOKING** done with a **GAS** stove in your home?

1 [ ] None
2 [ ] Less than 1 hour per **day**
3 [ ] 1–2 hours per **day**
4 [ ] More than 2 hours per **day**

97. On the average, how many **hours per WEEK** is (was) **BAKING** done with a **GAS** oven in your home?

1 [ ] None
2 [ ] Less than 1 hour per **week**
3 [ ] 1–2 hours per **week**
4 [ ] 3–5 hours per **week**
5 [ ] 6 or more hours per **week**

98. During the winter, how frequently is (was) the range or stove used to help heat your house?

1 [ ] Never
2 [ ] Monthly or less
3 [ ] Weekly
4 [ ] Daily

99. For how many years have you lived in a home where a gas cooking stove was used?

_____ **years**

100. Do you have a gas water heater?

1 [ ] No
IF YES, where is it located?
2 [ ] Inside the home or in a closet inside the home
3 [ ] In the garage
4 [ ] Carport
5 [ ] In a closet accessed from outside the home
[ ] Other (specify)

_____

PLEASE GO TO TOP OF NEXT COLUMN

DIET AND MISCELLANEOUS

101. How often do you currently eat meat, poultry or fish when you are following your usual routine?

1 [ ] Never
2 [ ] Less than once per MONTH
3 [ ] 1–2 times per MONTH
4 [ ] 1–2 times per WEEK
5 [ ] 3–4 times per WEEK
6 [ ] 5–6 times per WEEK
7 [ ] Once per DAY
8 [ ] More than once per DAY

102. Has your use of meat, poultry or fish changed since 1976?

1 [ ] Never used in 1976 or after
2 [ ] Decreased since 1976
3 [ ] No change since 1976
4 [ ] Increased since 1976

103. How often do you currently drink **DECAFFEINATED** coffee when you are following your usual routine. Please note that the choices refer to the number of "TIMES" you use coffee (NOT the number of cups).

1 [ ] Never
2 [ ] Less than once per WEEK
3 [ ] 1–3 times per WEEK
4 [ ] 4–6 times per WEEK
5 [ ] Once per DAY
6 [ ] 2 times per DAY
7 [ ] 3 times per DAY
8 [ ] 4 times per DAY
9 [ ] 5 times per DAY
10 [ ] Over 5 times per DAY

104. How often do you currently drink **REGULAR (NOT decaffeinated)** coffee when you are following your usual routine. Please note that the choices refer to the number of "TIMES" you use coffee (NOT the number of cups).

1 [ ] Never
2 [ ] Less than once per WEEK
3 [ ] 1–3 times per WEEK
4 [ ] 4–6 times per WEEK
5 [ ] Once per DAY
6 [ ] 2 times per DAY
7 [ ] 3 times per DAY
8 [ ] 4 times per DAY
9 [ ] 5 times per DAY
10 [ ] Over 5 times per DAY

PLEASE GO TO TOP OF NEXT PAGE

105. If you drink coffee, on the average how many CUPS do you usually drink at one sitting? Don't forget refills at coffee shops or restaurants.

1 [ ] Never drink coffee
2 [ ] 1 Cup
3 [ ] 2 Cups
4 [ ] 3 Cups
5 [ ] 4 or more cups

106. If you drink coffee, what size cup do you usually use? The average cup contains 8 ounces, but some cups are larger or smaller.

1 [ ] Never drink coffee
2 [ ] 6 ounce cup or smaller
3 [ ] 8 ounce cup
4 [ ] 10 ounce cup
5 [ ] 12 ounce cup
6 [ ] 16 ounce cup or larger

107. Has your use of **DECAFFEINATED** coffee changed since 1976?

1 [ ] Never used in 1976 or after
2 [ ] Decreased since 1976
3 [ ] No change since 1976
4 [ ] Increased since 1976

108. Has your use of **REGULAR** coffee changed since 1976?

1 [ ] Never used in 1976 or after
2 [ ] Decreased since 1976
3 [ ] No change since 1976
4 [ ] Increased since 1976

109. How often do you currently drink **soft drinks** containing **caffeine** (such as Pepsi, Coca-Cola, Dr. Pepper, Mountain Dew, etc.)?

1 [ ] Never
2 [ ] Less than once per MONTH
3 [ ] 1-2 times per MONTH
4 [ ] 1-2 times per WEEK
5 [ ] 3-4 times per WEEK
6 [ ] 5-6 times per WEEK
7 [ ] Once per DAY
8 [ ] More than once per DAY

110. Has your use of **soft drinks** containing **caffeine** changed since 1976?

1 [ ] Never used in 1976 or after
2 [ ] Decreased since 1976
3 [ ] No change since 1976
4 [ ] Increased since 1976

PLEASE GO TO TOP OF NEXT COLUMN

111. What is your best estimate of your present weight in normal indoor clothing WITHOUT shoes?

_____ **pounds**

112. What is your sex?

1 [ ] Male
2 [ ] Female

113. What is your date of birth?

_____/_____/_____
month day year

114. What is your current affiliation with the Seventh-day Adventist (SDA) Church?

1 [ ] Current baptized member
2 [ ] Affiliated, but never baptized
3 [ ] Former SDA
4 [ ] No affiliation

115. Have you been hospitalized since January 1, 1983?

1 [ ] No
2 [ ] Yes

116. Since January 1, 1983, has a doctor told you (FOR THE FIRST TIME) that you had a tumor or cancer of any kind?

1 [ ] No
2 [ ] Yes → please give location or type of tumor_____
and date of diagnosis ____/____
month year

117. Since January 1, 1983 has a doctor told you (FOR THE FIRST TIME) that you had a Heart Attack or "Coronary" (Myocardial Infarction)?

1 [ ] No
2 [ ] Yes → Date of diagnosis ____/____
month year

MEN, This is the end of your questionnaire.

Please check the questionnaire to make sure that you have not left any questions blank which should have been answered.

Thank you very much for completing the questionnaire. Please fold it and mail it in the return envelope as soon as possible.

WOMEN, please continue with the **WOMEN ONLY** questions on the attached pink page.

WOMEN, please answer all the questions on both sides of this pink page.

118. Are you currently pregnant or nursing a baby?

1 [ ] No
2 [ ] Yes

119. Has your uterus been removed surgically?

1 [ ] No
2 [ ] Yes → AT WHAT AGE _____

120. Have one or both ovaries been removed surgically?

1 [ ] No
2 [ ] Not sure, but had surgery near my ovaries.
3 [ ] Had surgery on ovaries but not sure whether one or both were removed
4 [ ] Both ovaries removed → AT WHAT AGE(S)_____
5 [ ] Only one ovary removed → AT WHAT AGE_____

121. Are you currently having menstrual periods?

1 [ ] Yes, regularly
2 [ ] Yes, irregularly
3 [ ] Menstrual periods have completely stopped due to natural change of life
4 [ ] Past surgery stopped my menstrual periods

122. Have you EVER taken birth control pills (oral contraceptives)?

1 [ ] No → skip to question 128
2 [ ] Yes

123. When did you **FIRST** take birth control pills _____/_____
month year

124. When did you **LAST** take birth control pills _____/_____
month year

125. Approximately how many **years, in total**, did you take birth control pills (sum all years of use, but do not include gaps in between different periods of use)?
_____ **years**

126. What was the brand name of the **LAST** birth control pill that you used?_____

127. For how many **years** did you use this particular brand? _____ **years**

PLEASE GO TO TOP OF NEXT PAGE

128. **Other than birth control pills**, have you EVER taken female hormones (such as Estrogen or Premarin, Progesterone or Provera, etc.)?

1 [ ] No
2 [ ] Yes → If yes: Female hormones can be taken in four different ways. Have you taken hormones in any of the following ways, and if so, when and how long? Please **CIRCLE** no or yes for **EACH** of the four ways.

			Age Started	Age of most recent use	Total Years (excluding gaps)
Injections:	No	Yes →	_____	_____	_____
Vaginal creams or suppositories:	No	Yes →	_____	_____	_____
Pills by mouth:	No	Yes →	_____	_____	_____
Skin Patches:	No	Yes →	_____	_____	_____

129. If you have you ever taken **ORAL** estrogen pills (often called Premarin), were you **ALSO TAKING** progesterone (often called Provera) at the same time?

1 [ ] No
2 [ ] Yes → If yes: Out of every 30 day period, for **how many days** did you take?

Estrogen _____**days**

Progesterone _____**days**

130. If you have taken estrogen or progesterone pills **by mouth** for reasons **other than birth control**, please circle **EACH AGE** at which you took them.

