LOMA LINDA UNIVERSITY

School of Public Health

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

By

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A Dissertation in Partial Fulfillment of the Requirements for the

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ABSTRACT OF DISSERTATION

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

By

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Doctor of Public Health in Epidemiology

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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).

CHAPTER 4

SECOND PUBLISHABLE PAPER

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

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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.

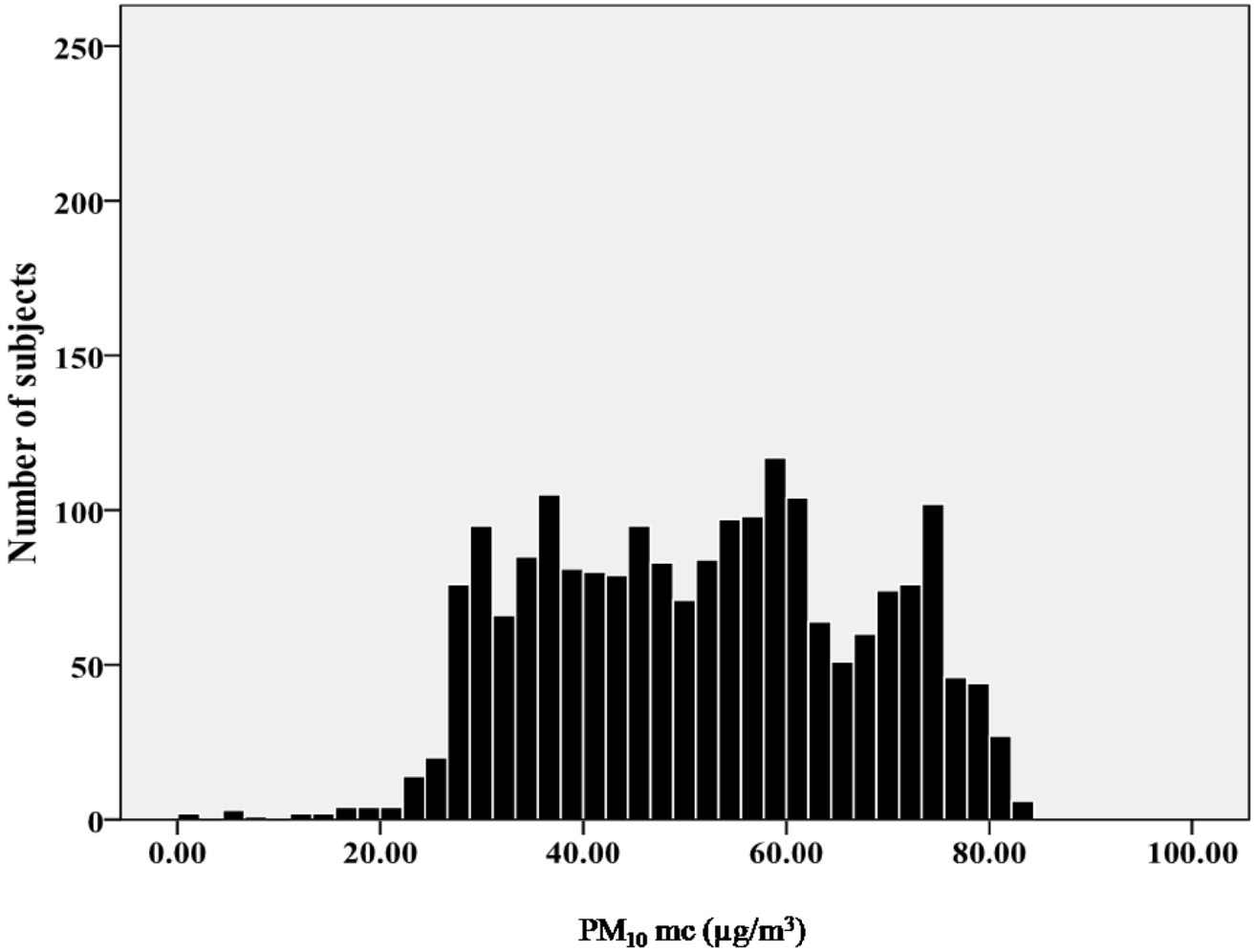

Figure 4.1 Frequency Distribution of Mean Ambient Concentration of PM_{10}, 1973-Censoring Month (n=4,830)

