Semester

LITERATURE REVIEW

AIR POLLUTION & MENTAL HEALTH

DR. SADIE COSTELLO

Dr. Sadie Costello is an epidemiologist, a faculty at UC Berkeley, Environmental Health Science- School of Public Health with an interest in occupational and environmental exposures, chronic disease and the use of DAGs and causal inference to understand bias. She received her PhD in epidemiology from the University of California, Los Angeles. Her doctoral work focused on environmental risk factors, specifically pesticide exposure, and Parkinson disease.

GOAL

To teach the students the basics of epidemiology using the topic of air pollution and mental health and how we can distinguish between a study that shows a *correlation between air pollution and mental health and one that suggest that air pollution actually causes poor mental health outcomes.*

WHEN

September 1, 2018– December, 2018

HOW

Please join the meeting by using your computer, tablet or smartphone
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WHAT

1. **Students will read an example of a review article- video call will be scheduled to discuss how the article is organized**
2. **Paper critique form will be served as guideline for how to read and critique a paper**
3. **One paper will be selected to read and critique first- a video call to follow to review students critiques with guidance from Dr. Sadie**
4. **Students will read and review the other papers and start organizing an outline for a review article**
5. **Students will consolidate their critiques into one critique per paper for Dr. Sadie to review– feedback on the critiques and the outline will be provided**
6. **Students will begin writing and filling in the outline**

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Outline for Critiques

Author and Journal Title:

Answer the following questions within 2 typed pages (or written on this form).

1. **Objective.** What is the primary scientific objective of the study?

2. **Study methods.** What is the study design? What is the study population and its size?

3. **Exposure.** What is the exposure(s) of interest? How was it measured? What was the metric and how was it treated in the analysis (eg binary, continuous)?

4. **Outcome.** What is the outcome(s) of interest? How was it determined?

5. **Findings.** What statistical methods were used? What measures of association were reported? How was effect modification considered?
    a. What were the most important findings in the study?
    b. Comment on the generalizability of these findings.

6. **Potential for bias:** Use a simplified DAG to illustrate potential biases.

    A. Confounding. How did authors deal with confounding in the design and/or data analysis? Was it adequate? If not, what direction do you think the residual confounding bias would go?

    B. Information bias. Was misclassification of exposure and/or outcome likely? Was it differential or nondifferential? How this would affect the findings?

    C. Selection bias. Was selection bias likely? How this would affect findings?

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AIR POLLUTION AND EMERGENCY DEPARTMENT VISITS FOR DEPRESSION IN EDMONTON, CANADA

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Abstract
Objectives: Depression is a common cause of morbidity. Sufferers are very sensitive to many external factors. Emergency department (ED) visits for this condition can be associated with the concentration of ambient air pollutants. The study objective was to examine and assess the associations between ED visits for depression and ambient air pollution. **Design and Methods:** The present study analyzed 15 556 ED visits for depression (ICD-9: 311) at Edmonton hospitals between 1992 and 2002. The data were clustered based on the triplet {year, month, day of the week}. The generalized linear mixed models (GLMM) technique was used to regress the logarithm of the clustered counts for ED visits for depression on the levels of air pollutants (CO, NO_2, SO_2, O_3, PM_{10} and $PM_{2.5}$) and the meteorological variables. The number of ED visits for depression was analyzed separately for all patients, and males and females. An analysis by season was also conducted: for the whole year (I–XII), warm season (IV–IX), and cold season (X–III). **Results:** After adjusting for temperature and relative humidity, the following increments in daily depression-related ED visits could be noted: 6.9% (95% CI: 1.3, 12.9) for carbon monoxide (CO) for all patients in warm season; 7.4% (95% CI: 0.5, 14.8) for nitrogen dioxide (NO_2) for female patients in warm season; 4.5% (95% CI: 0.1, 9.1) for sulphur dioxide (SO_2) for female patients in warm season; 6.9% (95% CI: 0.6, 13.6) for ground level ozone (O_3, 1-day lagged) for female patients in warm season; 7.2% (95% CI: 2.7, 12.0) for particulate matter (PM_{10}) for females in cold season; and 7.2% (95% CI: 2.0, 12.8) for particulate matter ($PM_{2.5}$) for females in cold season. **Conclusions:** The findings provide support for the hypothesis that ED visits for depression are associated with exposure to ambient air pollution.

Key words:
Air pollution, Depression, Emergency department visit, Relative humidity, Temperature

INTRODUCTION

Depression, which is a common cause of morbidity, is an important health problem. The condition is associated with an imbalance of brain chemicals, triggered by stress, life events as well as a combination of biological, psychological and social factors, and the physical components of air pollution along with other factors. There is no single cause of depression, neither is it fully understood. The burden of the disease in terms of human suffering cannot be estimated. Some people experience seasonal cycles of depression, particularly in winter.

The goal of this study was to verify a hypothesis that environmental exposure to ambient air pollutants may be associated with an elevated number of depression episodes. We conducted a time-series study to analyze how emergency department visits (ED) for depression can be linked to the concentrations of ambient air pollutants and weather variables. We did not design any experiment or sample selection procedure and used the data from hospital records as they had been recorded. The number of ED visits for depression depends on a variety of external factors. The present study concerned exposure to air pollutants, and weather conditions. Statistical models were constructed for different air pollutants: gases (CO, NO_2, SO_2, and O_3) and airborne particulates (PM_{10} and $PM_{2.5}$). The current day, 1-day lagged and 2-day lagged concentrations of air pollutants were considered. The models were fitted for temperature and relative humidity

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as confounders. The final models were constructed with one pollutant and two weather factors (temperature and relative humidity).

The literature on the association between exposure to ambient air pollutants and ED visits for depression is rather scarce [1]. Some studies link cardiovascular and psychiatric disorders [2]. Other health conditions which are affected by air pollution can be linked to depressive symptoms [3]. Jasper et al. [4] who conducted a prospective longitudinal study of carbon monoxide poisoning found that CO poisoning may result in significant depression and anxiety that persists for at least 12 months. Other studies also demonstrated a relationship between depression and exposure to air pollutants [5–6]. These references provide justification for the present study. To our knowledge, no-one has attempted a time-series study to investigate a possible link between exposure to air pollutants and depression episodes.

MATERIALS AND METHODS

The data on ED visits were supplied by Capital Health for all the five hospitals in Edmonton area. Capital Health is an academic-based health system and one of the largest integrated health regions in Canada. The system provides complete health services to one million residents. The data covered the period between April 1, 1992 and March 31, 2002. The ED visits for depression were identified based on a discharge diagnosis of depression using the International Classification for Diseases, 9th Revision (ICD-9), rubric 311 [7]. In the database used, the diagnosis, expressed by the ICD-9 code, was also accompanied by a standardized string labelled "DEPRESSIVE DISORDERS NEC". In total, the analysis concerned 15,556 ED visits for depression over a span of 3,652 days. This represents approximately 0.5% of all 2,946,714 ED visits to these hospitals recorded over the study period. The study population were people serviced by EDs of the five Edmonton area hospitals.

In addition, to verify the analysis, the ED visits for anxiety were studied as well. There were 23,178 ED visits for anxiety identified by the ICD-9, rubric 300 [7].

Meteorological data

Environment Canada supplied data for selected weather variables that were recorded and made available hourly. In the present study, temperature and relative humidity were considered in the analysis. The daily mean, as an average of hourly readings (24 measurements), was used to represent these weather parameters. In the final models, the weather variables were used as confounders in a linear and spline form.

Air pollution data

The hourly air pollution data were obtained from fixed monitoring stations in Edmonton. These data were also supplied by Environment Canada. For every ambient air pollutant, we obtained data on 24 measurements carried out at the monitoring station at hourly intervals. These covered gaseous pollutants: carbon monoxide (CO), nitrogen oxide (NO_2), sulphur dioxide (SO_2), ozone (O_3), and airborne particulates: with median aero-diameter of 2.5 μm or less ($PM_{2.5}$) and with median aero-diameter of 10 μm or less (PM_{10}). As regards the daily shared population exposures, they were expressed as the arithmetic mean of the results of calculations of the mean daily concentration from all the daily measurements performed by a single monitoring station for a given pollutant.

Statistical analysis

To estimate the short-term effect of air pollution on the number of daily ED visits for depression, we applied a multilevel modeling methodology. At first, we defined clusters for available data. The records were clustered by the days of the week within one month of the same year. The data were grouped and analyzed according to the defined clusters. The clusters represent embedded multilevel hierarchical relations: days are nested in week days, week days are nested in months, and months are nested in years. With this convention, ED visit days were grouped according to the specified triplet {year, month, day of week}, which expresses the hierarchical structure. We used Poisson models. Random intercept Poisson regression was applied to respect the hierarchical structure of the cluster. Random effects were introduced to express

dependency and unobserved heterogeneity. We built the models with the number of daily visits for depression as a response. A given pollutant and two weather parameters, temperature and relative humidity as confounders, were used as independent variables in the constructed models. All the variables used in the models were lagged by the same number of days (0, 1, or 2). The analysis was performed using R software with the *glmmPQL* function [8]. This function implements the algorithm related to the generalized linear mixed models (GLMM) methodology. The GLMM method used on the triplet {year, month, day of week} begins to be called the Polish method [9–10].

RESULTS

The results are presented in three tables and two figures. Table 1 contains the number of ED visits for depression in Edmonton hospitals by age and sex. Of the total number of ED visits for depression (N = 15,556), 59.4% (n = 9,238) referred to female patients. More than half (70.9%) concerned patients aged between 20 and 50 years. The percentage of total visits by months was 7.7% in February, and 8.8% in May. The percentage of total visits by the days of the week varied from 13.0% on Sundays (13.0% on Saturdays) to 15.2% on Mondays. The daily mean number of visits was 4.3 (SD = 2.5) with minimum = 0, and maximum = 15.

Table 1. Frequency of emergency department visits for depression by age group and gender, Edmonton, Canada (April 01, 1992 – March 31, 2002)

Age group	No. visits	%	No. females	No. males
< 20	2,065	13.3	1,272	793
20–< 30	3,617	23.3	2,103	1,514
30–< 40	4,208	27.1	2,441	1,767
40–< 50	3,187	20.5	1,978	1,209
50–< 60	1,275	8.2	708	567
60–< 70	592	3.8	350	242
70–< 80	417	2.7	248	169
≥ 80	191	1.2	138	53
Total	15,552+4	100	9,238	6,314

Table 2. Number of days with data, mean, standard deviation (SD), median, interquartile range (IQR). Edmonton, Canada (April 01, 1992 – March 31, 2002)

Variable (unit)	Days	Mean	SD	Median	IQR
CO (ppm)	3,652	0.7	0.4	0.6	0.4
NO_2 (ppb)	3,652	21.9	9.4	19.7	12.8
SO_2(ppb)	3,616	2.6	1.8	2.2	2.3
O_3 (ppb)	3,652	18.6	9.3	17.8	14.0
PM_{10} ($\mu g/m^3$)	2,813	22.6	13.1	19.4	15.0
$PM_{2.5}$ ($\mu g/m^3$)	1,444	8.5	6.2	7.2	6.2
Temperature (^oC)	3,652	3.9	11.9	5.4	17.9
Relative humidity (%)	3,652	66.0	13.6	66.1	18.5

Table 2 displays mean daily concentrations of the study pollutants and weather variables.

Figure 1 illustrates the results by gender (none — both sexes, f — female, m — male) and season (A: I–XII, S: IV–IX, W: X–III) for all the pollutants and their lagged values (none, 1-day, 2-day). The percentage values of the changes in relative risk (% RR) are also shown. Figure 2 shows the results for the same scenarios that were yielded by models where temperature and relative humidity were included as splines (nonlinear). Natural splines were applied with 3 degrees of freedom.