Estrogen: (Premarin) under 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54
55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 70+

Progesterone: (Provera) under 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54
55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 70+

WOMEN, Please check the whole questionnaire to make sure that you have not left questions blank which should have been answered.

Thank you very much for completing the questionnaire. Please fold it and mail it in the return envelope as soon as possible.

APPENDIX C: 1992 AHSMOG Questionnaire

LOMA LINDA UNIVERSITY

Adventist Health Study
Evans Hall Room 204
Loma Linda, CA 92350
(714) 824-4268

Make sure you are the person named and that your address and telephone number are correct. See * below if this person is no longer living here.
If your **address** or **phone number** has **changed** please indicate your **new address** and **phone:**

_____
_____

New Phone (____) _____
area

Dear Friend,

In 1987, you were one of a select group from the Adventist Health Study who participated in a special study that was sponsored by the California Air Resources Board. Your response to previous questionnaires has been very much appreciated and the results of this study have been widely recognized and used by State and National Agencies. Once again we are seeking your cooperation and assistance in completing the following questionnaire.

It is important to the scientific validity of the study that all participants fill out the questionnaire as close as possible to the same point in time. Please take a few minutes now to complete this questionnaire and mail it in the enclosed, stamped, return envelope.

All the information will be kept strictly confidential and will be reported only in statistical summaries of large groups of people. Thank you for your important contribution to this research project.

Sincerely,

David E. Abbey, Ph.D.
Co-Director, Adventist Health Study

*If this person is no longer living at this address, please indicate the person's status and a new address if available or the contact name and address of a close relative and RETURN the **uncompleted** questionnaire in the enclosed envelope.

[ ] This person is deceased
[ ] This person is now living at a new address:

Name of contact person _____

Address _____

_____

A Seventh-day Adventist Institution

RESPIRATORY SYMPTOMS AND RESIDENCE
HISTORY QUESTIONNAIRE - 1992

INSTRUCTIONS

Check your **name, address** and **telephone number** on the first page adding or correcting address and telephone number if necessary. **Make sure you are the person named on the label.**

Please answer EVERY question. For some questions you may not remember the exact detail. If this is the case, then guess as closely as you can. DO NOT LEAVE QUESTIONS BLANK UNLESS ASKED TO SKIP THEM.

If you have any problems with some of the questions we will be glad to help you by phone. If this is the case, please answer all the questions as best you can, circle those you need help with, mail the questionnaire in, and we will call you back.

A number of the questions will ask what has happened to you since March, 1987. To help you remember if an event was before or after that date, it may be helpful for you to think back to that time in your life and remember major events that were happening.

1. Please enter today's date _____/___/___
month day year

COUGH

2. Do you usually cough first thing in the morning?

   [ ] Yes
   [ ] No

3. Do you usually cough at other times during the day or night?

   [ ] Yes
   [ ] No

4. Do you cough on most days for 3 months or more?

   [ ] Yes
   [ ] No

5. For how many years have you had a cough?

   [ ] Never
   [ ] Less than 1 year
   [ ] More than 1 but less than 2 years
   [ ] 2-5 years
   [ ] More than 5 years

SPUTUM

6. Do you usually bring up phlegm, sputum, or mucus from your chest first thing in the morning?

   [ ] Yes
   [ ] No

7. Do you usually bring up phlegm, sputum, or mucus from your chest at other times during the day or night?

   [ ] Yes
   [ ] No

8. Do you bring up phlegm, sputum, or mucus from your chest on most days for 3 months of the year or more?

   [ ] Yes
   [ ] No

9. For how many years have you raised phlegm, sputum, or mucus from your chest?

   [ ] Never
   [ ] Less than 1 year
   [ ] More than 1 but less than 2 years
   [ ] 2-5 years
   [ ] More than 5 years

PLEASE TURN PAGE OVER FOR NEXT QUESTION

SINUS

10. Have you ever had sinus trouble?

    [ ] Yes, still have it (Continue)
    [ ] Yes, but no longer have it (Continue)
    [ ] No (Skip to #14)

11. Was your sinus trouble ever diagnosed by a doctor?

    [ ] Yes, as sinusitis
    [ ] Yes, as something else
    [ ] No

12. At what age did you first have sinus trouble?

    _____ (age)

13. During the past year, how often were you unable to do your usual activities because of sinus trouble?

    [ ] None
    [ ] 1 time
    [ ] 2-5 times
    [ ] More than 5 times

WHEEZING

14. Does your breathing ever sound wheezy or whistling?

    [ ] Yes
    [ ] No

15. Does your chest ever sound wheezy or whistling? **(Check No or Yes for each)**

No	Yes	
[ ]	[ ]	When you have a cold
[ ]	[ ]	Occasionally apart from colds
[ ]	[ ]	Most days or nights

16. Have you ever had attacks of shortness of breath with wheezing?

    [ ] Yes (Continue)
    [ ] No (Skip to #19)

17. Have you had 2 or more such episodes?

    [ ] Yes
    [ ] No

18. Have you ever required medicine or treatment for the(se) attack(s)?

    [ ] Yes
    [ ] No

BREATHLESSNESS

19. Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?

    [ ] Yes
    [ ] No

20. Do you get short of breath when walking at a normal pace with other people of your own age on level ground?

    [ ] Yes
    [ ] No

RESPIRATORY ILLNESS

21. During the PAST YEAR, how often were you unable to do your usual activities because of illnesses such as chest colds, bronchitis, or pneumonia?

    [ ] None
    [ ] 1 time
    [ ] 2-5 times
    [ ] More than 5 times

22. Do you think you have ever had any of these chest disorders--asthma, any kind of bronchial condition, or emphysema?

    [ ] Yes
    [ ] No

PLEASE TURN PAGE OVER FOR NEXT QUESTION

23. Has a doctor ever told you that you had asthma, some kind of bronchial condition, or emphysema?

[ ] No (Skip to #36)
[ ] Yes
↳ IF YES, please check which conditions apply below and continue with #24

[ ] Asthma
[ ] Bronchial condition
[ ] Emphysema

THE FOLLOWING QUESTIONS REQUEST ADDITIONAL INFORMATION. PLEASE READ THEM CAREFULLY. WE NEED TO KNOW IF YOU HAVE HAD THESE AND OTHER CONDITIONS, AND THE AGE OF FIRST DIAGNOSIS.

ASTHMA

24. Have you ever had asthma?

[ ] Yes, still have it (Skip to #26)
[ ] Yes, but no longer have it (Continue)
[ ] No (Skip to #28)

25. If you no longer have it, at what age did it stop?

_____ (age)

26. Was your asthma ever confirmed by a doctor?

[ ] No
[ ] Yes
↳ At what age was it diagnosed?
_____ (age)

27. Are you currently taking medication for your asthma?

[ ] Yes
[ ] No

CHRONIC BRONCHITIS

28. Have you ever had chronic bronchitis?

[ ] Yes, still have it (Skip to #30)
[ ] Yes, but no longer have it (Continue)
[ ] No (Skip to #32)

29. If you no longer have it, at what age did it stop?

_____ (age)

30. Was your chronic bronchitis ever confirmed by a doctor?

[ ] No
[ ] Yes
↳ At what age was it diagnosed?
_____ (age)

31. Are you currently taking medication for your chronic bronchitis?

[ ] Yes
[ ] No

EMPHYSEMA

32. Have you ever had emphysema?

[ ] Yes, still have it (Skip to #34)
[ ] Yes, but no longer have it (Continue)
[ ] No, (Skip to #36)

33. If you no longer have it, at what age did it stop?

_____ (age)

34. Was your emphysema confirmed by a doctor?

[ ] No
[ ] Yes
↳ At what age was it diagnosed?
_____ (age)

35. Are you currently taking medication for your emphysema?

[ ] Yes
[ ] No

RESPIRATORY ALLERGIES

36. Do you currently experience seasonal respiratory allergies?

[ ] Yes, diagnosed by a physician
[ ] Yes, not diagnosed by a physician
[ ] No

PLEASE TURN PAGE OVER FOR NEXT QUESTION

POST NASAL DRIP

37. How many **days per month** during the SUMMER (June through September) are you bothered by stuffy nose or post-nasal drip (i.e. drainage from the back of your nose into your throat)?

    [ ] None
    [ ] 1-5 days
    [ ] 6-10 days
    [ ] 11-20 days
    [ ] 21 days or more

38. How many **days per month** during the **WINTER** (October through May) are you bothered by stuffy nose or post-nasal drip (i.e. drainage from the back of your nose into your throat)?