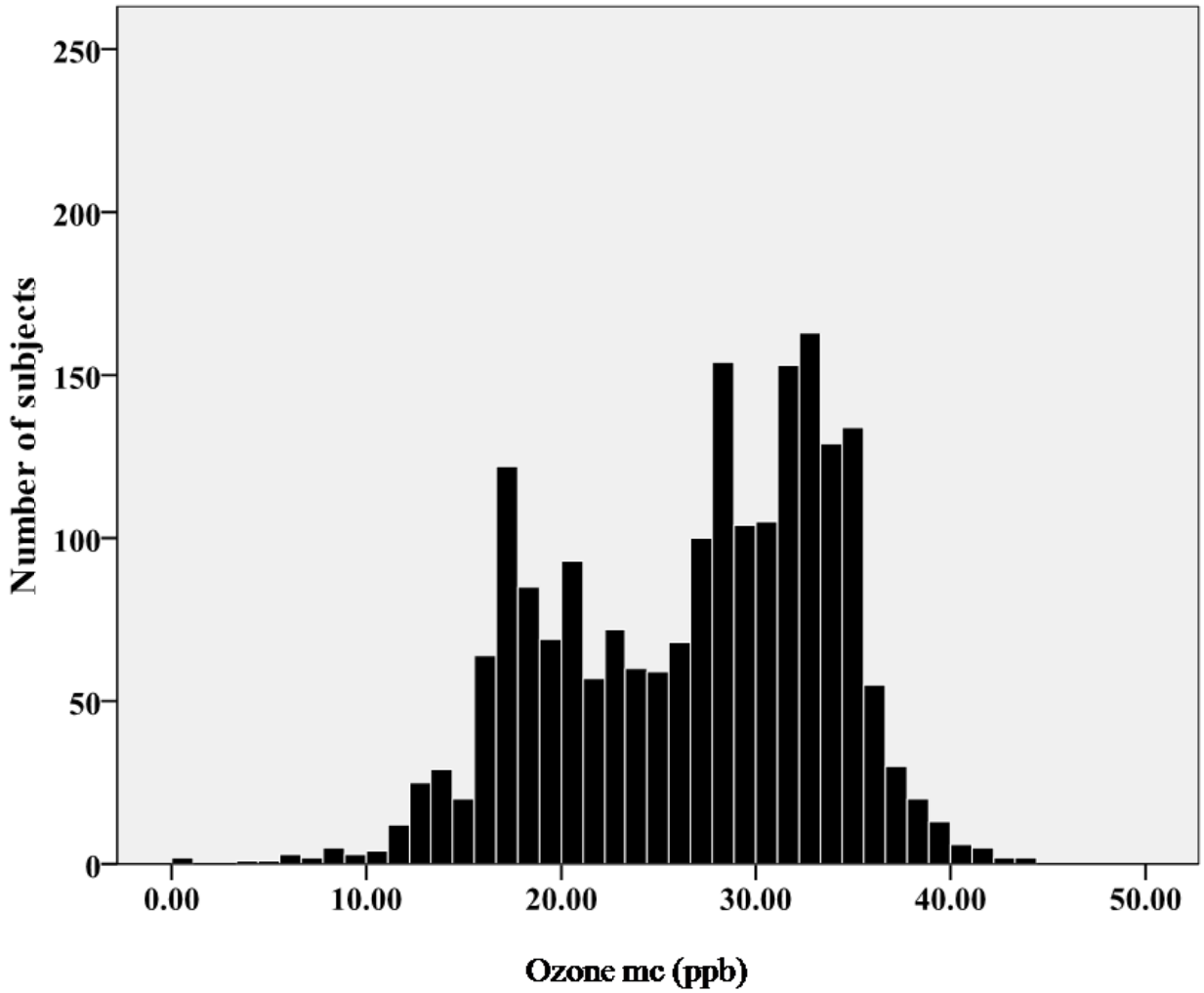

Figure 4.2 Frequency Distribution of Mean Ambient Concentration of O_3, 1973-Censoring Month (n=4,830)