Table 3 provides numerical values of the results presented in Figure 1. The table reports the percentage changes (% RR) in ED visits for depression and 95% confidence intervals (95% CI) associated with an increase in the

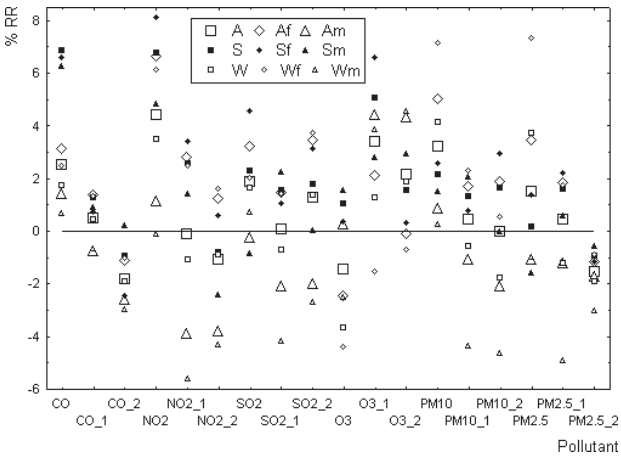

Fig. 1. The percentage changes in relative risk (%RR) by air pollutants (0, 1-, 2-day lagged), gender, and season. A linear form for temperature and relative humidity.

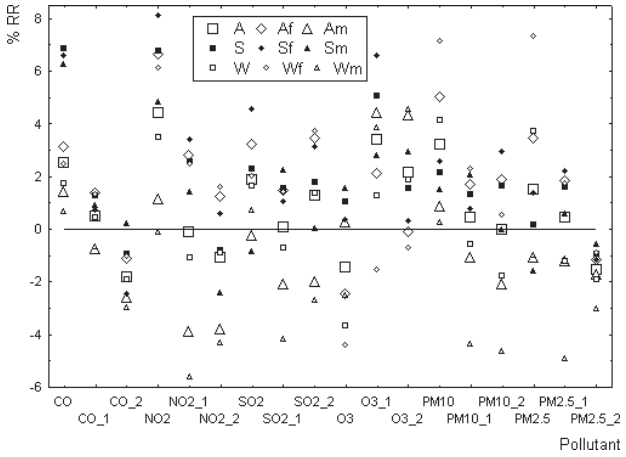

Fig. 2. The percentage changes in relative risk (%RR) by air pollutants (0, 1-, 2-day lagged), gender and season. A spline form for temperature and relative humidity.

Table 3. Positive and statistically significant percentage changes in relative risk (%RR) adjusted for relative humidity and temperature, and ED visits for depression, in relation to an increase in IQR of ambient air pollutants in Edmonton. The results are presented for the whole period (I–XII), warm season (IV–IX) and cold season (X–III) by gender (all, male, female)

Pollutant	Period, patients	%RR	95% CI
CO	I–XII, all	2.4	0.4, 4.4
CO	I–XII, female	2.8	0.3, 5.4
CO	IV–IX, all	6.9	1.3, 12.9
NO_2	I–XII, all	3.9	1.3, 6.6
NO_2	I–XII, female	5.5	2.1, 9.0
NO_2	IV–IX, all	6.6	1.2, 12.4
NO_2	IV–IX, female	7.4	0.5, 14.8
NO_2	X–III, female	5.2	0.8, 9.8
SO_2	I–XII, female	3.0	0.2, 5.8
SO_2	IV–IX, female	4.5	0.1, 9.1
SO_2_2	I–XII, female	3.5	0.7, 6.3
SO_2_2	X–III, female	3.8	0.1, 7.7
O_3_1	IV–IX, female	6.9	0.6, 13.6
PM_{10}	I–XII, all	2.7	0.4, 5.0
PM_{10}	X–III, all	4.2	0.6, 7.9
PM_{10}	I–XII, female	4.4	1.4, 7.4
PM_{10}	X–III, female	7.2	2.7, 12.0
$PM_{2.5}$	X–III, female	7.2	2.0, 12.8

%RR calculated as 100% *(RR-1), where RR is the relative risk estimated for IQR.

interquartile range (IQR, the 75th–25th percentile of pollutant concentrations) of exposure to the study pollutants after adjusting for temperature and relative humidity. Only the results that showed positive and statistically significant associations between exposure and ED visits for depression were included in the table. We found statistically significant associations between emergency admissions for depression and exposure to CO, NO_2, SO_2, O_3, PM_{10} and $PM_{2.5}$. The results indicate that the influence of air pollution on depression episodes was more pronounced in the female patients.

The same analysis was applied to ED visits for anxiety. All the results were negative; the ED visits were not related to the ambient air pollutants under study.

DISCUSSION AND CONCLUSIONS

In this study, the short-term effect of ambient air pollution exposures on daily ED visits for depression in Edmonton, Canada, was found to be positive and statistically significant. The highest percentage increase in ED visits, 7.2% for current day exposure, was found for exposure to PM_{10} (as well as $PM_{2.5}$) in a cold season (X–III) and applied to female patients. Significant associations were also found for exposure to CO and NO_2. The increased levels of CO and NO_2 (later O_3) are due to motor vehicle traffic. It is thus possible that road traffic may contribute to an increased incidence of ED visits for depression. The study results revealed between-gender differences in depression risk related to air pollution. Females appeared to be more susceptible to the effects of air pollution [11]. The obtained results indicate the potential association of ED visits for depression with some ambient air pollutants. Our study covered the depression episodes that made the patient seek emergency treatment. In this context, it is important to say that in most cases the patients with depression do not need to visit an emergency department; the treatment they receive is usually enough. However, a certain group of patients with depression are seen in the ED. Many of them may visit the ED with air pollution-related illness as a chief complaint. There is a possibility that depression may be a consequence of other morbidities that

are associated with air pollution. In Great Britain and Germany, there are health systems which predict the number of ED visits basing on the concentrations of ambient air pollutants. In Great Britain, the system is available to ED services, and in Germany, it is available to the public.

The findings of the present study should be interpreted as follows: elevated concentration of air pollutants is associated with elevated number of ED visits for depression. Such associations are well known for ED visits for cardiorespiratory problems.

The limitations of this study are typical of this type of research. They include the impact of measurement errors for the factors considered (ambient air pollutants) and recorded (diagnosed) ED visits for depression. Also the adequacy of the covariates used in the models is important. The models applied in this study were based on the triplet {year, month, days of week}. This is the most convenient cluster structure. It naturally maps the date of ED visits and many properties related to the calendar time.

It should be emphasized that the dependency of ED visits for depression on ambient air pollution, reported in this paper, is correlational in nature and may not reflect a causal process. The study results show that an increase in the concentration levels of ambient air pollutants is related to an increase in the number of such visits.

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RESEARCH ARTICLE

Association between Air Pollution and Suicide in South Korea: A Nationwide Study

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Competing Interests: The authors have declared that no competing interests exist.

Abstract

Suggestive associations of suicide with air pollutant concentrations have been reported. Recognizing regional and temporal variability of pollutant concentrations and of suicide, we undertook a detailed meta-analysis of completed suicides in relation to 5 major pollutants over 6 years in the 16 administrative regions of the Republic of Korea, while also controlling for other established influences on suicide rates. Of the 5 major pollutants examined, ozone concentrations had a powerful association with suicide rate, extending back to 4 weeks. Over the range of 2 standard deviations (SD) around the annual mean ozone concentration, the adjusted suicide rate increased by an estimated 7.8% of the annual mean rate. Particulate matter pollution also had a significant effect, strongest with a 4-week lag, equivalent to 3.6% of the annual mean rate over the same 2 SD range that approximated the half of annual observed range. These results strongly suggest deleterious effects of ozone and particulate matter pollution on the major public health problem of suicide.

Introduction

Suicide is a leading cause of death worldwide and increasingly recognized as a serious public health problem [1–2]. The adverse effects of air pollution on general health are well known: air pollution contributes to excess mortality and increased hospital admissions for respiratory and cardiovascular events [3–4]. Several studies have reported an association between suicide and air pollution. Air pollution is associated with increased emergency room visits for suicide attempts [5], and increased airborne concentration of particulate matter is associated with increased risk of completed suicide [6]. Also, a recent study in Taiwan found an influence of sulfur dioxide and ozone on suicide risk [7]. However, such reports have been inconsistent [6–7], possibly because these studies were conducted in limited geographic areas and did not consider some important covariates (e.g., celebrity suicide or economic variables) [8]. Here we report on a nationwide study in the Republic of Korea (ROK, population 50 million), testing for associations between 5 major air pollutants

and suicide. Recognizing the wide geographic variability of air pollution, we conducted a meta-analysis of regional data, while also controlling for other established factors associated with suicide.

Methods

Regional suicide data

We obtained the daily number of completed suicide events in each of the 16 administrative regions of ROK over 6 years from January 1 2006 to December 31 2011. The data were thoroughly examined and verified by the Korea National Statistical Office (http://kostat.go.kr/portal/english). Data for those years were considered because contemporaneous daily regional air pollution data were available. Suicide data were extracted from death records defined as suicides according to the International Classification of Diseases-10 (ICD-10) codes X60-X84, which include suicides from all causes, including intentional self-poisoning and self-harm [8]. Average national weekly suicide numbers from January 2001 through December 2005 also were computed so as to allow adjustment for seasonal variation [9]. We used population and housing census data to calculate the suicide rate per 10 million persons in each region.

Celebrity suicides

In order to control for the influence of celebrity suicides, we noted the periods following those events. We defined celebrity suicide as a suicide exposed during more than two weeks in news programs of the three major Korean national television networks (KBS, MBC and SBS) [8]. Eight suicides met the definition of celebrity suicide during the 6 years of this study. In addition, we defined the affected period as a month (30 days) after the first report of the celebrity suicide [8,10]. Time points within or partly within this 30-day window were coded 1, while all others were coded 0 on the celebrity variable.

Air pollution, economic and meteorological data

Daily regional air pollution data were obtained from the Korean Ministry of Environment (http://www.airkorea.or.kr/airkorea/eng/) during the study period. They provided comprehensive data from 251 sites in 79 cities or areas nationwide. These data were grouped according to the 16 administrative regions of ROK (a mean of 15.7 sites per administrative region). Averaged values for each region were used in the analyses. Five major air pollution variables were considered: ozone, PM-10 (Particulate Matter, particulates with size of 10 μm in diameter or smaller), nitrogen dioxide, carbon monoxide and sulfur dioxide. The daily meteorological data (sunlight hours and temperature) [11] were obtained from the Korea Meteorological Administration (KMA, http://web.kma.go.kr/eng). The economic data [12] including consumer price index, unemployment rate, and stock index valuations (Korea Composite Stock Price Index, KOSPI), were extracted from the Korea National Statistical Office. The end-of-week and holiday closing values of the KOSPI were carried forward to the next active trading day. The most recent monthly data for the consumer price index and the unemployment rate were used each day.

Ethics statement

Our research analyzes existing data that are publicly available in a manner that does not allow individual subjects to be identified; therefore ethics approval was deemed unnecessary.

Statistical analysis

For data reduction, we averaged all daily variables in discrete weekly epochs. There were 313 epochs during the study period. All computations were performed using these binned weekly numbers. This data reduction step controlled for the known day-of-week effect on suicide rate [13].