    [ ] None
    [ ] 1-5 days
    [ ] 6-10 days
    [ ] 11-20 days
    [ ] 21 days or more

EXPOSURE TO TOBACCO SMOKE

39. **SINCE MARCH OF 1987**, have you **EVER** smoked cigarettes, cigars, or a pipe?

    [ ] No
    [ ] Yes

40. Have you **EVER** lived for six months or more with someone who smoked?

    [ ] Yes (Please continue)
    [ ] No (Skip to #47)

41. How many years over your **lifetime** have you **lived** with someone who smoked?
    _____ years.

42. **SINCE MARCH, 1987**, have you ever **lived** for six months or more with someone who smoked?

    [ ] No (Skip to #47)
    [ ] Yes, but not currently (Continue)
    [ ] Yes, currently (Continue)

43. Which years **SINCE MARCH, 1987**, have you lived with someone who smoked? (Please check all that apply below)

    [ ] In 1987
    [ ] In 1988
    [ ] In 1989
    [ ] In 1990
    [ ] In 1991
    [ ] In 1992

44. During this period of time that you **lived** with someone who smoked, **SINCE MARCH, 1987**, check which years **you** were exposed to the tobacco smoke of:

    Your spouse
    [ ] None
    [ ] 1987
    [ ] 1988
    [ ] 1989
    [ ] 1990
    [ ] 1991
    [ ] 1992

    Others
    [ ] None
    [ ] 1987
    [ ] 1988
    [ ] 1989
    [ ] 1990
    [ ] 1991
    [ ] 1992

45. During the majority of these years that you lived with someone who smoked tobacco, **SINCE MARCH, 1987**, how many hours per day **on the average** were you exposed to tobacco smoke?

    [ ] None
    [ ] Less than 1 hour per day
    [ ] 1-2 hours per day
    [ ] 3-5 hours per day
    [ ] 6-8 hours per day
    [ ] 9 or more hours per day

PLEASE TURN PAGE OVER FOR NEXT QUESTION

46. How many people regularly smoked **inside your home** during this period of time?

[ ] None
[ ] 1
[ ] 2
[ ] 3 or more

47. Are cigarettes, pipes, or cigars **currently** smoked **in** your home?

[ ] No (Skip to #50)
[ ] Yes (Continue)

48. How many people currently smoke in your home?

[ ] None
[ ] 1
[ ] 2
[ ] 3 or more

49. Approximately how many cigarettes, pipefulls, and/or cigars are currently smoked in your home during the average day? (1 pack = 20 cigarettes)

_____ # cigarettes
_____ # pipefulls
_____ # cigars

WORK EXPOSURE TO TOBACCO SMOKE

50. **SINCE MARCH, 1987,** have you **ever** worked where someone smoked in the same room or enclosed space in which you **worked?**

[ ] No (Skip to #53)
[ ] Yes, but not currently (Please continue)
[ ] Yes, currently (Please continue)

51. **SINCE MARCH, 1987, how many years** have you **worked** where someone smoked in the same room or enclosed space in which you worked?

_____ number of years → **Which years?** **(Check all that apply below)** ↓

[ ] In 1987 [ ] In 1988 [ ] In 1989
[ ] In 1990 [ ] In 1991 [ ] In 1992

52. During the years that you **worked SINCE MARCH, 1987,** where someone smoked tobacco in the same room or enclosed space as you worked, how many hours per day **on the average** were you exposed to tobacco smoke?

[ ] None
[ ] Less than 1 hour per day
[ ] 1-2 hours per day
[ ] 3-5 hours per day
[ ] 6 or more hours per day

53. Please estimate the **total** number of hours per day on the average that you are **CURRENTLY** exposed to someone else's tobacco smoke. Then do the same for exposure **DURING THE LAST FIVE YEARS.** (Include time in the home, work, in automobiles, public transport and social situations that you are/were exposed to other people's tobacco smoke.)

AVERAGE **CURRENT** EXPOSURE
[ ] None
[ ] Less than 1 hour per day
[ ] 1-2 hours per day
[ ] 3-5 hours per day
[ ] 6-8 hours per day
[ ] 9 or more hours per day

AVERAGE **DURING THE LAST 5 YEARS**
[ ] None
[ ] Less than 1 hour per day
[ ] 1-2 hours per day
[ ] 3-5 hours per day
[ ] 6-8 hours per day
[ ] 9 or more hours per day

PLEASE TURN PAGE OVER FOR NEXT QUESTION

54. In total, approximately how many **hours per week** do you usually spend **driving** or **riding** on **any type of roadway?**

[ ] Never ride or drive on a weekly basis
[ ] 2 or less hours per week
[ ] 3-4 hours per week
[ ] 5-6 hours per week
[ ] 7-10 hours per week
[ ] 11-15 hours per week
[ ] 16-20 hours per week
[ ] Over 20 hours per week

55. How long are you usually away from home during the **SUMMER (June through September?)**

[ ] 2 weeks or less
[ ] 3-4 weeks
[ ] 5-6 weeks
[ ] 7-8 weeks
[ ] 9 weeks or more

56. How many hours per **WEEK**, including weekends, do you **exercise vigorously** or do heavy physical labor (e.g. jogging, tennis, gardening, etc.) in the **open air** during the **SUMMER (June through September)?**

[ ] None
[ ] 1-3 hours
[ ] 4-7 hours
[ ] 8-14 hours
[ ] 15-21 hours
[ ] 22-28 hours
[ ] 29-35 hours
[ ] 36-42 hours
[ ] more than 42 hours

Keep going, you're halfway there!

57. How many hours per **WEEK**, including weekends, do you **exercise vigorously** or do heavy physical labor (e.g. jogging, tennis, gardening, etc.) in the **open air** during the **REST OF THE YEAR (October through May)?**

[ ] None
[ ] 1-3 hours
[ ] 4-7 hours
[ ] 8-14 hours
[ ] 15-21 hours
[ ] 22-28 hours
[ ] 29-35 hours
[ ] 36-42 hours
[ ] more than 42 hours

58. How many hours per **WEEK**, including weekends, are you **outside of buildings** in the **SUMMER (June through September)?**

[ ] None
[ ] 1-7 hours
[ ] 8-14 hours
[ ] 15-21 hours
[ ] 22-28 hours
[ ] 29-35 hours
[ ] 36-42 hours
[ ] more than 42 hours

59. How many hours per **WEEK**, including weekends, are you **outside of buildings** during the **REST OF THE YEAR (October through May)?**

[ ] None
[ ] 1-7 hours
[ ] 8-14 hours
[ ] 15-21 hours
[ ] 22-28 hours
[ ] 29-35 hours
[ ] 36-42 hours
[ ] more than 42 hours

60. Have you moved or been away from home for **more than one month at a time since March, 1987?**

[ ] No (Skip to #62)
[ ] Yes, I have moved (Continue with #61)
[ ] Yes, I have been away for more than 1 month.
_____ How many months?
(Continue with #61)

PLEASE TURN PAGE OVER FOR NEXT QUESTION

61. For each community in which you have lived or stayed for one month or more SINCE MARCH, 1987, please give the information requested below. For large cities, please give the section of the city. **Please start with your residence in 1987 and work toward the present.**

Town	State	Zip	When did you start living in this town? Month	Year

62. Have you worked (even on a part time or volunteer basis) **SINCE MARCH, 1987?**

[ ] No (Skip to #83)
[ ] Yes (Please continue)

63. **SINCE MARCH, 1987,** have you changed your **occupation** or your **location** of work?

[ ] No
[ ] Yes

64. **SINCE MARCH, 1987,** have you worked for 1 month or more at a location more than 5 miles from your home?

[ ] No (Skip to #66)
[ ] Yes (Continue)

65. If you have **worked more than 5 miles** from home **SINCE MARCH, 1987,** give the work locations and dates.

Started Job: MO.	YR.	Ended Job: MO.	YR.	TOWN OF WORK	STATE	ZIP CODE OF WORK PLACE

PLEASE TURN PAGE OVER FOR NEXT QUESTION

66. What is your current employment status?

[ ] Unemployed (Skip to #71)
[ ] Full time homemaker
[ ] Working part time
[ ] Working full time
[ ] Retired and not working
[ ] Retired and working part time
[ ] Retired but working full time
→ IF RETIRED, please give date of retirement

_____/_____ **(Skip to #71 if not currently working)**
month year

67. Do you work at least part time away from your home?

[ ] Yes (Please continue)
[ ] No (Skip to #71)

68. What time of day do you usually arrive at your work place? (Please check the nearest hour).

[ ] I am not currently working (Skip to #71)
[ ] 7 a.m.
[ ] 8 a.m.
[ ] 9 a.m.
[ ] Other (Please specify _____)

69. What time of day do you usually leave your workplace? (Please check the nearest hour).

[ ] 4 p.m.
[ ] 5 p.m.
[ ] 6 p.m.
[ ] Other (Please specify _____)

70. What type of air cooling system do you currently have at your work place?

[ ] None
[ ] Evaporative cooler (swamp cooler)
[ ] Refrigerating type (air conditioner)
[ ] Both

71. **SINCE MARCH, 1987,** have you worked at least part time?