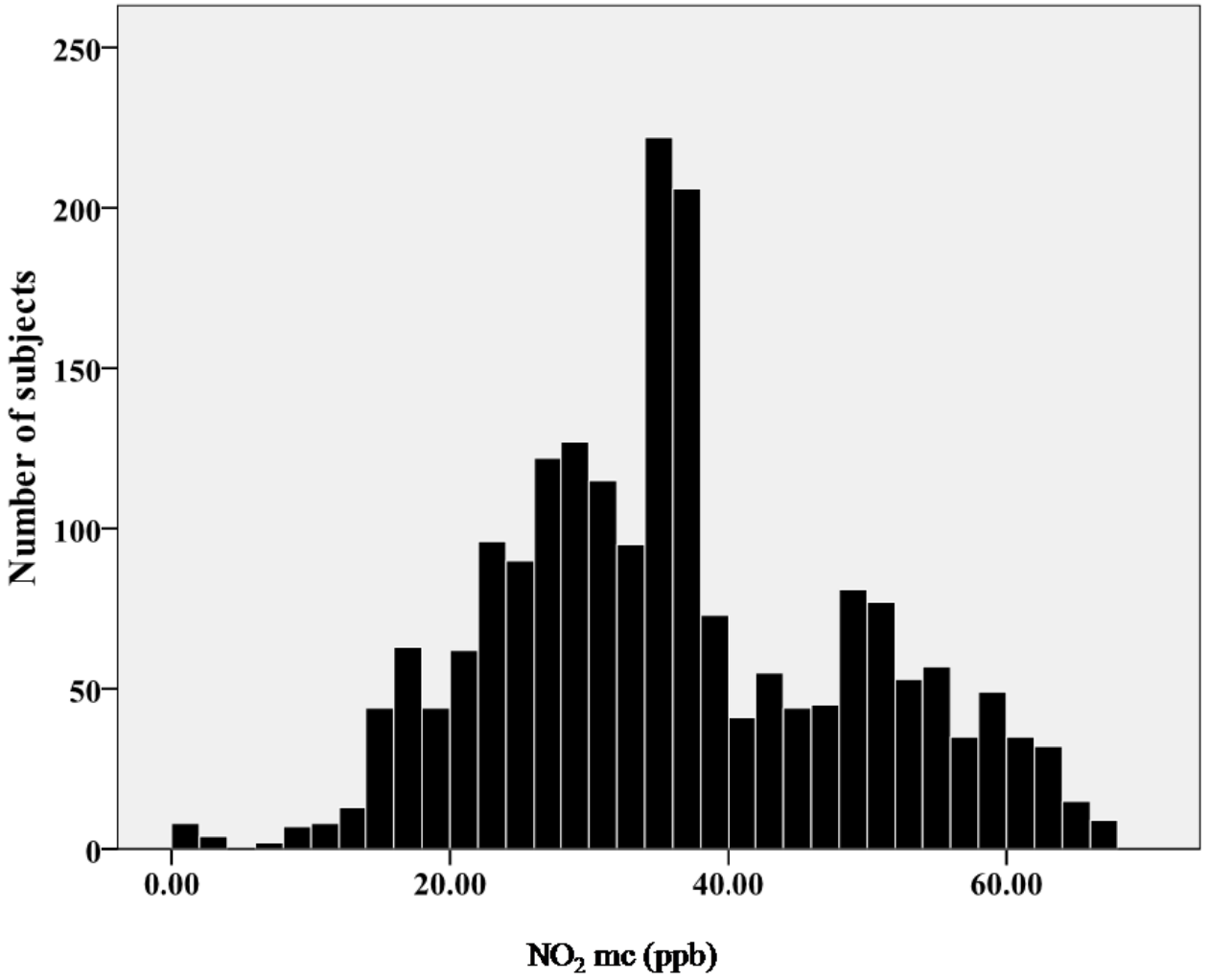

Figure 4.3 Frequency Distribution of Mean Ambient Concentration of NO_2, 1973-Censoring Month (n=4,830)