We employed linear regression modeling to evaluate the association between five air pollution variables and suicide number in each of the sixteen regions. The regional weekly suicide rate per 10 million persons was considered as the dependent variable. Celebrity suicides, economic and meteorological variables were entered as covariates in the linear regression model. We included the regional weekly suicide rate per 10 million in the preceding week as a covariate to control for short-term trending of suicide, which we previously identified as a significant predictor of weekly suicide rate [8]. The average national monthly suicide number for the past 5 years by month matching each weekly data set also was entered as a covariate in order to control for seasonality. We examined the air pollutant data lagged weekly by up to 6 weeks preceding the suicide events (time lag 0 through time lag 6). The presence of statistical heterogeneity was assessed with the I-square heterogeneity test and Cochran's Q test [14]. Then, these regional results were meta-analyzed with the DerSimonian-Laird random effect model which accounts for heterogeneity among meta-analyzed studies [15] using Metasoft software [16]. We present the outputs of the meta-analysis as the regression coefficients (beta) and their standard deviations expressed as increased suicide numbers associated with unit increases of pollutant concentrations. Because multiple testing can raise type I error, *P* values of different time lags were controlled by Bonferroni's correction. All statistical analyses were performed using the R 2.9.1 public statistics software (R package, http://www.r-project.org). Results were considered significant at a threshold of $P < 0.05$. The detailed definitions of the variables and formula of the linear regression model are given in S4 Table. All relevant data are within the Supporting Information file named S1 Data.

Results

Trend of suicide number and air pollution levels

Over the six years of the study (2006–2011), national suicide numbers trended upwards and showed seasonal variation with peaks in the spring months and troughs in the fall months (S1 Fig.). The average national weekly suicide rate per 10 million persons was 55.81 in the period, which corresponds to an average annual suicide rate of 29.1 per 100,000 persons per year. This rate for the ROK is one of the highest among OECD (Organization for Economic Co-operation and Development) nations [17]. The weekly suicide rate varied considerably by region (range 44.18 to 80.44—S1 Table). Trends of nationwide weekly average air pollutant levels are shown in S2 Fig. All five pollutants displayed marked variability from week to week and by region (S1 Table). For instance, the weekly average ozone concentration showed a 2-fold range across regions from 0.019 ppm (Seoul) to 0.037 ppm (Jeju). Temporal coefficients of variation of regional weekly ozone concentrations over the 6 years ranged from 0.28 to 0.45, with a national average of 0.33 (S1 Table). The annual range of concentrations of ozone was over 3-fold from trough to peak (S2A Fig.). However, these annual pollutant rhythms were not closely synchronized.

The association between suicide rate and pollutant concentrations

As the effect of the five pollutants was heterogeneous among different regions and different time points (I-square statistic >30 and Cochran's Q test $P < 0.05$, see S2 Table for details), we

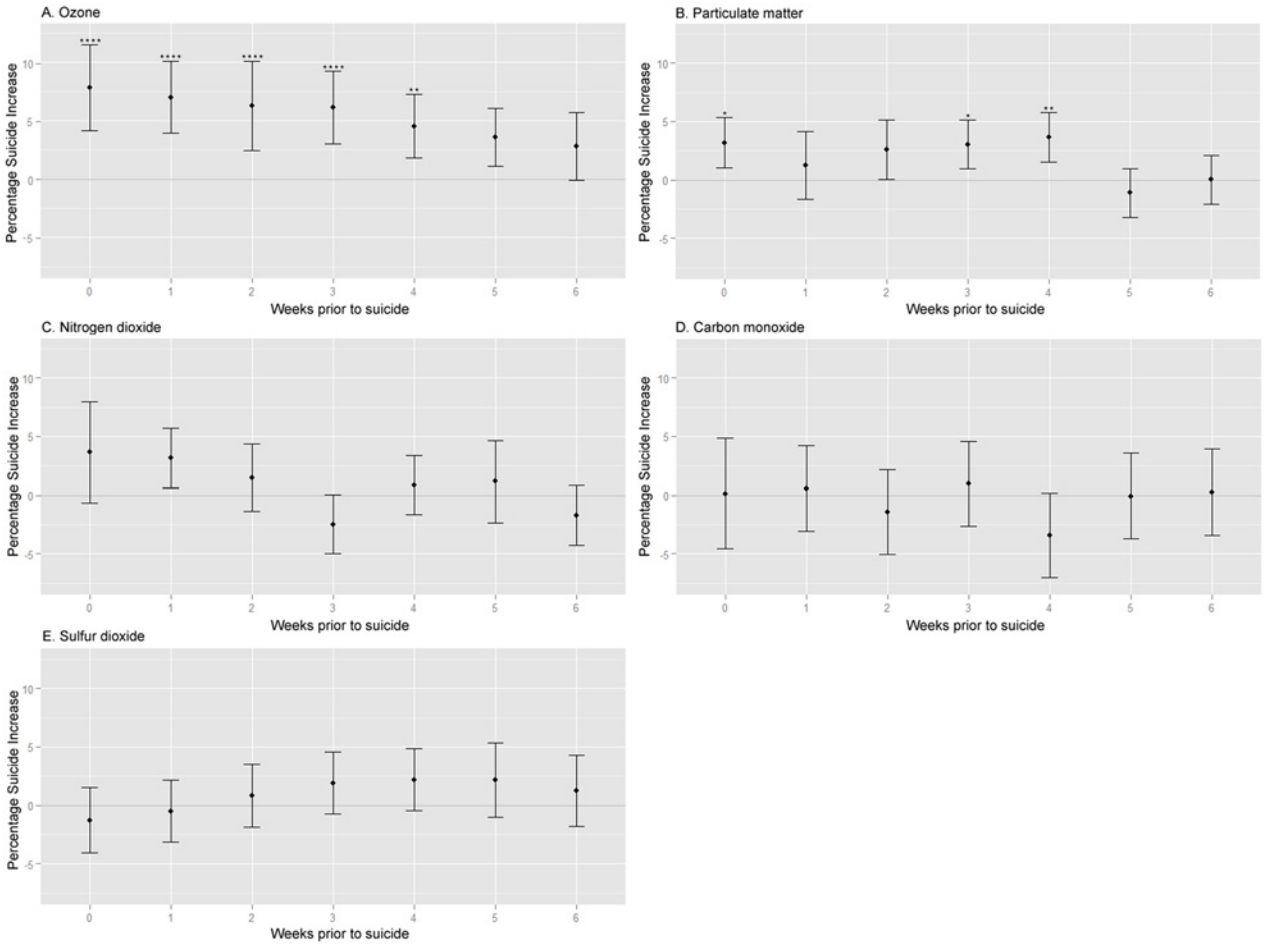

Fig 1. Suicide Increase Associated with Air Pollution Increase According To Weeks Prior to suicide. (*A*) Ozone; (*B*) Particulate matter; (*C*) Nitrogen dioxide; (*D*) Carbon monoxide; (*E*) Sulfur dioxide. *Corrected $P< 0.05$, **corrected $P< 0.01$, ***corrected $P< 0.001$, ****corrected $P< 0.0001$. Percentage suicide increase was calculated by multiplication of beta, range of pollutant concentration from-1SD to +1SD relative to the annual mean value (2 SD range) and inverse number of national weekly suicide rate per 10 million persons.

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performed random-effects meta-analysis (S2 Table). Fig. 1 shows the summary of meta-analyses of the effect of the five air pollutants with time lags from 0 to 6 weeks.

From time lag 0 to time lag 4, the level of ozone was significantly associated with suicide rate (Table 1). The greatest magnitude of effect was shown with time lag 0. The magnitude of this effect can be illustrated using the national average data: At time lag 0, for an increase in ozone concentration from-1SD to +1SD relative to the annual mean (an increase of 0.016 ppm) the weekly suicide rate increased by 4.37 per 10 million or 7.8% of the national weekly suicide rate of 55.81 per 10 million documented from January 2006 through December 2011 (suicide rate increase per 2 SD range ozone increase = 7.8%, 95% CI = 4.2%−11.5%, corrected $P < 0.0001$, meta-analysis of 16 linear regression analyses). This 2 SD range of ozone concentration corresponds to half of the observed annual range of ozone concentrations (S2A Fig.). As shown in Fig. 1A, the effect of ozone on suicide rate subsided gradually with increasing time lag.

The PM-10 level also had significant associations with the weekly suicide rates in time lags 0, 3 and 4 (corrected $P = 0.03$ for time lag 0, $P = 0.03$ for time lag 3, and $P < 0.01$ for time lag 4, Table 1). As the PM-10 increased by 1 unit (1 μg/m^3), weekly suicides per 10 million persons

Table 1. Associations of Pollutants with Averaged Weekly Suicide Rate per 10 million Persons from Lag 0 to Lag 4.

Pollutants	Weeks prior to suicide	Beta [a.]	S.E.	% of Suicide Increase Relative to Annual Mean Rate for an Increase in Pollutant Concentration from-1SD to +1SD [b.]	95% CI, Lower	95% CI, Upper	Corrected *P* [c.]	I-square heterogeneity(%) [d.]	Cochran's Q's *P* [d.]
Ozone	0	274.01	65.61	7.8	4.2	11.5	<0.0001	42.77	0.04
Ozone	1	245.12	55.00	7.0	3.9	10.1	<0.0001	29.68	0.13
Ozone	2	220.28	68.38	6.3	2.5	10.1	<0.0001	54.99	0.004
Ozone	3	215.08	55.69	6.1	3.0	9.3	<0.0001	33.89	0.09
Ozone	4	158.15	48.46	4.5	1.8	7.2	<0.01	14.50	0.29
PM-10	0	0.047	0.016	3.2	1.0	5.3	0.03	0	0.89
PM-10	1	0.018	0.022	1.2	-1.7	4.1	1	37.04	0.07
PM-10	2	0.039	0.019	2.6	0.1	5.2	0.31	22.18	0.20
PM-10	3	0.045	0.016	3.0	0.9	5.1	0.03	0	0.91
PM-10	4	0.054	0.016	3.6	1.5	5.7	<0.01	0	0.90

Table 1. are results of meta-analyses of regional data in South Korea from 2006 through 2011.

Abbreviations: S.E., Standard Error; SD, Standard Deviation; CI, Confidence Interval; PM-10, Particulate Matter (particulates with size of 10 μm in diameter or smaller).

[a.] Increased weekly suicides per 10 million persons when the level of air pollution increases by 1 unit.

[b.] Calculated by multiplication of beta, 2 SD range of national level of air pollution and inverse number of national weekly suicide rate per 10 million persons.

[c.] Corrected by Bonferroni's method for the tests of the number of time lags.

[d.] I-square heterogeneity test and Cochran's Q test were employed for testing the presence of statistical heterogeneity in meta-analyses.

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increased by 0.047 in time lag 0. Using the national average data, for an increase in PM-10 concentration from-1SD to +1SD relative to the annual mean (an increase of 37.82 μg/m^3) the weekly suicide rate increased by 1.76 per 10 million or 3.2% of the national weekly suicide rate of 55.81 per 10 million at time lag 0. This 2 SD range of PM-10 concentration (32.72–70.54μg/m^3) corresponds approximately to half of the observed annual range of PM-10 concentrations (S2B Fig.). This association disappeared at time lags 1 and 2. The most prominent effect of PM-10 occurred with a four week interval, when the effect corresponded to a weekly suicide rate increase of 2.03 per 10 million or 3.6% of the national weekly suicide rate of 55.81 per 10 million (suicide rate increase per 2 SD range PM-10 increase = 3.6%, 95% CI = 1.5%–5.7%, corrected $P < 0.01$, meta-analysis of 16 linear regression analyses).