[ ] Yes (Please continue)
[ ] No (Skip to #83)

72. **SINCE MARCH, 1987,** what type of air cooling system/systems have you had at your place or places of work most of the time?

[ ] None
[ ] Evaporative cooler (swamp cooler)
[ ] Refrigerating type (air conditioner)
[ ] Both

73. **SINCE MARCH, 1987,** what has been your usual or **MAIN** type of work when you have worked?

Job Title _____

Type of business or industry:

_____

Major duties or responsibilities:

_____

74. Which of the following describes the setting at this type of work? Please check the **one** main category and give hours per day.

[ ] Indoors → _____ hours per day
[ ] Outdoors → _____ hours per day
(Skip to #76)
[ ] In a vehicle → _____ hours per day
(Skip to #76)

75. Which of the following best describes the **indoor** setting at this type of work?

[ ] Office, educational facility
[ ] Medical facility
[ ] Warehouse, factory, plant
[ ] Retail, sales
[ ] Other (Specify)

_____

76. **SINCE MARCH, 1987,** how many years have you done this type of work?

_____ years **SINCE MARCH, 1987.**

77. Are you currently employed in this type of work?

[ ] No
[ ] Yes (Skip to #79)

78. When were you last employed in this type of work? _____/_____
month year

PLEASE TURN PAGE OVER FOR NEXT QUESTION

79. **SINCE MARCH, 1987,** have you ever worked (for 3 months or more) where you were exposed much of the time as a **part of your job** to any of the following? If so, write in the approximate number of years you were exposed to each agent and the year when last exposed.

[ ] Check here if no **regular** exposure to any of the below and skip to #81

Number of **Years** of Exposure **Since March, 1987**	**Year When Last Exposed**	
_____	_____	Radiation, X-ray
		DUSTS
_____	_____	Sand or rock dust
_____	_____	Asbestos
_____	_____	Talc, graphite
_____	_____	Fiberglass, rock wool
_____	_____	Sawdust
_____	_____	Metal dust
_____	_____	Road, soil dust
		Other dusts (specify **dates & dusts**)
_____	_____	_____
_____	_____	_____
_____	_____	_____
		FUMES
_____	_____	Paint fumes
_____	_____	Formaldehyde
_____	_____	Solvents
_____	_____	Insecticides
_____	_____	Resins or glue
_____	_____	Diesel fumes
_____	_____	Freon or refrigerates
_____	_____	Auto exhaust
_____	_____	Solder (or flux) fumes
_____	_____	Welding fumes/ nitrogen oxides
		Other **fumes** or airborne contaminants (specify **dates & fumes**)
_____	_____	_____
_____	_____	_____
_____	_____	_____

80. Please specify the types of jobs or industries where you have had the above exposures **SINCE MARCH, 1987.**

Industries	**Job Duties**
_____	_____
_____	_____
_____	_____

81. Would you rate your exposures to **dust** at work (**SINCE MARCH, 1987,** or at present if currently exposed) as

[ ] None
[ ] Mild
[ ] Moderate
[ ] Severe

82. Would you rate your exposures to **fumes** or **airborne contaminants** at work (**SINCE MARCH, 1987,** or at present if currently exposed) as:

[ ] None
[ ] Mild
[ ] Moderate
[ ] Severe

HOBBIES

83. Have you ever had hobbies where you were exposed to moderate or severe levels of **dust or fumes** for three months or more?

[ ] No
[ ] Yes → How many years? _____

RESIDENCE

84. Are you currently living in the same home where you lived in **MARCH, 1987**?

[ ] Yes
[ ] No

85. How many years have you lived in your present home?

_____ Years

PLEASE TURN PAGE OVER FOR NEXT QUESTION

86. What type of building do you live in?

[ ] Single family home detached from any other house
[ ] Single family home attached to one or more houses (for example, a townhouse, duplex, triplex)
[ ] Mobile home or trailer
[ ] Apartment, condominium with more than 3 units
[ ] Other, please specify _____

87. About when was your home originally built? Please consider when it was originally built, not when it was remodeled, added to, or converted (please check only one box).

[ ] 1949 or earlier
[ ] 1950-1959
[ ] 1960-1969
[ ] 1970-1974
[ ] 1975-1979
[ ] 1980-1984
[ ] 1985 to present

88. How many rooms do you have in your home? (Do not count bathrooms, porches, balconies, foyers, or halls)

_____ rooms

89. How many **bedrooms** are there in your home?

_____

90. Approximately what percentage of the total usable floorspace in your home is covered by rugs or carpets? Please check nearest category.

[ ] None
[ ] 1 - 20%
[ ] 21 - 40%
[ ] 41 - 60%
[ ] 61 - 80%
[ ] 81 - 100%

91. How many individuals live in your home **including** yourself?

_____

92. Do you have any pets, such as dogs or cats or other **FURRY** animals, which usually spend some time each day in your home?

[ ] Yes
[ ] No

93. Do you have any birds in your home?

[ ] Yes
[ ] No

94. Is there a dirt drive, road or alley within 100 yards of your home?

[ ] Yes
[ ] No

95. Where are cars/vehicles usually parked near your living quarters? (Check all that apply)

[ ] In an underground garage
[ ] In an attached garage
[ ] In an attached carport
[ ] Garage or carport detached from your living quarters
[ ] On the street next to living quarters
[ ] In the yard or driveway next to living quarters
[ ] Other (specify) _____

96. What type of air cooling system do you have in your home?

[ ] None
[ ] Evaporative cooler (swamp cooler)
[ ] Refrigerating type (air conditioner)
[ ] Both

97. How many years have you had this type of air cooling system in your home?

_____ years

98. Do you have central air conditioning?

[ ] Yes
[ ] No

99. Which months of the year do you usually use **a cooling system** in your home? (Please check all that apply below)

[ ] None

[ ] January	[ ] May	[ ] September
[ ] February	[ ] June	[ ] October
[ ] March	[ ] July	[ ] November
[ ] April	[ ] August	[ ] December

PLEASE TURN PAGE OVER FOR NEXT QUESTION

100. Which months of the year do you use **natural ventilation** (open doors or windows) in your home? (Please check all that apply below)

[ ] None
[ ] January [ ] May [ ] September
[ ] February [ ] June [ ] October
[ ] March [ ] July [ ] November
[ ] April [ ] August [ ] December

101. How frequently are the following **heating** systems used in your home during the **winter months**? Be sure to check one of the categories for each type of heating, (a) through (i) as well as other types you may write in. **Please check never if not used or you do not have.**

		Never	Monthly or less	Weekly	Daily
a.	Gas forced air furnace	[ ]	[ ]	[ ]	[ ]
b.	Gas wall furnace	[ ]	[ ]	[ ]	[ ]
c.	Gas floor furnace	[ ]	[ ]	[ ]	[ ]
d.	Gas space heater	[ ]	[ ]	[ ]	[ ]
e.	Kerosene space heater	[ ]	[ ]	[ ]	[ ]
f.	Fireplace with **wood**	[ ]	[ ]	[ ]	[ ]
g.	Fireplace with **gas logs**	[ ]	[ ]	[ ]	[ ]
h.	Wood stove	[ ]	[ ]	[ ]	[ ]
i.	Electric	[ ]	[ ]	[ ]	[ ]
j.	Other (please specify)				
	_____	[ ]	[ ]	[ ]	[ ]
	_____	[ ]	[ ]	[ ]	[ ]

102. Which years **SINCE MARCH, 1987,** have **each of the following types** of heating been used in your home? Please check **none if never used or you do not have.** Be sure to answer each of the questions (a) through (d) below.

	None	87	88	89	90	91	92
a. GAS	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
b. WOOD	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
c. COAL or OIL	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
d. ELECTRIC	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
e. OTHER (Please specify) _____	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]

103. Did you check **never** or **none** in questions 101 & 102, for the types of heating you do not have or have not used? If not, please go back now, and mark the approriate boxes.