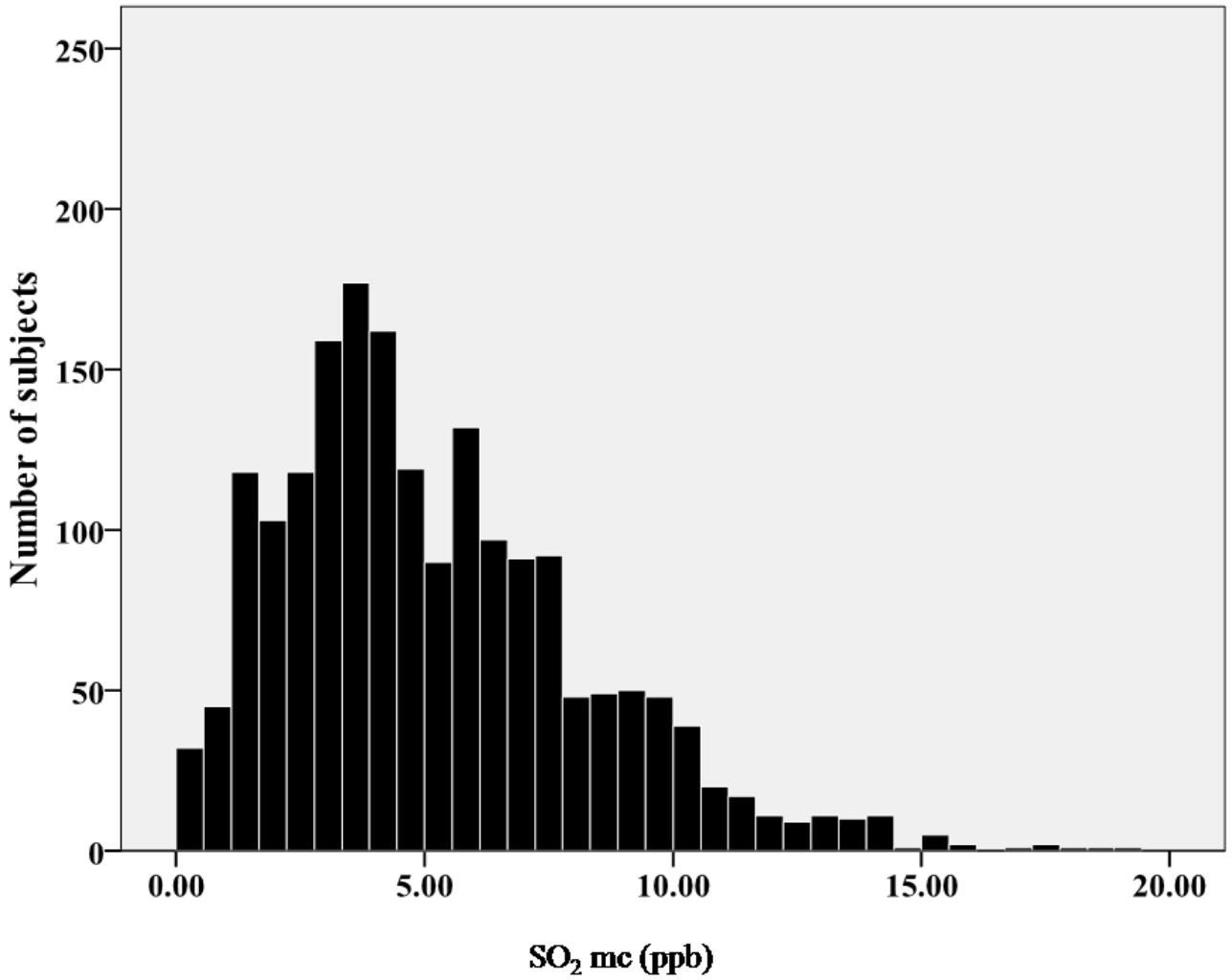

Figure 4.4 Frequency Distribution of Mean Ambient Concentration of SO_2, 1973-Censoring Month (n=4,830)