Regional plots (S3 Fig.) and forest plots (S4 Fig.) for ozone and PM-10 in their most prominent associated time lag (lag 0 for ozone, lag 4 for PM-10) are presented. We found regional differences in the association between air pollutants and suicide rates (S3 Fig.). A notable finding is that the three providences with high suicide rate (Chungnam, Gangwon and Chungbuk) showed the largest increases of suicide associated with a 2 SD increase of ozone concentration (S4A Fig.).

We found no significant associations for nitrogen dioxide, carbon monoxide and sulfur dioxide in meta-analyses of all time lags. All results of linear regression modeling in 16 regions with 7 different time lags and their meta-analyses are provided in S2 and S3 Tables.

Discussion

In this nationwide study, we found that increasing concentrations of ozone and atmospheric particulate matter were related to suicide rate. Of all 5 pollutants we examined, ozone had the strongest associations with suicide rate, extending back to 4 weeks before the suicide events. Increase of ozone concentration over a 2 SD range (0.016 ppm) that approximated half of the observed annual range was associated with a 7.8% increase of weekly suicide rate relative to the annual mean weekly suicide rate. Increase of PM-10 concentration over a 2 SD range (37.82μg/m^3) that also approximated half of the observed annual range was associated with a 3.2% to 3.6% increase of weekly suicide rate at time lags 0 and 4, respectively.

There have been previous studies that suggest multiple mechanisms for the effect of air pollution on the central nervous system (CNS). First, air pollution can affect the immune system and thereby induce behavioral changes through effects on neurotransmitter systems [18–19]. Ozone can induce inflammation in the lungs of exposed subjects [20], and this peripheral inflammation could impact on the CNS through circulating cytokines [21]. In addition, exposure to particulate matter for several weeks increases proinflammatory cytokines in mouse brain [22]. Furthermore, exposure to particulate matter has been associated with hypomethylation of the gene for inducible nitric oxide synthase (*iNOS*), which regulates a key step during inflammatory reactions [23]. Considering that the immune system could affect the development of depression [24], the reported effects of ozone and particulate matter on cytokines may be relevant to our observation on suicide rates. Second, stress hormones could be linked to air pollution and suicide. According to Errol et al., brief exposure of rats to ozone and particulate matter results in activation of the hypothalamo-pituitary-adrenal (HPA) axis [25]. Continuous exposure to air pollutants could cause HPA axis dysregulation, which is associated with the pathobiology of suicide in mood disorder [26]. Third, ozone or its reaction products could influence the metabolism of serotonin [27], one of the neurotransmitters associated with aggressive behavior and suicide [28–30]. These previous findings are relevant to our observed strong association of ozone concentration with suicide rate. Meanwhile, air pollution can influence suicide indirectly. For example, exposure to air pollutants aggravates respiratory disease [3] and increases the risk of depressive episodes among individuals with pre-existing cardiovascular disease or diabetes mellitus [31]. In addition, exposure to air pollutants is associated with a high incidence of spontaneous abortion which is a risk factor for depression [32]. These physical burdens could increase the risk of suicide in the population [33–34]. In our results, the association between PM-10 and suicide rate was observed at time lag 0, however, it was absent at time lags 1 and 2. We speculated that the effects of disease aggravations, bereavement or increase of physical burdens on suicide rate require intervals to link with consequent suicide events. Further studies with individual risks of suicide such as psychiatric or medical disease could be helpful to clarify this hypothesis.

In prior research, Yang et al, found that air pollutants such as sulfur dioxide and ozone influence the risk of suicide over longer time scales [7]. Also, Kim et al, have reported that transient increases of particulate matter concentration are related to suicide risk [6]. In addition, a German study conducted by Biermann et al, reported an association between ozone level and completed suicide.[35] However, those studies had some limitations. First, their results were limited to the data from metropolitan areas, and data from rural areas were excluded. Since the suicide rates vary by region [36], region-specific studies risk confounding by Type I error (false positive). Our analyses also suggest that the level of association between air pollution and suicide varies among regions (S1 Table, S3 and S4 Figs.), supporting the possibility of non-generalizable findings in prior studies. In addition, the earlier studies did not consider multiple other variables that affect suicide risk. For instance, celebrity suicides have a marked effect on

the national suicide rate [8,10,37]. Economic factors, including consumer price index, unemployment rate, and stock index valuations, also are well known for their association with suicide rates [12,38]. In addition, meteorological factors, like sunlight hours and temperature, have established associations with suicide rate [39].

To complement these prior studies, we performed a nationwide regional meta-analysis while controlling for important covariates like celebrity suicide, economic factors, and meteorological factors, as well as seasonality of suicide rates. We also controlled for short term trending as revealed by our previous report [8]. For this purpose we included the previous week's suicide rate as a covariate. In addition, we examined multiple time periods from 0 to 6 weeks prior to the day of suicide, to test for immediate and delayed effects of pollutants. Thus, this study is the first nationwide analysis assessing the proximate and near-term delayed effects of air pollution on suicide rate.

As a result of pollution control policy in all countries of the world, sulfur dioxide concentrations, which result from fossil fuel combustion, have been significantly reduced [3]. That may be a factor in our finding of no significant association between ambient sulfur dioxide concentration and suicide. Consequently, other air pollutants like ozone and particulate matter which are less related to fossil fuels, have received increasing attention recently [3]. Guidelines issued by the World Health Organization (WHO) aim at reduction of ozone and particulate matter because of their association with overall mortality [40]. Our results showing strong associations of ozone and PM-10 concentrations with suicide add to the public health urgency for reduction of these pollutants.

A limitation of our study is retrospective design based on national databases, so that we could not test the effect of other recognized air pollutants such as PM-2.5 (Particulate Matter, particulates with size of 2.5 μm in diameter or smaller) [5], lead, ammonia, radioactive pollutants or volatile organic compounds. There is also a possibility that ozone, a highly reactive molecule, could exert its effects through secondary reaction products. Further studies with expanded data will be required.

As previously mentioned, the strength of associations between suicide rates and pollutant concentrations varied among regions. Factors influencing these differences could be analyzed in further studies. Nevertheless, the overall meta-analysis revealed a highly significant association of suicide rate with ozone concentration, as well as a strong association with particulate matter pollution. In conclusion, our analysis expands the evidence for a link between suicide and air pollutants through this regional meta-analysis. Our data direct attention especially to ozone and particulate matter as the significant drivers of this association.

Supporting Information

S1 Data. Data File.
(XLSX)

S1 Fig. Trend of weekly national suicide number per 10 million persons in Korea.
(TIF)

S2 Fig. Trend of weekly average air pollution levels in Korea.
(TIF)

S3 Fig. Regional plots for ozone and PM-10 in their most prominent associated time lag (lag 0 for ozone; lag 4 for PM-10).
(TIF)

S4 Fig. Forest plots for ozone and PM-10 in their most prominent associated time lag (lag 0 for ozone; lag 4 for PM-10).
(TIF)

S1 Table. Weekly suicide rate and weekly averages of air pollution levels in 16 regions of South Korea 2006 through 2011.
(DOCX)

S2 Table. Meta-analyses of linear regression modeling in 16 regions with 7 different time lags.
(XLSX)

S3 Table. Linear regression modeling in 16 regions with 7 different time lags.
(XLSX)

S4 Table. Variables included in the analysis and their detailed descriptions.
(DOCX)

Author Contributions

Conceived and designed the experiments: WM YK SS HJJ JC DKK. Analyzed the data: WM HHW. Contributed to the writing of the manuscript: YK, WM, HHW, BJC.

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PLOS ONE

RESEARCH ARTICLE

Long-term exposure to ambient air pollutants and mental health status: A nationwide population-based cross-sectional study

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Abstract

There is a suspected but unproven association between long-term exposure to ambient air pollution and mental health. The aim of this study is to investigate the association between long-term exposure to ambient air pollution and subjective stress, depressive disorders, health-related quality of life (QoL) and suicide. We selected 124,205 adults from the Korean Community Health Survey in 2013 who were at least 19 years old and who had lived in their current domiciles for > five years. Based on the computer-assisted personal interviews to measure subjective stress in daily life, EuroQoL-5 dimensions, depression diagnosis by a doctor, suicidal ideation, and suicidal attempts, we evaluated the risk of mental disorders using multiple logistic regression analysis according to the quartiles of air pollutants, such as particulate matter <10μm (PM_{10}), nitrogen dioxide (NO_2), carbon monoxide (CO), and sulfur dioxide, using yearly average concentration between August 2012 and July 2013. The prevalence of high stress, poor QoL, depressiveness, diagnosis of depression, and suicide ideation was positively associated with high concentrations of PM_{10}, NO_2, and CO after adjusting for confounding factors. Men were at increased risk of stress, poor QoL, and depressiveness from air pollution exposure than were women. The risk of higher stress or poor QoL in subjects < age 65 increased with air pollution more than did that in subjects ≥ age 65. Long-term exposure to ambient air pollution may be an independent risk factor for mental health disorders ranging from subjective stress to suicide ideation.

Introduction

Ambient air pollution is composed of a heterogeneous mixture of compounds, including particulate matter (PM), nitrogen dioxide (NO_2), carbon monoxide (CO), and sulfur dioxide (SO_2). These particles are composed of both solid and liquid components that originate from multiple sources, including vehicle exhaust, road dust, and windblown soil [1].

A growing body of evidence indicates that elevated levels of air pollution are associated with mental disorders such as depression and suicide. Elderly subjects experienced the aggravation of their depressive symptoms after 3-day exposure to air pollutants [2]. Emergency

Competing interests: The authors have declared that no competing interests exist.

department visits for depressive episode were associated with increased levels of air pollutants during 0–3 days in 4,985 Korean elderly patients with cardiovascular or respiratory disease [3]. Emergency department visits with depressive disorders and suicide attempts showed associations with CO, NO_2, SO_2, and PM_{10} in 27,047 Canadians [4, 5]. However, these associations were different according to seasons [6] or represent only sort-term exposure to air pollutants. Although a few studies have addressed the incidence of mental health disorders in patients with long-term exposure to air pollution, the association between newly diagnosed major depressive disorder and PM $\leq$ 2.5μm has been minimally assessed [7]. A study of increased suicide rate after 4 weeks' exposures to air pollution did not adjust for known risk factors [8]. Moreover, there is inconsistent evidence that ambient air pollution is associated with depressive symptoms among older adults $\geq$ 65 years of age living in a metropolitan area of U.S. or European general population [9, 10].

In other words, there was insufficient evidence to support an association between long-term exposure to ambient air pollution and mental health status in general population. Therefore, for this study, we used nationwide population data to investigate the association between long-term exposure to ambient air pollution and mental health status, including subjective stress, depressive disorders, health-related quality of life and suicide.

Materials and methods

Study participants

For this study, we evaluated data from the Korean Community Health Survey (KCHS) 2013, which has been collected by the Korea Centers for Disease Control and Prevention annually since 2008. We collected the data via computer-assisted personal interviews with 900 people in each of the 253 community units between August and October in 2013, including 17 metropolitan areas and provinces. Study participants aged 19 or older in each area who were selected by the probability proportional sampling method and the systematic sampling method [11]. Among total surveyed 228,781 adults in 2013, we selected subjects who had lived in the same domicile for > five years. After we matched the domicile code of participants and the location code of air pollution surveillance station because of using same code system, we ultimately analyzed 124,205 persons (unweighted number).