104. Which months of the year do you usually **heat** your home? (Please check all that apply below.)

[ ] None
[ ] January [ ] May [ ] September
[ ] February [ ] June [ ] October
[ ] March [ ] July [ ] November
[ ] April [ ] August [ ] December

105. Do you have central heating?

[ ] Yes
[ ] No

106. Does your kitchen have a separate ceiling/exhaust fan that vents air to the outside?

[ ] No
[ ] Yes
↓→ If YES, how often do you use it?

[ ] Rarely or never
[ ] Occasionally (when kitchen is smoky)
[ ] At least half the time stove is on
[ ] Always/almost always, when stove is on

107. **SINCE MARCH, 1987,** have you ever lived in a home with a gas cooking stove?

[ ] No (Skip to #113)
[ ] Yes, CURRENTLY
[ ] Yes, BUT ONLY IN THE PAST
↓→ Year last used 19_____

If you answered CURRENTLY to question 107, answer questions 108-111 for CURRENT use only.
If you answered IN THE PAST to question 107, answer questions 108-111 in terms of PAST use.

108. How is (was) your gas cooking stove lighted?

[ ] Light by hand
[ ] Electronic ignition
[ ] Pilot light →→ **how many pilots in range and oven?** _____

PLEASE TURN PAGE OVER FOR NEXT QUESTION

109. On the average, how many hours per DAY is (was) COOKING done with a GAS stove in your home?

[ ] None
[ ] Less than 1 hour per day
[ ] 1-2 hours per day
[ ] More than 2 hours per day

110. On the average, how many hours per WEEK is (was) BAKING done with a GAS oven in your home?

[ ] None
[ ] Less than 1 hour per **week**
[ ] 1-2 hours per **week**
[ ] 3-5 hours per **week**
[ ] 6 or more hours per **week**

111. During the winter, how frequently is (was) the range or stove used to help heat your house?

[ ] Never
[ ] Monthly or less
[ ] Weekly
[ ] Daily

112. **SINCE MARCH, 1987,** which years have you lived in a home where a gas cooking stove was used? (Please check all that apply.)

[ ] Never
[ ] 1987
[ ] 1988
[ ] 1989
[ ] 1990
[ ] 1991
[ ] 1992

113. Do you have a gas water heater?

[ ] No
[ ] Yes
→ IF YES, where is it located?

[ ] Inside the home or in a closet inside the home
[ ] In the garage
[ ] Carport
[ ] In a closet accessed from outside the home
[ ] Other (specify)
_____

114. Do you have an **unvented** gas heater in the house or an attached structure?

[ ] Yes
[ ] No

115. Do you have an **unvented** kerosene heater in the house or an attached structure?

[ ] Yes
[ ] No

116. What is your best estimate of your present weight in normal indoor clothing WITHOUT shoes?

_____ **pounds**

117. What is your sex?

[ ] Male
[ ] Female

118. What is your date of birth?

_____/_____/_____
month day year

119. What is your current affiliation with the Seventh-day Adventist (SDA) Church?

[ ] Current baptized member
[ ] Affiliated, but never baptized
[ ] Former SDA
[ ] No affiliation

120. Have you been hospitalized **since March, 1987?**

[ ] No
[ ] Yes

121. **Since March, 1987,** has your doctor told you (for the first time) that you had a tumor or cancer of any kind?

[ ] No (Skip to #124)
[ ] Yes
→ Please give location, type of tumor _____
_____
→ and date of diagnosis _____/____
month year

PLEASE TURN PAGE OVER FOR NEXT QUESTION

122. Please give the name and address of the physician and name and address of the hospital where your cancer was diagnosed.

Physician name and address:

_____

_____

_____

Hospital name and address:

_____

_____

_____

123. In order to keep track of the occurrence of serious illness among participants in this study, we need to review the medical records regarding your cancer diagnosis. Please sign the statement below giving permission to review these records. This permission will make it possible for your doctor or hospital to allow us to review your records.

I hereby authorize the Adventist Health Study of Loma Linda University to examine my medical records filed in the above mentioned hospital or doctor's office.

_____ _____

Your signature *Date*

124. Please give the name and address of someone who is not living with you who will always know your address if you move.

Name_____

Address_____

City_____State_____Zip_____

Phone(_____)_____
area code

Please check the questionnaire to make sure that you have not left any questions blank which should have been answered.

Thank you very much for completing the questionnaire. Please fold it and mail it in the return envelope as soon as possible.

APPENDIX D: 1993 AHSMOG Lung Health Questionnaire

LOMA LINDA UNIVERSITY

Adventist Health Study
Evans Hall Room 215
Loma Linda, CA 92350
(909) 824-4268

LUNG HEALTH QUESTIONNAIRE - 1993

Dear Friend:

We sincerely appreciate your participation in this study since 1976. As the study goes on, your continued participation becomes more and more important. We thank you for coming to the testing today and ask your cooperation in answering the enclosed questions.

Sincerely,

David E. Abbey

David E. Abbey, Ph.D.
Principal Investigator, Adventist Health Study

INSTRUCTIONS

Make sure you are the person named on the label. Please answer EVERY question. Some of the questions are similar to those which were on the 1992 questionnaire, but we need them to update information. For some questions you may not remember the exact detail. If this is the case, then guess as closely as you can.

A number of the questions will ask what has happened to you **SINCE** completing the 1992 questionnaire. **This date was:** _____/_____/**1992**

1. Please enter today's date ___/___/___
   month day year

COUGH

2. Do you usually cough first thing in the morning?

   1[ ]Yes
   2[ ]No

3. Do you usually cough at other times during the day or night?

   1[ ] Yes
   2[ ] No

4. Do you cough on most days for 3 months or more?

   1[ ] Yes
   2[ ] No

5. For how many years have you had a cough?

   1[ ] Never
   2[ ] Less than 1 year
   3[ ] More than 1 but less than 2 years
   4[ ] 2-5 years
   5[ ] More than 5 years

SPUTUM

6. Do you usually bring up phlegm, sputum, or mucus from your chest first thing in the morning?

   1[ ] Yes
   2[ ] No

7. Do you usually bring up phlegm, sputum, or mucus from your chest at other times during the day or night?

   1[ ] Yes
   2[ ] No

8. Do you bring up phlegm, sputum, or mucus from your chest on most days for 3 months of the year or more?

   1[ ] Yes
   2[ ] No

9. For how many years have you raise phlegm, sputum, or mucus from your chest?

   1[ ] Never
   2[ ] Less than 1 year
   3[ ] More than 1 but less than 2 years
   4[ ] 2-5 years
   5[ ] More than 5 years

WHEEZING

10. Does your breathing ever sound wheezy or whistling?

    1[ ] Yes
    2[ ] No

11. Does your chest ever sound wheezy or whistling?
    (Check No or Yes for each).

No	Yes	
1[ ]	2[ ]	When you have a cold
1[ ]	2[ ]	Occasionally apart from colds
1[ ]	2[ ]	Most days or nights

PLEASE GO TO TOP OF NEXT COLUMN

PLEASE GO TO TOP OF NEXT PAGE

12. Have you ever had attacks of shortness of breath with wheezing?

1[ ] Yes **(Continue)**
2[ ] No **(Skip to #16)**

13. DURING THE PAST YEAR, how many attacks of shortness of breath with wheezing have you had?

1[ ] No attacks **(Skip to #16)**
2[ ] A few (1-3) attacks
3[ ] Several (4-12) attacks
4[ ] Many (13 or more) attacks
5[ ] Attacks almost every day

14. DURING THE PAST YEAR, have you seen a doctor about these attacks?

1[ ] Yes
2[ ] No

15. DURING THE PAST YEAR, have you required medicine or treatment for the(se) attack(s)?

1[ ] Yes
2[ ] No

BREATHLESSNESS

16. Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?