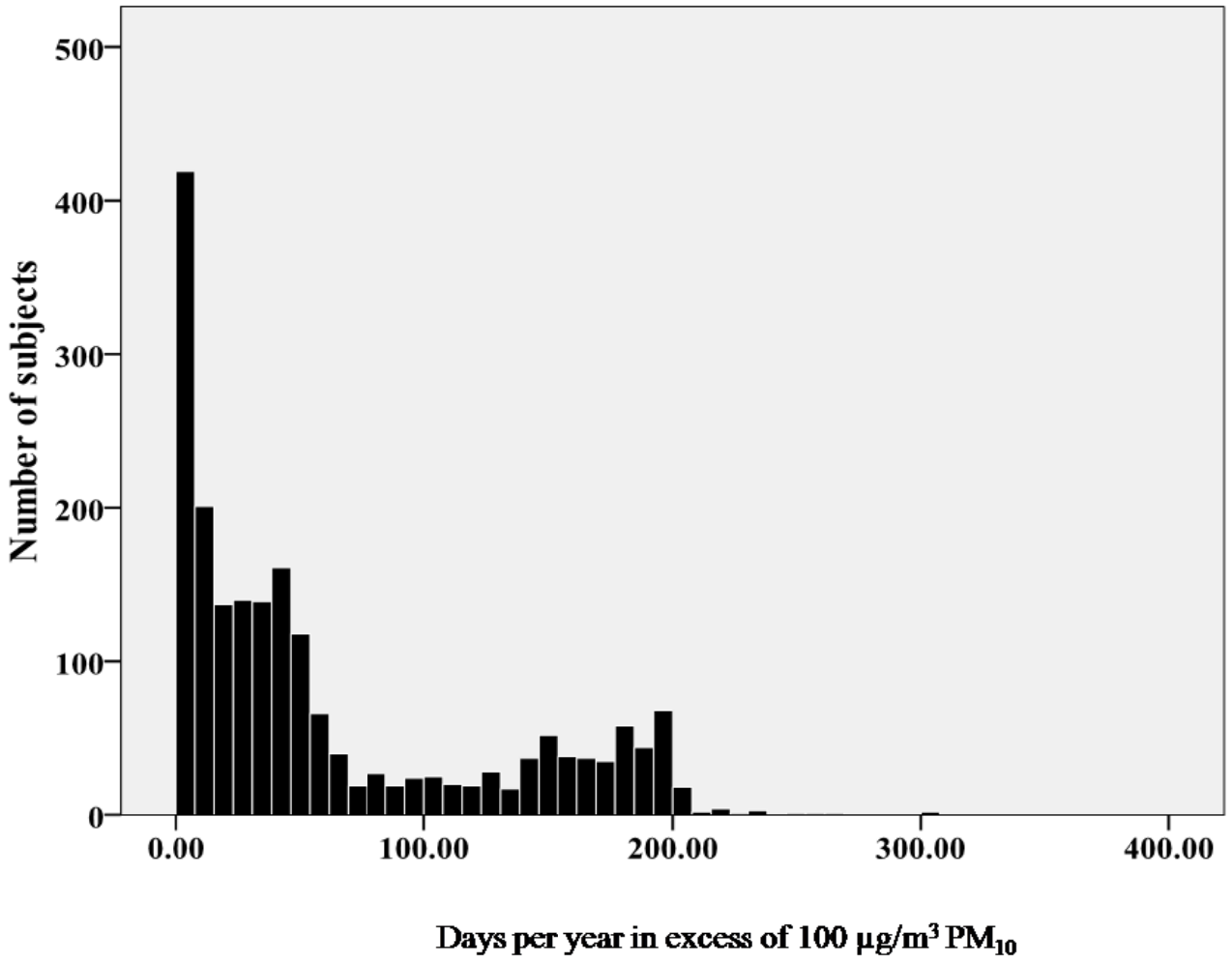

Figure 4.5 Frequency Distribution of Days per Year in Excess of 100 µg/m^3 PM_{10}, 1973-Censoring Month (n=4,830)