Air pollutant variables

We obtained the daily average concentrations of hourly measured particulate matter <10 μm (PM_{10}), NO_2, CO, and SO_2 as air pollutant variables at nationwide air pollution surveillance stations from the Korean Air Pollutants Emission Service. We calculated quartiles of air pollutants using yearly average concentration between August 2012 and July 2013. These air pollutant measurements followed the standard reference protocol of the Korean Air Pollutants Emission Service [12]. PM_{10} had been measured using beta-ray attenuation method (MEZUS-610, KENTEK, Daejeon, Korea). NO_2 had been measured using chemiluminescence method (MEZUS-210, KENTEK). CO had been measured using non-dispersive infrared (MEZUS-310, KENTEK). SO_2 had been measured using UV fluorescence (MEZUS-110, KENTEK). We obtained meteorological data, including temperature, rainfall, and wind speed, from the National Meteorological Office in the same period [13, 14].

Mental health variables

The KCHS surveyed mental health-related indicators. These indicators were defined as subjective daily stress, the EuroQol-5 dimensions (EQ-5D) index, the presence or absence of

depressiveness (such as a feeling of sadness or hopelessness lasting more than two consecutive weeks), physician's diagnosis of depression, suicidal ideation, or a suicide attempt during the past year. We assessed subjective stress on a four-point rating scale ("very much," "a lot," "a little bit," "rarely"). Ultimately, we defined participants with subjective stress as those who responded with "very much" or "a lot" of stress. The EQ-5D index is broadly applied to evaluate health-related quality of life in five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and each dimension has one of three possible responses (no problems, some problems, or extreme problems). The EQ-5D index generates a single value from each dimension using the following weighted health scores: worst possible = 0; best possible = 1, and a score below zero equates to a health status worse than death [15]. We defined the fourth quartile of the EQ-5D index (which was 0.913 in this study) as a group with poor quality of life.

Other variables

We categorized patients as non-smokers, former smokers (smoked at one time but not currently), or current smokers (smoking daily or intermittently at the time of the survey). We defined alcohol consumption by drinking frequency of one time per week. We defined physical activity by intensity and frequency. Active group was doing moderate intense activity $\geq$ three times per week or vigorous activity $\geq$ one time per week. Inactive group was defined when participant was not met these criteria. Vigorous physical activity included running (jogging), climbing, fast biking, fast swimming, soccer, basketball, jumping rope, squash, or singles tennis, as well as occupational activities such as carrying heavy objects [16]. We also obtained the following demographic information: years of education ($<$ 9, 9–12, or $>$ 12); marital status (married/with partner, not married, or divorced/widowed); current employment status (employed or retired/unemployed); household income ($<$ 7,000,000 won/year or $\geq$ 7,000,000 won/year); hours of sleep duration ($<$ 7, 7–9, or $>$ 9); religion (yes or no); residence (rural or urban); and medical history according to physicians' diagnoses, including hypertension, diabetes mellitus, dyslipidemia, stroke, myocardial infarction, ischemic heart disease, asthma, and arthritis. We divided participants' length of residence into four groups, $5 \leq$ Q1 $<$ 10 years, $10 \leq$ Q2 $<$ 15 years, $15 \leq$ Q3 $<$ 20 years, or Q4 $\geq$ 20 years, after excluding those who had lived in their areas for $<$ 5 years.

Ethical considerations

The institutional review board (IRB) at the Korean Centers for Disease Control and Prevention approved the study protocol, and all of the participants provided written informed consent. The IRB at Gangnam Severance Hospital, Yonsei University College of Medicine approved this study as well (IRB File Number: 3-2017-0153).

Statistical analyses

We conducted all analyses considering the survey weight. Continuous variables are presented as means with standard errors, and categorical variables are presented as percentages. We conducted a univariate analysis to find out the association between the characteristics of participants and mental health status. We then evaluated mental disorder risk using multiple logistic regression analysis after adjusting for age, sex, smoking, drinking, physical activity, education, marital status, employment, household income, sleep duration, residence, and medical history (hypertension, diabetes mellitus, dyslipidemia, stroke, myocardial infarction, ischemic heart disease, asthma, arthritis). We conducted stratified analyses to investigate the possible effect modification by sex and age (divided by age 65) in subgroup analysis. EQ-5D index was

skewed distributed. We showed the meteorological data including mean temperature, rainfall and wind speed and the level of air pollutant in 2013 in S1 Table. The nationwide values of ambient air pollutants are also presented as means with standard deviations, medians and ranges in S1 Table. Therefore, it was analyzed using logarithmic transformation. We conducted all analyses using SAS software 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

The demographic, socioeconomic characteristics, health-related behaviors, and past medical history of the study population are summarized in **Table 1**. The mean age was 48.2 years, and the study population was 50.1% women. Approximately 70% of participants had lived in the same domicile for > 15 years.

The association between the characteristics of participants and mental health status was shown in **Table 2**. Mental health status was associated with various sociodemographic feature, health-related behaviors and medical factor. The risk of subjective stress decreased older age, education less than 12 years or unemployed participants. Subjects with current smoking and alcohol drinking more than one time per week represented a low risk of depressiveness and depression diagnosis by doctor.

The risk of a mental disorder according to the air pollutant quartile is represented in **Fig 1**. After we adjusted for confounding factors, there were positive associations between PM_{10}, NO_2, CO exposure and mental health status except suicidal attempts. The risk of depressiveness increased at the third quartile of CO exposure (odds ratio [OR]; 95% confidence interval [CI]: 1.635(1.497, 1.786)), the highest quartile of NO_2 (1.501(1.377, 1.635)) and the third quartile of PM_{10} (1.335(1.267, 1.408)). There was no association between SO_2 exposure and mental health status.

Compared with women, men had increased prevalence of subjective stress with exposure to PM_{10} and prevalence of poor QoL with exposure to CO and SO_2 in **Table 3**. And depressiveness in men also increased with exposure to NO_2, CO and SO_2. The risk of depression diagnosis by doctor and suicidal ideation had no difference according to sex (*Ps* > 0.05). The effect of SO_2 was inconsistent according to the quartiles.

The risk of higher stress and poor QoL with PM_{10} in subjects < age 65 were significantly increased than that in subjects ≥ age 65 in **Table 4**. Subjects < age 65 with high quartiles of PM_{10}, NO_2, CO and SO_2 had a higher risk of poor QoL than subjects ≥ age 65. In the higher levels of air pollutants, the risk of depressiveness, depression diagnosis by doctor and suicidal ideation increased, however, there had no significant difference according to age 65.

Discussion

In this study, we used Korean nationwide population-based data to identify associations between long-term exposure to ambient air pollutants and mental health status. After considering mental health-related confounding factors such as socioeconomic status, health-related behavior and medical history, air pollutants may be an independent predictor of mental health status, ranging from subjective stress level to suicidal ideation.

Our results were similar to those of a previous Korean study in which emergency department visits for depressive episodes in patients with a past history of depressive disorder were associated with recent air pollutant levels [3]. However, our study findings confirmed the associations between subjective stress in daily life or suicide attempts in the general population and long-term exposure to ambient air pollutants. In a three-year study from the National Health Insurance database, there was an association between major depressive disorder and $PM_{2.5}$ [7]. However, we additionally assessed the effects of SO_2, NO_2, and CO on mental health status,

Table 1. Baseline characteristics of study population.

Variables	Total	Men	Women
Age, years	48.2±0.04	47.0±0.06	49.4±0.05
Smoking			
Never	61.2	41.6	80.7
Former	16.1	30.9	1.3
Current	22.7	27.5	18.0
Alcohol intake			
Never or less than one time per week	87.1	85.4	88.8
More than one time per week	12.9	15.6	11.2
Physical activity			
Active	44.5	46.2	42.8
Inactive	55.5	53.8	57.2
Education			
< 9 years	22.4	19.1	25.7
9–12 years	31.8	33.0	30.6
> 12 years	45.9	47.9	43.7
Marital status			
Married/with partner	65.0	67.3	62.7
Not married	22.9	26.9	18.9
Divorced/widowed	12.1	5.8	18.4
Employment			
Employed	62.8	77.5	48.2
Retired/unemployed	37.2	22.5	51.8
Household income			
< 7,000,000 won/year	70.0	69.0	70.9
≥7,000,000 won/year	30.0	31.0	29.1
Sleep time, hours			
< 7 hours	48.7	47.6	49.8
7–9 hours	48.1	48.7	47.5
> 9 hours	3.2	3.7	2.7
Religion, yes	28.2	20.6	35.7
Residence of urban	79.7	79.6	79.8
Hypertension	19.5	19.3	19.7
Diabetes mellitus	7.4	8.0	6.9
Dyslipidemia	11.2	10.7	11.7
Stroke	1.4	1.6	1.3
Myocardial infarction	1.0	1.2	0.8
Ischemic heart disease	1.4	1.3	1.5
Asthma	2.4	2.1	2.7
Arthritis	9.6	4.1	15.0
Length of residence			
5–10 years	14.4	13.9	14.9
10–15 years	13.7	13.2	14.2
15–20 years	11.0	10.9	11.1
≥ 20 years	60.8	62.0	59.8
Subjective stress	27.5	32.0	23.0
Poor quality of life	21.7	18.4	32.9
Depressiveness	6.2	4.2	8.0

(*Continued*)

Table 1. (Continued)

Variables	Total	Men	Women
Depression diagnosis	2.5	1.3	3.7
Suicidal ideation	8.8	6.6	11.3
Suicide attempt	0.4	0.4	0.5

Data was shown by mean and standard error or percentage. Physical active group was defined as moderate intense activity ≥ 3 times per week or vigorous activity ≥1 time per week. Inactive group was not met these criteria. Length of residence with same domicile was counted. Medical history was defined as a physician's diagnosis. The subjects with subjective stress were defined as those responding with "very much" or "a lot" of stress. The fourth quartile of the EuroQol-5 dimensions index was defined as a group with poor quality of life.

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and thereby, we confirmed the associations between long-term exposure to ambient air pollutants including PM_{10}, NO_2, and CO and subjective stress, poor QoL, depressiveness, and suicide ideation.

In this study, we found no clear linear correlation between the risk of mental health disorders and the air pollutant concentration quartile. We believe that the reason for this finding is a threshold effect at low levels of air pollutants; if the concentration is above a certain cut-off value, a significant effect may be similar. We also identified a weak association between

Table 2. Univariate analysis for the association between the characteristics of participant and mental health status.