1[ ] Yes
2[ ] No

17. Do you get short of breath when walking at a normal pace with other people of your own age on level ground?

1[ ] Yes
2[ ] No

RESPIRATORY ILLNESS

18. Has a doctor ever told you that you had asthma, some kind of bronchial condition, or emphysema?

1[ ] No **(Skip to #30)**
[ ] Yes
↓→→ IF YES, please check which conditions apply below and **continue with #19**
1[ ] Asthma
1[ ] Bronchial condition
1[ ] Emphysema

ASTHMA

19. Have you ever had asthma?

1[ ] Yes, still have it **(Continue)**
2[ ] Yes, but no longer have it **(Continue)**
3[ ] No **(Skip to #24)**

20. DURING THE PAST YEAR, how many asthma attacks did you have?

1[ ] No attacks **(Skip to #24)**
2[ ] A few (1-3) attacks
3[ ] Several (4-12) attacks
4[ ] Many (13 or more) attacks
5[ ] Attacks almost every day

21. DURING THE PAST YEAR, have you ever awakened at night with an asthma attack or wheezing?

1[ ] Yes
2[ ] No

22. DURING THE PAST YEAR, have you seen a doctor for it?

1[ ] Yes
2[ ] No

23. Are you currently taking medication for your asthma?

1[ ] Yes
2[ ] No

PLEASE GO TO TOP OF NEXT COLUMN

PLEASE GO TO TOP OF NEXT PAGE

CHRONIC BRONCHITIS

24. Have you ever had Chronic Bronchitis?

1[ ] Yes, still have it **(Continue)**
2[ ] Yes, but no longer have it **(Continue)**
3[ ] No **(Skip to #27)**

25. DURING THE PAST YEAR, have you seen a doctor for it?

1[ ] Yes
2[ ] No

26. Are you currently taking medication for your chronic bronchitis?

1[ ] Yes
2[ ] No

EMPHYSEMA

27. Have you ever had emphysema?
1[ ] Yes, still have it **(Continue)**
2[ ] Yes, but no longer have it **(Continue)**
3[ ] No **(Skip to #30)**

28. DURING THE PAST YEAR, have you seen a doctor for it?
1[ ] Yes
2[ ] No

29. Are you currently taking medication for your emphysema?
1[ ] Yes
2[ ] No

RESPIRATORY ALLERGIES

30. Do you currently experience seasonal respiratory allergies?

1[ ] Yes, diagnosed by a physician
2[ ] Yes, not diagnosed by a physician
3[ ] No

31. Did your **BIRTH/NATURAL father EVER have any of the following conditions?** Please check NO or Yes for **each** condition.

1[ ] Check here if you don't know who your natural father was.

No Yes
1[ ] 2[ ] Chronic bronchitis
1[ ] 2[ ] Emphysema
1[ ] 2[ ] Asthma
1[ ] 2[ ] Lung Cancer
1[ ] 2[ ] Other Chest or Lung Condition
↓→→ Specify _____

1[ ] 2[ ] Cancer, other than lung
↓→→ Specify _____

1[ ] 2[ ] Hay fever
1[ ] 2[ ] Other severe allergies

32. Did your **BIRTH/NATURAL mother EVER have any of the following conditions?** Please check NO or Yes for **each** condition

1[ ] Check here if you don't know who your natural mother was.

No Yes
1[ ] 2[ ] Chronic bronchitis
1[ ] 2[ ] Emphysema
1[ ] 2[ ] Asthma
1[ ] 2[ ] Lung Cancer
1[ ] 2[ ] Other Chest or Lung Condition
↓→→ Specify _____

1[ ] 2[ ] Cancer, other than lung
↓→→ Specify _____

1[ ] 2[ ] Hay fever
1[ ] 2[ ] Other severe allergies

EXPOSURE TO TOBACCO SMOKE

33. During the past year have you **EVER** smoked cigarettes, cigars, or a pipe?

1[ ] Yes
2[ ] No

PLEASE GO TO TOP OF NEXT COLUMN

PLEASE GO TO TOP OF NEXT PAGE

34. **SINCE THE 1992 QUESTIONNAIRE,** have you **lived** with someone who smoked?

1[ ] No **(Skip to #40)**
2[ ] Yes, but not currently **(Continue)**
3[ ] Yes, currently **(Continue)**

35. When did you last **live** with someone who smoked?

_____month, _____year.

36. How many months, **SINCE THE 1992 QUESTIONNAIRE,** have you **lived** with someone who smoked?

1[ ] Less than 1 month
2[ ] 1-2 months
3[ ] 3-5 months
4[ ] 6-9 months
5[ ] more than 9 months

37. During this period of time that you **lived** with someone who smoked, **SINCE THE 1992 QUESTIONNAIRE,** were you exposed to the tobacco smoke of:

Your spouse
1[ ] Yes
2[ ] No

Others
1[ ] Yes
2[ ] No

38. During the majority of the time that you lived with someone who smoked tobacco, **SINCE THE 1992 QUESTIONNAIRE,** how many hours per day **on the average** were you exposed to tobacco smoke:

1[ ] None
2[ ] Less than 1 hour per day
3[ ] 1-2 hours per day
4[ ] 3-5 hours per day
5[ ] 6-9 hours per day
6[ ] More than 9 hours per day

39. How many people regularly smoked **inside your home** during this period of time?

1[ ] None
2[ ] 1
3[ ] 2
4[ ] 3 or more

40. Are cigarettes, pipes, or cigars **currently** smoked **in** your home?

1[ ] No **(Skip to #43)**
2[ ] Yes **(Continue)**

41. How many people currently smoke in your home?

1[ ] None
2[ ] 1
3[ ] 2
4[ ] 3 or more

42. Approximately how many cigarettes, pipefulls, and/or cigars are currently smoked in your home during the average day? (1 pack = 20 cigarettes)

_____ # cigarettes
_____ # pipefulls
_____ # cigars

WORK EXPOSURE TO TOBACCO SMOKE

43. **SINCE THE 1992 QUESTIONNAIRE,** have you **ever** worked where someone smoked in the same room or enclosed space in which you **worked?**

1[ ] No **(Skip to #46)**
2[ ] Yes, but not currently **(Continue)**
3[ ] Yes, currently **(Continue)**

44. **SINCE THE 1992 QUESTIONNAIRE,** how many months have you **worked** where someone smoked in the same room or enclosed space in which you worked?

1[ ] Less than 1 month
2[ ] 1-2 months
3[ ] 3-5 months
4[ ] 6-9 months
5[ ] More than 9 months

PLEASE GO TO TOP OF NEXT COLUMN

PLEASE GO TO TOP OF NEXT PAGE

45. During the months that you **worked SINCE THE 1992 QUESTIONNAIRE,** where someone smoked tobacco in the same room or enclosed space as you worked, how many hours per day **on the average** were you exposed to tobacco smoke?

1[ ] None
2[ ] Less than 1 hour per day
3[ ] 1-2 hours per day
4[ ] 3-5 hours per day
5[ ] 6 or more hours per day

46. Please estimate the **total** number of hours per day on the average that you are **CURRENTLY** exposed to someone else's tobacco smoke. Then do the same for exposure **DURING THE LAST 12 MONTHS.** (Include time in the home, work, in automobiles, public transport and social situations that you are/were exposed to other people's tobacco smoke.)

AVERAGE **CURRENT** EXPOSURE
1[ ] None
2[ ] Less than 1 hour per day
3[ ] 1-2 hours per day
4[ ] 3-5 hours per day
5[ ] 6-8 hours per day
6[ ] 9 or more hours per day

AVERAGE **DURING THE LAST 12 MONTHS**
1[ ] None
2[ ] Less than 1 hour per day
3[ ] 1-2 hours per day
4[ ] 3-5 hours per day
5[ ] 6-8 hours per day
6[ ] 9 or more hours per day

47. In total, approximately how many **hours per week** do you usually spend **driving** or **riding** on **any type of roadway?**

1[ ] Never ride or drive on a weekly basis
2[ ] 2 or less hours per week
3[ ] 3-4 hours per week
4[ ] 5-6 hours per week
5[ ] 7-10 hours per week
6[ ] 11-15 hours per week
7[ ] 16-20 hours per week
8[ ] Over 20 hours per week

48. How long were you away from home during the **SUMMER of 1992 (June throug' September?)**

1[ ] 2 weeks or less
2[ ] 3-4 weeks
3[ ] 5-6 weeks
4[ ] 7-8 weeks
5[ ] 9 weeks or more

49. How many hours per **WEEK,** including weekends, were you **outside of buildings** in the **SUMMER of 1992 (June through September)?**

1[ ] None
2[ ] 1-7 hours
3[ ] 8-14 hours
4[ ] 15-21 hours
5[ ] 22-28 hours
6[ ] 29-35 hours
7[ ] 36-42 hours
8[ ] more than 42 hours

50. How many hours per **WEEK,** including weekends, were you **outside of building** during the **REST OF THE YEAR (since September)?**

1[ ] None
2[ ] 1-7 hours
3[ ] 8-14 hours
4[ ] 15-21 hours
5[ ] 22-28 hours
6[ ] 29-35 hours
7[ ] 36-42 hours
8[ ] more than 42 hours

51. **SINCE THE 1992 QUESTIONNAIRE,** have you ever had hobbies where you were exposed to moderate or severe levels of **dust or fumes** for three months or more?
1[ ] No
2[ ] Yes → How many months? _____

52. What is your best estimate of your present weight in normal indoor clothing WITHOUT shoes?

_____ **pounds**

PLEASE GO TO TOP OF NEXT COLUMN

PLEASE GO TO TOP OF NEXT PAGE

53. What is your best estimate of your present height WITHOUT shoes?

_____ft _____ins.

54. What is your date of birth?

_____/_____/_____
month day year

55. What is your current affiliation with the Seventh-day Adventist (SDA) Church?

1[ ] Current baptized member
2[ ] Affiliated, but never baptized
3[ ] Former SDA
4[ ] No affiliation

56. Have you ever had an abnormal chest X-ray?

1[ ] No
2[ ] Yes
↓→→ IF YES, where:

Name of hospital/testing site:_____

Address of hospital/testing site: _____

_____

57. Please give the name and address of current physician. If you have more than one, please give name and address of the one you see for respiratory problems.