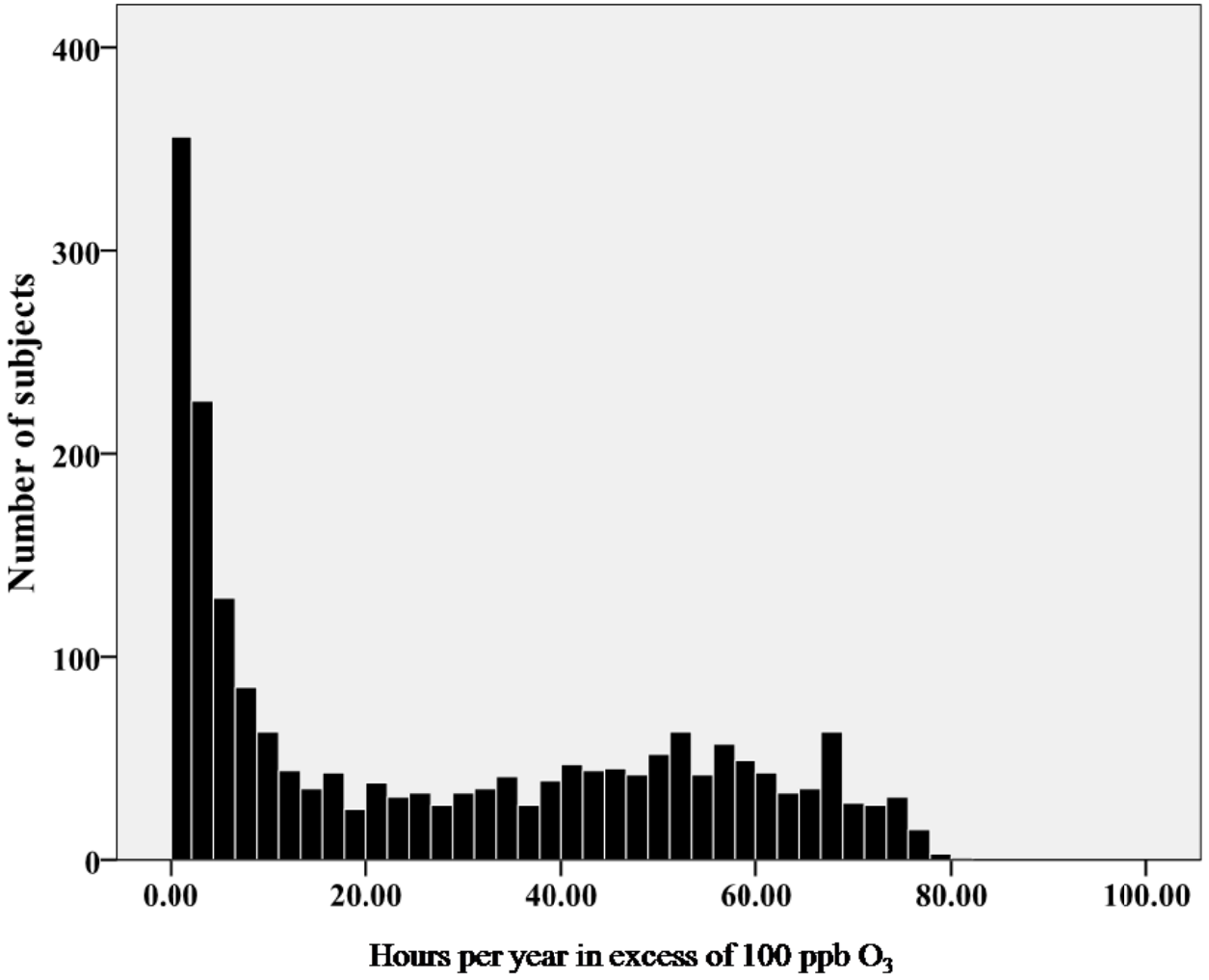

Figure 4.6 Frequency Distribution of Hours per Year in Excess of 100 ppb O_3, 1973-Censoring Month (n=4,830)