	Subjective stress	Poor quality of life	Depressiveness	Depression diagnosis by doctor	Suicidal ideation	Suicide attempt
Age	0.991 (0.990,0.992)	1.049(1.048,1.051)	1.010 (1.009,1.012)	1.021 (1.019,1.024)	1.024 (1.022,1.025)	1.007 (1.001,1.013)
Women	1.005 (0.977,1.034)	2.325 (2.256,2.396)	1.926 (1.819,2.039)	2.765 (2.523,3.029)	1.731 (1.654,1.811)	1.301 (1.059,1.600)
Current smoking	1.591 (1.539,1.646)	1.713 (1.645,1.784)	0.916 (0.857,0.980)	0.783 (0.707,0.867)	0.996 (0.944,1.051)	2.090 (1.699,2.573)
Alcohol (≥1/week)	1.303 (1.259,1.348)	1.619 (1.555,1.686)	0.880 (0.822,0.943)	0.632 (0.566,0.705)	0.951 (0.900,1.004)	1.570 (1.254,1.967)
Physically inactive	1.101 (1.068,1.134)	1.757 (1.700,1.815)	1.122 (1.061,1.187)	1.381 (1.270,1.502)	1.323 (1.264,1.386)	1.454 (1.179,1.974)
Education, ≤ 12 years	0.939 (0.911,0.967)	2.818 (2.720,2.921)	1.594 (1.502,1.692)	2.280 (2.070,2.511)	2.273 (2.155,2.398)	3.100 (2.414,3.980)
Divorced/widowed	1.091 (1.057,1.125)	1.324 (1.282,1.368)	1.405 (1.330,1.485)	1.395 (1.284,1.516)	1.309 (1.250,1.371)	1.589 (1.297,1.947)
Unemployed	0.728 (0.706,0.750)	2.949 (2.858,3.044)	1.759 (1.665,1.859)	2.784 (2.566,3.020)	1.736 (1.659,1.816)	2.010 (1.638,2.468)
Household income < 7,000,000	1.077 (1.038,1.117)	1.714 (1.643,1.788)	1.453 (1.349,1.564)	1.728 (1.542,1.936)	1.608 (1.509,1.713)	2.312 (1.693,3.158)
Sleep time <7,or ≥9	1.518 (1.474,1.564)	1.443 (1.399,1.488)	1.493 (1.412,1.579)	1.586 (1.461,1.721)	1.509 (1.443,1.579)	1.952 (1.584,2.405)
Residence of urban	1.030 (0.989,1.073)	0.795 (0.761,0.829)	1.083 (1.005,1.167)	1.069 (0.949,1.204)	0.847 (0.797,0.900)	0.888 (0.686,1.149)
Hypertension	0.962 (0.918,1.018)	2.905 (2.810,3.003)	1.381 (1.299,1.469)	1.883 (1.731,2.049)	1.793 (1.708,1.882)	1.559 (1.246.1.950)
Diabetes Mellitus	1.023 (0.969,1.079)	2.754 (2.625,2.888)	1.512 (1.390,1.645)	2.056 (1.829,2.310)	1.956 (1.828,2.093)	2.205 (1.636,2.973)
Dyslipidemia	1.175 (1.125,1.228)	2.170 (2.082,2.261)	1.658 (1.546,1.779)	2.747 (2.511,3.006)	1.776 (1.674,1.885)	1.614 (1.260.2.068)
Stroke	1.316 (1.182,1.465)	9.142 (8.160,10.243)	2.523 (2.172,2.931)	3.513 (2.941,4.197)	3.402 (3.024,3.828)	4.156 (2.718,6.353)
Myocardial infarction	1.158 (1.020,1.316)	4.391 (3.903,4.940)	2.297 (1.938,2.723)	2.730 (2.158,3.453)	2.733 (2.354,3.172)	3.237 (1.847,5.675)
Ischemic heart disease	1.142 (1.025,1.272)	4.276 (3.879,4.713)	2.195 (1.874,2.571)	3.885 (3.267,4.621)	2.712 (2.397,3.069)	2.344 (1.357,4.049)
Asthma	1.495 (1.368,1.635)	2.844 (2.615,3.094)	2.629 (2.327,2.970)	3.073 (2.594,3.642)	2.763 (2.498,3.055)	2.554 (1.681,3.882)
Arthritis	1.219 (1.165,1.276)	7.433 (7.114,7.767)	2.440 (2.279,2.613)	3.747 (3.434,4.088)	2.949 (2.789,3.118)	2.405 (1.876,3.083)

Physically inactive group was defined when participant was doing moderate intense activity < three times per week or vigorous activity < one time per week; years of education (≤ 12, or > 12); marital status (married/with partner, not married, or divorced/widowed); current employment status (employed or retired/unemployed); household income (< 7,000,000 won/year or ≥ 7,000,000 won/year); hours of sleep duration (7–9, and <7 or > 9); residence (rural or urban); and medical history according to physicians' diagnoses, including hypertension, diabetes mellitus, dyslipidemia, stroke, myocardial infarction, ischemic heart disease, asthma, and arthritis.

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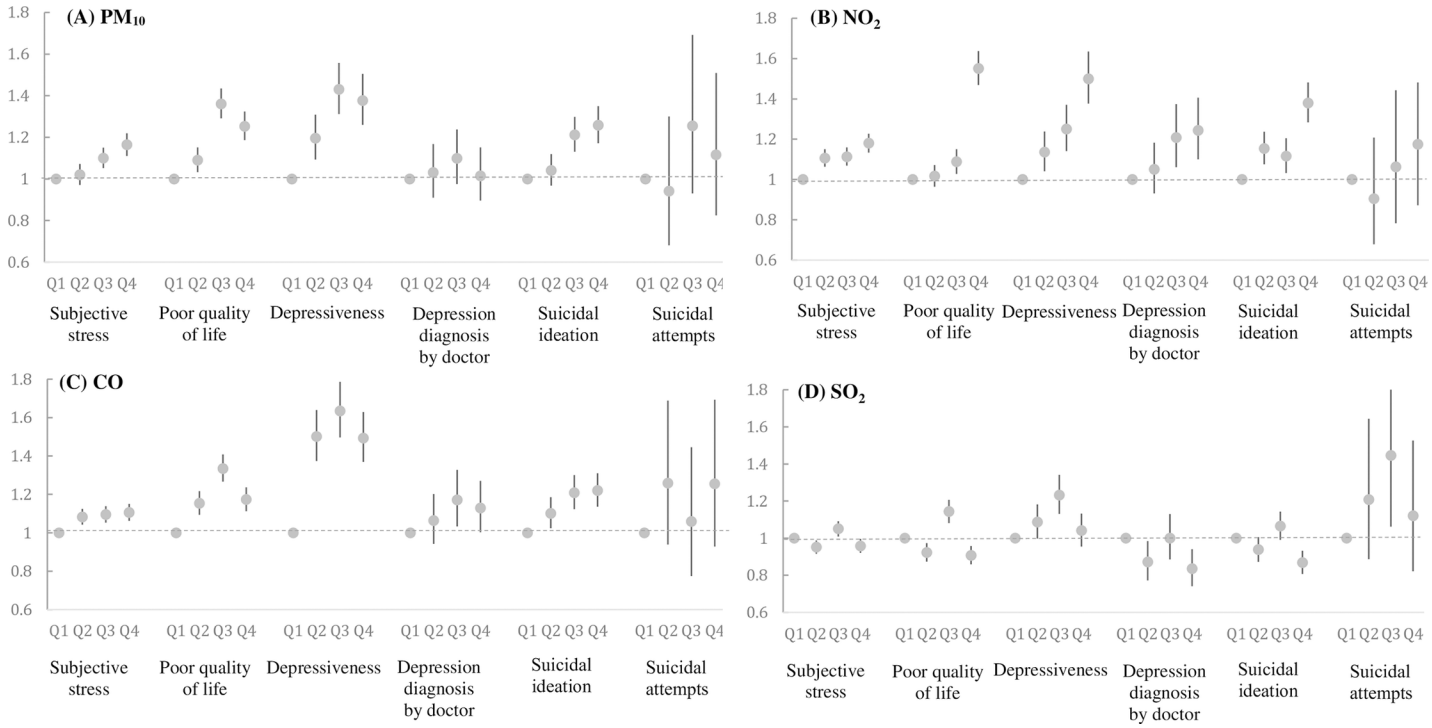

Fig 1. The odds ratios and 95% confidence intervals of a mental health disorder according to the air pollutant quartile. (A) PM_{10} (B) NO_2 (C) CO (D) SO_2.

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depression diagnosis by a physician and ambient air pollution quartile. This association may decrease after adjustment of the known risk factors for depression diagnosis, but a strong association between air pollution and parameters of other mental health status was maintained. Therefore, air pollution may be an unknown risk factor in other mental health parameters. In addition, undiagnosed depressive patients may have other risk factors. In generally, it was known that the risk of mental health disorder was higher in women and the elderly, but air pollution may be an important risk factor for men or persons < 65 years old because these groups may be exposed to air pollution more frequently with high activity [17, 18]. Except the rate of subjective stress, women's mental health status showed more poor than men in this study, though the rates of suicide attempt were similar. It has been proposed that men's mental health status may be masked by alcohol and physical violence, and their diagnosis of depression may be underdiagnosed [19]. Accordingly, known confounding factors may be correlated with women's diagnosed depression from the previous studies [19]. Therefore, air pollutants, as a new association factor of mental health status, may be found out an independent risk factor and enhanced the risk for men. Further research is needed to support any such causal relationship or biological difference. In this study, there was no association between suicide attempts and air pollution exposure. Suicide attempts represent acute symptom worsening, which may be more influenced by short-term rather than long-term exposure to ambient air pollutants [5, 20].

Air pollutants may be strong inflammatory agents in psycho-endocrine-immune connections through an inflammatory process; cyclooxygenase-2, interleukin-1β and particulate-matter–associated lipopolysaccharides [21]. Exposure to air pollutants leads to elevated hippocampal pro-inflammatory cytokine expression, and in addition, there are architectural changes in the dendrites of the hippocampus that can increase depressive-like behaviors in animal models [22]. Neuroinflammation caused by exposure to air pollution can alter innate immune responses and even influence human neurodegenerative disease [21].

Table 3. Air pollution and mental health status according to sex.

	Subjective stress		Poor quality of life		Depressiveness		Depression diagnosis by doctor		Suicidal ideation	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
PM_{10}										
Q4	**1.121(1.062, 1.183)**	**1.089 (1.036,1.145)**	1.256 (1.175,1.337)	1.236(1.137, 1.344)	1.342 (1.158,1.556)	1.385 (1.248,1.536)	0.978 (0.758,1.263)	1.022 (0.886,1.179)	1.241 (1.109,1.388)	1.256 (1.154,1.368)
Q3	**1.078 (1.028,1.131)**	1.033(0.981, 1.087)	1.360 (1.278,1.446)	1.338(1.233, 1.451)	1.442 (1.250,1.662)	1.409 (1.275,1.557)	1.076 (0.849,1.363)	1.101 (0.960,1.262)	1.246 (1.117,1.391)	1.175 (1.081,1.277)
Q2	**1.005 (0.955,1.058)**	0.998(0.945, 1.053)	1.088 (1.020,1.159)	1.078(0.989, 1.175)	1.208 (1.040,1.403)	1.184 (1.066,1.314)	1.034 (0.804,1.331)	1.026 (0.890,1.182)	1.013 (0.899,1.141)	1.051 (0.965,1.144)
Q1	1	1	1	1	1	1	1	1	1	1
p-interaction	**0.009**		0.593		0.741		0.969		0.583	
NO_2										
Q4	1.205(1.140, 1.274)	1.161 (1.104,1.220)	1.587(1.458, 1.727)	1.518 (1.426,1.617)	**1.707 (1.479,1.970)**	**1.389 (1.252,1.542)**	1.280(1.010, 1.623)	1.223 (1.066,1.403)	1.319 (1.177,1.478)	1.402 (1.286,1.529)
Q3	1.119(1.057, 1.184)	1.108 (1.053,1.167)	1.140(1.042, 1.274)	1.057 (0.989,1.129)	**1.440 (1.238,1.675)**	**1.158 (1.038,1.291)**	1.125(0.879, 1.440)	1.241 (1.069,1.441)	1.074 (0.957,1.205)	1.134 (1.031,1.247)
Q2	1.139(1.079, 1.202)	1.072 (1.021,1.126)	1.054(0.972, 1.142)	0.996 (0.937,1.059)	**1.146 (0.991,1.325)**	**1.128 (1.017,1.251)**	1.005(0.783, 1.290)	1.059 (0.929,1.208)	1.045 (0.943,1.158)	1.197 (1.098,1.304)
Q1	1	1	1	1	1	1	1	1	1	1
p-interaction	0.054		0.391		**0.011**		0.765		0.205	
CO										
Q4	1.123(1.064, 1.186)	1.091 (1.038,1.147)	**1.196 (1.123,1.274)**	**1.135(1.045, 1.232)**	**1.535 (1.338,1.663)**	**1.524 (1.375,1.689)**	1.204(0.946, 1.533)	1.100 (0.964,1.256)	1.318 (1.178,1.476)	1.162 (1.069,1.263)
Q3	1.111(1.051, 1.173)	1.085 (1.032,1.140)	**1.433 (1.346,1.526)**	**1.186(1.091, 1.290)**	**1.697 (1.465,1.966)**	**1.584 (1.424,1.763)**	1.091(0.852, 1.397)	1.197 (1.039,1.378)	1.290(1.148, 1.450)	1.152(1.057, 1.256)
Q2	1.089(1.032, 1.150)	1.079 (1.027,1.134)	**1.212 (1.139,1.290)**	1.065(0.980, 1.158)	**1.389 (1.176,1.593)**	**1.369 (1.112,1.643)**	0.999(0.776, 1.286)	1.086 (0.951,1.241)	1.163(1.034, 1.307)	1.061(0.975, 1.155)
Q1	1	1	1	1	1	1	1	1	1	1
p-interaction	0.580		**<0.001**		**0.045**		0.633		0.324	
SO_2										
Q4	0.944(0.894, 0.997)	0.973 (0.925,1.023)	0.909 (0.852,0.970)	0.905 (0.835,0.981)	1.146 (0.933,1.323)	0.986 (0.891,1.091)	0.944(0.738, 1.208)	0.804 (0.701,0.922)	0.879 (0.785,0.984)	0.861 (0.791,0.938)
Q3	1.042(0.986, 1.101)	1.059 (1.008,1.114)	**1.145 (1.074,1.220)**	**1.129 (1.037,1.229)**	**1.345 (1.162,1.557)**	**1.171 (1.059,1.294)**	1.082(0.848, 1.379)	0.977 (0.849,1.125)	1.091 (0.972,1.224)	1.045 (0.959,1.139)
Q2	0.939(0.890, 0.991)	0.962 (0.917,1.010)	0.972 (0.912,1.035)	0.851 (0.783,0.925)	1.013 (0.876,1.172)	1.131 (1.025,1.248)	1.018(0.797, 1.302)	0.834 (0.729,0.955)	0.909 (0.812,1.018)	0.962 (0.885,1.047)
Q1	1	1	1	1	1	1	1	1	1	1
p-interaction	0.738		**0.017**		**0.002**		0.527		0.488	