Name of physician: _____

Address of physician: _____

_____

_____

58. In order to keep track of the occurrence of serious illness among participants in this study, we need to review the medical records. Please sign the statement below giving permission to review the records of the above mentioned hospital or doctor's office. This permission will make it possible for your doctor to allow us to review your records.

I hereby authorize the Adventist Health Study of Loma Linda University to examine my medical records filed in the above mentioned hospital or doctor's office.

_____ _____
Your Signature *Date*

PLEASE GO TO TOP OF NEXT PAGE

59. Please give the name and address of someone who is not living with you who will always know your address if you move.

Name _____ (relationship, if any:)_____

Address _____

City _____ State _____ Zip _____

Phone (_____)_____
area code

Please check the questionnaire to make sure that you have not left any questions blank which should have been answered.

Thank you very much for completing the questionnaire.

APPENDIX E: 2000 AHSMOG Questionnaire

LOMA LINDA UNIVERSITY

Adventist Health Study
Evans Hall Room 215
Loma Linda, CA 92350
(800) 247-1699

Make sure you are the person named and that your address and telephone number are correct.
See * below if this person is no longer living here.
If your **address** or **phone number** has **changed** please indicate your **new address** and **phone:**

_____

_____

New Phone (____)_____

Dear Friend,

In 1992, you were one of a select group from the Adventist Health Study who participated in a special study that was sponsored by the Environmental Protection Agency. Your response to previous questionnaires has been very much appreciated and the results of this study have been widely recognized in the scientific community and has contributed to establishing standards for cleaner air in the US and elsewhere. Once again we are seeking your cooperation and assistance.

Please take a few minutes now to complete this questionnaire and mail it in the enclosed stamped, return envelope.

All the information will be kept strictly confidential and will be reported only in statistical summaries of large groups of people. Thank you for your important contribution to this research project.

Sincerely,

Synnove F. Knutsen, MD, PhD
Principal Investigator
Sub-Study of Adventist Health Study

David E. Abbey, Ph.D.
Co-Investigator
Sub-Study of Adventist Health Study

*If this person is no longer living at this address, please indicate the person's status and a new address if available or the contact name and address of a close relative and RETURN the **uncompleted** questionnaire in the enclosed envelope.

[ ] This person is deceased
[ ] This person is now living at a new address:

Contact Name _____ Phone (____)_____

Address _____

_____

A SEVENTH-DAY ADVENTIST HEALTH SCIENCES INSTITUTION

RESPIRATORY SYMPTOMS AND RESIDENCE HISTORY QUESTIONNAIRE - 2000

INSTRUCTIONS

Check your **name, address** and **telephone number** on the first page, adding or correcting address and telephone number if necessary. **Make sure you are the person named on the label.**

Please answer EVERY question. For some questions, you may not remember the exact detail. If this is the case, then guess as closely as you can. DO NOT LEAVE ANY QUESTIONS BLANK UNLESS ASKED TO SKIP THEM.

If you should have any problems with some of the questions, we will be glad to help you by phone. If this is the case, please answer all the questions as best you can, circle those you need help with, mail the questionnaire in, and we will call you back.

A number of the questions will ask what has happened to you since completing the 1992 questionnaire. To help you remember if an event was before or after that date, it may be helpful for you to think back to that time in your life and remember major events that were happening close to the time of completing your 1992 questionnaire.

1. Please enter today's date _____/____/____
month day year

2. Has a doctor ever told you that you had asthma, some kind of bronchial condition, or emphysema?

[ ]$_1$ No (Skip to #4)
[ ]$_2$ YES, please check [x] which conditions below
[ ]$_a$ Asthma (continue with #3)
[ ]$_b$ Bronchial condition (Skip to #4)
[ ]$_c$ Emphysema (Skip to #4)

3. Was your asthma ever confirmed by a doctor?

[ ]$_1$ No
[ ]$_2$ Yes → at what age _____

EXPOSURE TO TOBACCO SMOKE

4. **SINCE MARCH OF 1992**, have you **EVER** smoked cigarettes, cigars, or a pipe?

[ ]$_1$ No
[ ]$_2$ Yes

5. **SINCE MARCH, 1992,** have you ever **lived** for six months or more with someone who smoked?

[ ]$_1$ No (Skip to #7)
[ ]$_2$ Yes, but not currently (Continue)
[ ]$_3$ Yes, currently (Continue)

6. **SINCE MARCH, 1992,** which years have you **lived** with someone who smoked? (Please check all that apply below)

[ ]$_0$ None (Skip to #7)

[ ]$_a$ In 1992 [ ]$_d$ In 1995 [ ]$_g$ In 1998
[ ]$_b$ In 1993 [ ]$_e$ In 1996 [ ]$_h$ In 1999
[ ]$_c$ In 1994 [ ]$_f$ In 1997 [ ]$_i$ In 2000

PLEASE GO TO THE NEXT PAGE FOR NEXT QUESTION

7. Have you been employed (even on a part time or volunteer basis) **SINCE MARCH, 1992**?

[ ]$_1$ No (Skip to #16)
[ ]$_2$ Yes (Continue with #8)

WORK EXPOSURE TO TOBACCO SMOKE

8. **SINCE MARCH, 1992,** have you **ever** worked where someone smoked in the same room or enclosed space in which you **worked**?

[ ]$_1$ No (Skip to #10)
[ ]$_2$ Yes, but not currently (Continue)
[ ]$_3$ Yes, currently (Continue)

Continue with #9 ➚

9. **SINCE MARCH, 1992, how many years** have you worked where someone smoked in the same room or enclosed space in which you worked?

_____ years

10. **SINCE MARCH, 1992,** have you changed your **occupation** or your **location** of work?

[ ]$_1$ No
[ ]$_2$ Yes

11. **SINCE MARCH, 1992**, have you worked for one month or more at a location more than 5 miles from your home?

[ ]$_1$ No (Skip to #13)
[ ]$_2$ Yes (Continue with #12 below)

12. If you have **worked more than 5 miles** from your home **SINCE MARCH, 1992,** give the work locations and dates.

Started Job: MO.	YR.	Ended Job: MO.	YR.	TOWN OF WORK	STATE	ZIP CODE OF WORK PLACE
___	___	___	___	_____	_____	_____
___	___	___	___	_____	_____	_____
___	___	___	___	_____	_____	_____
___	___	___	___	_____	_____	_____
___	___	___	___	_____	_____	_____
___	___	___	___	_____	_____	_____

PLEASE GO TO THE NEXT PAGE FOR NEXT QUESTION

13. **SINCE MARCH, 1992,** have you ever worked for 3 months or more where you were exposed much of the time to **dusts** as part of your job?

[ ]$_1$ No (Skip to #14)
[ ]$_2$ Yes → Specify jobs/industry

_____

_____

Total number of years exposed to **dusts** since **March 1992:**

_____

How would you rate your exposure to dust in this job?

[ ]$_1$ Mild
[ ]$_2$ Moderate
[ ]$_3$ Severe

14. **SINCE MARCH, 1992,** have you ever worked for 3 months or more where you were exposed much of the time to **fumes** or airborne contaminants as part of your job?

[ ]$_1$ No (Continue with #15)
[ ]$_2$ Yes → Specify jobs/industries

_____

_____

Total number of years exposed to **fumes** since **March 1992:**

_____years

How would you rate your exposure to fumes in this job?