Bold characteristics means *P*–value <0.05 among the values with *p*-interaction < 0.05. EQ-5D index was analyzed by logarithmic transformation. Adjustment for age, smoking, drinking, physical activity, education, marital status, employment, household income, sleep duration, residence and medical history (hypertension, diabetes mellitus, dyslipidemia, stroke, myocardial infarction, ischemic heart disease, asthma, arthritis).

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Particulate and gaseous pollutants coexist in the air and may induce adverse health effects. PM rarely exists by itself within the ambient environment because gaseous, semi-volatile, and volatile compounds (i.e., aldehydes and polycyclic aromatic hydrocarbons) are constantly changing and interacting. Many vapor-phase compounds attach to the surface of PM and/or by themselves form secondary aerosolized particles [1]. The concentrations of PM_{10} and NO_2

Table 4. Air pollution and mental health status according to age.

	Subjective stress		Poor quality of life		Depressiveness		Depression diagnosis by doctor		Suicidal ideation	
	Age ≥ 65	Age < 65	Age ≥ 65	Age < 65	Age ≥ 65	Age < 65	Age ≥ 65	Age < 65	Age ≥ 65	Age < 65
PM_{10}										
Q4	0.940(0.872, 1.014)	**1.150 (1.101,1.201)**	0.949(0.867, 1.038)	**1.338 (1.277,1.456)**	1.329 (1.137,1.555)	1.383 (1.246,1.535)	0.866 (0.707,1.059)	1.061 (0.910,1.237)	1.192(1.067, 1.331)	1.269 (1.165,1.382)
Q3	0.986(0.918, 1.060)	**1.062 (1.018,1.108)**	**1.101(1.012, 1.198)**	**1.473 (1.383,1.569)**	1.327 (1.142,1.542)	1.446 (1.310,1.600)	0.907 (0.752,1.049)	1.154 (0.996,1.338)	1.211(1.094, 1.341)	1.206 (1.108,1.312)
Q2	0.919(0.854, 0.988)	1.025 (0.979,1.073)	1.006(0.926, 1.094)	**1.122 (1.049,1.201)**	1.189 (1.028,1.376)	1.200 (1.079,1.334)	1.027 (0.856,1.232)	1.022 (0.874,1.194)	1.054(0.945, 1.175)	1.033 (0.945,1.130)
Q1	1	1	1	1	1	1	1	1	1	1
p-interaction	<**0.001**		<**0.001**		0.688		0.218		0.765	
NO_2										
Q4	1.182 (1.095,1.277)	1.171 (1.120,1.225)	**1.203 (1.101,1.314)**	**1.706 (1.598,1.821)**	1.550 (1.341,1.792)	1.478 (1.337,1.633)	1.071 (0.884,1.299)	1.289 (1.107,1.501)	1.319 (1.177,1.478)	1.702 (1.286,1.529)
Q3	1.189 (1.101,1.284)	1.093 (1.044,1.144)	0.843 (0.771,0.923)	**1.207 (1.127,1.294)**	1.334 (1.144,1.556)	1.223 (1.098,1.362)	1.123 (0.929,1358)	1.231 (1.049,1.444)	1.074 (0.957,1.205)	1.134 (1.031,1.247)
Q2	1.096 (1.023,1.174)	1.109 (1.061,1.160)	0.932 (0.861,1.009)	1.068 (0.999,1.141)	1.101 (0.963,1.258)	1.139 (1.027,1.262)	0.974 (0.818,1.153)	1.080 (0.929,1.254)	1.045 (0.943,1.158)	1.197 (1.098,1.304)
Q1	1	1	1	1	1	1	1	1	1	1
p-interaction	0.060		<**0.001**		0.662		0.893		0.181	
CO										
Q4	1.091 (1.014,1.173)	1.111 (1.063,1.162)	0.971 (0.890,1.061)	**1.249 (1.172,1.332)**	1.626 (1.398,1.891)	1.463 (1.322,1.618)	1.213 (1.006,1.462)	1.110 (0.961,1.284)	1.115(0.999, 1.244)	1.255 (1.152,1.368)
Q3	1.060 (0.984,1.142)	1.098 (1.051,1.148)	0.999 (0.916,1.090)	**1.470 (1.379,1.567)**	1.600 (1.368,1.872)	1.635 (1.475,1.811)	1.094 (0.898,1.331)	1.187 (1.020,1.382)	1.145(1.027, 1.277)	1.229 (1.125,1.343)
Q2	1.097 (1.019,1.182)	1.069 (1.025,1.116)	0.997 (0.913,1.089)	**1.234 (1.157,1.316)**	1.473 (1.260,1.721)	1.504 (1.359,1.666)	1.103 (0.905,1.343)	1.050 (0.905,1.218)	1.027(0.920, 1.147)	1.131 (1.035,1.236)
Q1	1	1	1	1	1	1	1	1	1	1
p-interaction	0.758		<**0.001**		0.329		0.602		0.265	
SO_2										
Q4	0.994 (0.921,1.072)	0.955 (0.914,0.998)	0.934 (0.855,1.022)	0.902 (0.846,0.961)	1.272 (1.094,1.479)	0.987 (0.894,1.089)	0.977 (0.804,1.187)	0.901 (0.775,1.043)	0.947 (0.850,1.056)	0.839 (0.771,0.914)
Q3	1.041 (0.962,1.126)	1.047 (1.002,1.095)	1.025 (0.934,1.125)	**1.181 (1.109,1.258)**	1.341 (1.149,1.563)	1.203 (1.091,1.326)	0.987 (0.817,1.191)	1.195 (0.944,1.271)	1.022 (0.916,1.141)	1.074 (0.986,1.169)
Q2	0.957 (0.889,1.030)	0.947 (0.907,0.989)	0.995 (0.910,1.086)	0.908 (0.851,0.969)	1.193 (1.027,1.386)	1.066 (0.968,1.175)	0.954 (0.781,1.166)	0.935 (0.805,1.085)	0.934 (0.841,1.038)	0.942 (0.865,1.026)
Q1	1	1	1	1	1	1	1	1	1	1
p-interaction	0.500		<**0.001**		0.092		0.825		0.104	

Bold characteristics means *P*–value <0.05 among the values with *p*-interaction < 0.05. EQ-5D index was analyzed by logarithmic transformation. Adjustment for sex, smoking, drinking, physical activity, education, marital status, employment, household income, sleep duration, residence and medical history (hypertension, diabetes mellitus, dyslipidemia, stroke, myocardial infarction, ischemic heart disease, asthma, arthritis)

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are highly correlated because they share the same pathway as that for depression and neurologic disorders [23]; in contrast, NO_2 and SO_2 may have different physiologic influences on human health. Although both are gaseous molecules, NO_2 is poorly soluble in water, whereas SO_2 is highly water soluble [24].

This study has a number of strengths. For one, we used large, heterogeneous, nationwide population-based data. We also considered a wide range of known covariates related to depression, including socioeconomic status [25]. Therefore, we were able to determine the effects of ambient air pollution as an independent risk factor for poor mental health. In particular, previously known risk factors were related to women and the elderly, but this study confirmed that air pollution was a risk factor for mental health disorders in men and individuals < 65 years old.

This study also has several limitations. First, it was not possible to establish causality between air pollution and mental health disorders in this cross-sectional study. Second, we matched the community and air pollutant levels using participants' home territories. Therefore, if participants worked far from their domiciles, the matching would not have accurately reflected air pollutant levels at their dwellings. Third, we focused on each pollutant and its respective effect on mental health status. However, the adverse effects of pollution on mental health may be caused by unmeasured pollutants, such as $PM_{2.5}$ or ozone [26], or combinations of multiple pollutants [6], which the effects of complex mixtures of constituent toxins on mental health cannot be explained in this study. Additionally, KCHS did not include the surveyed day to protect personal information, which linked each other. Weather condition may affect the level of air pollution and human activity, however, we cannot adjust them [13]. However, KCHS surveyed during three months, which had stable weather conditions from August to October without monsoon. Therefore, the weather effect would be relatively minimized. Lastly, the prevalence of depression in this study (2.49%) was lower than that found in previous studies of Koreans (3.7%) and Canadians (3.9%) [27, 28]. Therefore, we may have underestimated the prevalence of mental health disorders in these nationwide population-based KCHS data.

Conclusions

Long-term exposure to ambient air pollution was a risk factor of a wide range of potential mental health disorders. Future investigations must not only include more studies to determine the mechanisms of action but also examine the effect of demographic characteristics. This information is helpful to make a policy to control air pollution and to understand the action of air pollutant on the body correctly.

Supporting information

S1 Table. The ambient air pollutants and meteorological data in Korea. Particulate matter <10 μm (PM_{10}); Sulfur dioxide (SO_2); Nitrogen dioxide (NO_2); Carbon monoxide (CO). Temperature, rainfall and wind speed were shown at Seoul (Lat.(N) 37˚34′, Long.(E) 126˚57′). Korea Meteorological Administration, Seoul, Korea (Aug. 2012- July. 2013) http://www.kma.go.kr/repositary/sfc/pdf/sfc_ann_2013.pdf.
(DOCX)

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BMJ Open

Association between neighbourhood air pollution concentrations and dispensed medication for psychiatric disorders in a large longitudinal cohort of Swedish children and adolescents

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ABSTRACT

Objective: To investigate associations between exposure to air pollution and child and adolescent mental health.