[ ]$_1$ Mild
[ ]$_2$ Moderate
[ ]$_3$ Severe

15. **SINCE MARCH, 1992,** what has been your usual occupation or job - the one you have worked at the longest?

_____

_____

16. What is your current employment status?

[ ]$_1$ Full time homemaker
[ ]$_2$ Working part time
[ ]$_3$ Working full time
[ ]$_4$ Unemployed
[ ]$_5$ Retired and not working
[ ]$_6$ Retired and working part time
[ ]$_7$ Retired but working full time

IF RETIRED, please give date of retirement

_____/_____
Month Year

17. How long are you usually away from home during the **SUMMER** (June through September?)

[ ]$_1$ 2 weeks or less
[ ]$_2$ 3-4 weeks
[ ]$_3$ 5-6 weeks
[ ]$_4$ 7-8 weeks
[ ]$_5$ 9 weeks or more

18. How many hours per **WEEK**, including weekends, do you **exercise vigorously** or do heavy physical labor (e.g. jogging, tennis, gardening, etc.) in the **open air** during the **SUMMER** (June through September)?

[ ]$_1$ None
[ ]$_2$ 1-3 hours
[ ]$_3$ 4-7 hours
[ ]$_4$ 8-14 hours
[ ]$_5$ 15-21 hours
[ ]$_6$ 22-28 hours
[ ]$_7$ 29-35 hours
[ ]$_8$ 36-42 hours
[ ]$_9$ more than 42 hours

PLEASE GO TO THE NEXT PAGE FOR NEXT QUESTION

19. How many hours per **WEEK**, including weekends, do you **exercise vigorously** or do heavy physical labor (e.g. jogging, tennis, gardening, etc.) in the **open air** during the **REST OF THE YEAR** (October through May)?

[ ]$_1$ None
[ ]$_2$ 1-3 hours
[ ]$_3$ 4-7 hours
[ ]$_4$ 8-14 hours
[ ]$_5$ 15-21 hours
[ ]$_6$ 22-28 hours
[ ]$_7$ 29-35 hours
[ ]$_8$ 36-42 hours
[ ]$_9$ more than 42 hours

20. How many hours per **WEEK**, including weekends, are you **outside of buildings** in the **SUMMER** (June through September)?

[ ]$_1$ None
[ ]$_2$ 1-7 hours
[ ]$_3$ 8-14 hours
[ ]$_4$ 15-21 hours
[ ]$_5$ 22-28 hours
[ ]$_6$ 29-35 hours
[ ]$_7$ 36-42 hours
[ ]$_8$ More than 42 hours

21. How many hours per **WEEK**, including weekends, are you **outside of buildings** during the **REST OF THE YEAR** (October through May)?

[ ]$_1$ None
[ ]$_2$ 1-7 hours
[ ]$_3$ 8-14 hours
[ ]$_4$ 15-21 hours
[ ]$_5$ 22-28 hours
[ ]$_6$ 29-35 hours
[ ]$_7$ 36-42 hours
[ ]$_8$ More than 42 hours

22. Do you use any type of air cooling system in your home?

[ ]$_1$ No (Skip to #23)
[ ]$_2$ Yes ↓
What type of air cooling system? (Check all that apply)
[ ]$_a$ Central Evaporative (swamp) cooler
[ ]$_b$ Window Evaporative (swamp) cooler
[ ]$_c$ Central refrigerating type (air condition)
[ ]$_d$ Window refrigerating type (air condition)
[ ]$_e$ Other, specify _____

23. **Since MARCH, 1992,** have you moved or been away from home for **more than one month at a time**?

[ ]$_1$ No, (Skip to #25)
[ ]$_2$ Yes, I have moved or been away from home for more than one month. (Continue with #24)

PLEASE GO TO THE NEXT PAGE FOR NEXT QUESTION

24. For each community in which you have lived or stayed for one month or more **SINCE MARCH, 1992**, please give the information requested below. For large cities, please give the section of the city. **Please start with your residence in 1992 and work toward the present.**

Town	State	Zip	When did you start living in this town? Month	Year	If not a move how many months did you stay? Months

25. What is your best estimate of your present weight in normal indoor clothing WITHOUT shoes?

_____ pounds

26. What is your gender?

[ ]$_1$ Male
[ ]$_2$ Female

27. What is your date of birth?

_____/_____/_____
Month Day Year

28. What is your current affiliation with the Seventh-day Adventist (SDA) Church?

[ ]$_1$ Current baptized member
[ ]$_2$ Affiliated, but never baptized
[ ]$_3$ Former SDA
[ ]$_4$ No affiliation

29. Have you been hospitalized **since March, 1992**?

[ ]$_1$ No
[ ]$_2$ Yes

30. **Since the age of 35**, have you had any fractures (broken bones) that were due to ***MINOR*** trauma (falling from standing heights or less, tripping over an object, falling from one step, etc.) or a broken bone without a known cause?

[ ]$_1$ No (skip to #32)
[ ]$_2$ Yes - Please report below which site(s) and your approximate age when the earliest fracture **after age 35** occurred at each site.

Site	Age at time of fracture
[ ] Hip	_____
[ ] Wrist	_____
[ ] Spine	_____
[ ] Other	_____ Location _____

PLEASE GO TO THE NEXT PAGE FOR NEXT QUESTION

31. Were any of the fractures mentioned in question 30 due to cancer or cancer metastasis, Pagets disease, myelomatosis or Osteogenesis Imperfecta?

[ ]$_1$ No
[ ]$_2$ Yes➜Which sites? _____

32. Have you ever been told by a doctor that you had osteoporosis?

[ ]$_1$ No
[ ]$_2$ Yes

33. **Since March of 1992** has your doctor told you (for the first time) that you had a **tumor or cancer** of any kind?

[ ]$_1$ No (Skip to #35)
[ ]$_2$ Yes ➜ Please give location, type of tumor _____

➘and date of diagnosis _____/____
Month Year

34. Please give the name and address of the physician and name and address of the hospital where your cancer or tumor was diagnosed.

Physician name and address: Hospital name and address:

_____ _____

_____ _____

_____ _____

Phone (_____)_____ Phone (_____)_____
area code area code

35. Since **MARCH, <u>1987</u>** (not 1992 as in the previous questions), has a doctor told you (for the first time) that you had a **Heart Attack** or "Coronary" (Myocardial Infarction)?

[ ]$_1$ No (Skip to #37)
[ ]$_2$ Yes ➜ Date of diagnosis _____/____
Month Year

PLEASE GO TO THE NEXT PAGE FOR NEXT QUESTION
6

36. Please give the name and address of the physician and name and address of the hospital where your Heart Attack was diagnosed.

Physician name and address:

_____

_____

_____

Phone (_____)_____
area code

Hospital name and address:

_____

_____

_____

Phone (_____)_____
area code

37. In order to keep track of the occurrence of serious illness among participants in this study, we need to review the medical records regarding your cancer or heart attack diagnosis. Please sign the statement below giving permission to review these records. This permission will make it possible for your doctor or hospital to allow us to review your record.

Remember that all your records will be kept strictly confidential. No individual information will be released to another organization or entity.

I hereby authorize the Adventist Health Study of Loma Linda University to examine my medical records filed in the above mentioned hospital or doctor's office.

_____ _____
Your signature *Date*

38. Please give the name and address of someone, who is not living with you, who will always know your address if you move.

Name _____

Address _____

_____

Phone (_____)_____
area code

Please check the questionnaire to make sure that you have not left any questions blank which should have been answered.

Thank you very much for completing the questionnaire. Please fold it and mail it in the return envelope as soon as possible.

APPENDIX F: Confirmation of IRB Approval

LOMA LINDA UNIVERSITY

Synnove Knutsen, MF, MD PhD
Professor, Department of Epidemioloogy/Biostatistics
School of Public Health

Re: IRB # 52238"*Relating cardiovascular disease risk to ambient air pollutants using Geographic Information Systems technology and Bayesian neural networks: the AHSMOG study"*

December 17, 2010

Dear Dr. Knutsen:

Reference is made to your correspondance today regarding the role of Lie Hong Chen in the activity cited above.

Based on the information provided, we have determined that this student's role does not constitute human subject research as defined in the federal regulations 45 CFR 46.102(f), in that she did not receive data containing individual or identifiable private information and did not interact or intervene with living individuals.

Thus this student's participation in IRB #52238 and her subsequent research do not require IRB review or approval. However, your cooperation in LLU's shared responsibility for the ethical conduct of research is appreciated.

Sincerely,

Linda G. Halstead

Linda G. Halstead, MA
IRB Administrator