Design: Observational study.

Setting: Swedish National Register data on dispensed medications for a broad range of psychiatric disorders, including sedative medications, sleeping pills and antipsychotic medications, together with socioeconomic and demographic data and a national land use regression model for air pollution concentrations for NO_2, PM_{10} and $PM_{2.5}$.

Participants: The entire population under 18 years of age in 4 major counties. We excluded cohort members whose parents had dispensed a medication in the same medication group since the start date of the register. The cohort size was 552 221.

Main outcome measures: Cox proportional hazards models to estimate HRs and their 95% CIs for the outcomes, adjusted for individual-level and group-level characteristics.

Results: The average length of follow-up was 3.5 years, with an average number of events per 1000 cohort members of ~21. The mean annual level of NO_2 was 9.8 µg/m^3. Children and adolescents living in areas with higher air pollution concentrations were more likely to have a dispensed medication for a psychiatric disorder during follow-up (HR=1.09, 95% CI 1.06 to 1.12, associated with a 10 µg/m^3 increase in NO_2). The association with NO_2 was clearly present in 3 out of 4 counties in the study area; however, no statistically significant heterogeneity was detected.

Conclusion: There may be a link between exposure to air pollution and dispensed medications for certain psychiatric disorders in children and adolescents even at the relatively low levels of air pollution in the study regions. The findings should be corroborated by others.

Strengths and limitations of this study

- Longitudinal cohort approach covering the entire population under 18 in four major counties in Sweden (roughly half of the Swedish population).
- High statistical power allowing for separate analyses in the four counties.
- Register-based data reduce risk of certain bias.
- The outcome, any dispensed medication in the group N05, is a very crude measure of mental health.

INTRODUCTION

Mental disorders are experienced by 10–20% of all children and adolescents worldwide. These disorders may severely influence children's development, educational attainment and the potential to live fulfilling and productive lives. Air pollution is a complex mixture that most likely affects human health through multiple pathways, and air pollution has been named by the WHO as one of the biggest health threats of our time.[1] Oberdörster and Utell[2] first suggested that the brain might be vulnerable to ultrafine ambient particulate matter. Recently, concern has been raised over the effect of air pollution on the central nervous system.[3] Two early studies linked ambient photochemical oxidants to anxiety symptoms[4] and depression[5] in humans in California. Monthly or weekly levels of air pollution were observed to be associated with anxiety symptoms in the Nurses' Health Study,[6] and with perceived stress in the Veterans Administration Normative Aging Study in the USA,[7] and a number of studies have observed associations between daily fluctuations in air pollution and mental health outcomes such as depressive symptoms, suicide and emergency calls.[8–16] Perceived environmental noise and low air quality have been linked to mental health outcomes in adults

such as depression.[17] Epidemiological studies have shown that living in areas with elevated concentration of air pollution is linked with decreased cognitive function,[18–23] lower neurobehavioural testing scores in children,[24] a decline in neuropsychological development in the first 4 years of life[25] and elevated risk of autism spectrum disorders.[26–32] Furthermore, children in Spain who attended schools with higher traffic-related air pollution have been observed to have a smaller improvement in cognitive development than children who attended schools with lower traffic-related air pollution.[33] In a review from 2012 on epidemiological studies on neuropsychological effects of air pollution, the authors conclude that there is evidence for air pollution to be associated with mental development and mental decline.[34] The National Institute of Environmental Health Sciences/National Institute of Health has convened an expert panel to identify research gaps and priority goals in the field of air pollution and mental disorders such as depression,[3] and expressed the need for well-designed studies with good data on exposure, outcomes and possible confounders or mediators of effect.[3] They were highlighting several methodological challenges when investigating air pollution and brain health. For example, parental mental health could influence exposure via socioeconomic status since there are often strong associations between socioeconomy and air pollution levels.

It has been argued that socially disadvantaged people tend to be segregated in relatively deprived areas with a worse environmental quality,[35 36] and there are often strong socioeconomic gradients in mental health.[37] Social characteristics may therefore modify the association between air pollution and mental health and also act as a major confounder. There is little consensus on the causal relationship between urbanisation and mental health, but it seems as if urban and rural environments can have pernicious and salutary consequences on mental health.[38] Factors with strong urban–rural gradients related to the environment such as air pollution concentrations are often neglected as a possible cause of mental health problems. Neighbourhood poverty has, for example, been observed to affect mental health in children,[39] but there were no adjustments done for neighbourhood air pollution concentrations.

The severe impact of child and adolescent mental health problems on society, together with the plausible and preventable association of exposure to air pollution, deserves special attention. In the present study, the hypothesis was that air pollution may be a risk factor for psychiatric disorders in children and adolescents. Our specific objective was to study associations between neighbourhood residential air pollution concentrations and mental health in children and adolescents. We did so in a longitudinal study, by assessing exposure to air pollution using a nationwide model, in combination with data on dispensed medications for a broad group of psychiatric disorders, and data on potential confounders from nationwide registries in a study population consisting of the entire population of the study area in Sweden.

METHODS

Study area

We used a longitudinal study design where the study subjects were all individuals under 18 years of age who at any time during the study period 1 January 2007–31 December 2010 had a registered residential address in any of the four Swedish counties Stockholm, Västra Götaland, Skåne and Västerbotten (figure 1). Stockholm County is located on the eastern coast of Sweden, includes the capital and had a population of just over 2.2 million in early 2015, with a population density of 338/km^2. Västra Götaland County is on the western coast and includes the second largest city in Sweden, Gothenburg; it had a population of 1.6 million people in early 2015, with a population density of 68/km^2. Skåne County is the southernmost county in Sweden and contains the third largest city, Malmö, with a population of nearly 1.3 million in early 2015, with a population density of 114/km^2. Västerbotten County is located in the Northern part of Sweden, with a total population of just over 260 000in early 2015, and with a population density of 5/km^2. The major part of the population in Västerbotten County lives near the coast, whereas large regions in the inland are very sparsely populated. The four counties are different not just in terms of geographic location, size and population density but also with respect to migration, socioeconomic characteristics, urbanisation and air pollution concentrations.

Swedish National Register data

We used register data from the Swedish National Board of Health and Welfare on a group of dispensed medication for medicine related to psychiatric diagnoses defined by the Board of Health and Welfare. Data on dispensed medications are available on the entire Swedish population from 1 July 2005. The medication group used as outcome in this study includes any medication with a Swedish ATC code starting with 'N05', hereafter referred to as N05. N05 consists of neuroleptics (antipsychotic medications), ataractics and sleeping pills (a broad group of sedative medications including hydroxyzine and melatonin-based medications). The majority of dispensed N05 medications for children and adolescents are sedative medications and sleeping pills. It should be noted that antidepressants or attention deficit hyperactivity disorder (ADHD) medications are not included in the N05 group. We had access to the number of times each year during follow-up an individual had dispensed an N05 medication (figure 2), but for integrity reasons, we could not obtain data on the exact type of medication within the N05 group. We defined an event as a dispensed N05 medication at least once

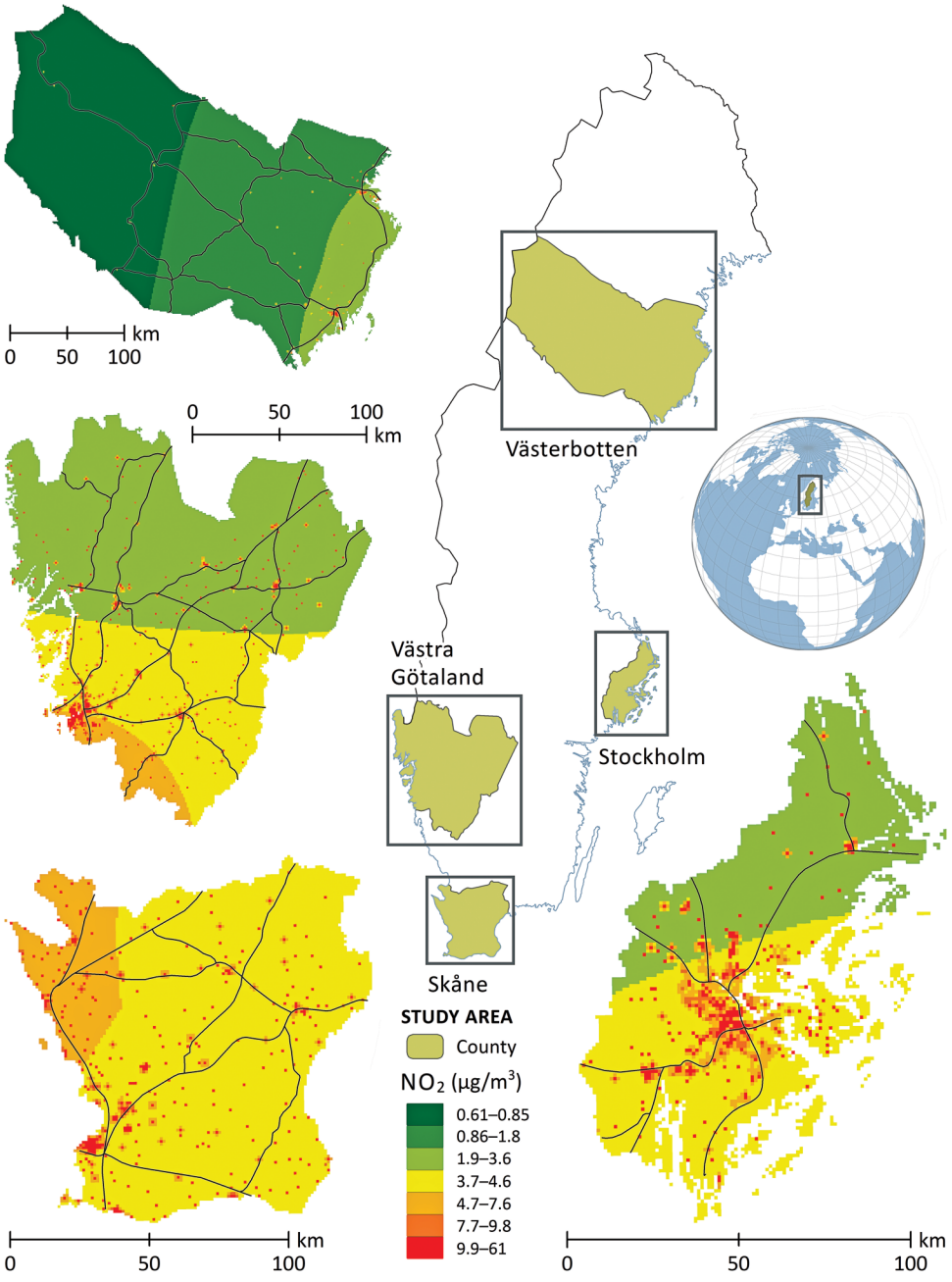

Figure 1 Study area with air pollution concentrations.

during follow-up. Individuals who had a record of an N05 dispensed medication from July 2005 (start date of the register) to 31 December 2006 (the year and a half before start of follow-up) were excluded from the analysis. An event was recorded the first year during follow-up that a N05 medication was dispensed and the event date was set to 1 July (we did not have access to the date each respective year the medication was dispensed). Each cohort member was followed up until an event occurred, loss-to-follow-up (meaning that they had no longer a registered address in the study area), death, 18th birthday or end of follow-up, whichever came first. We used an open cohort approach and continuously included cohort members from date of birth, or individuals moving to the study area from 1 January the year after they moved in. For practical reasons, an individual who moved out of the study area was censored and not included again if he or she moved back. We excluded individuals whose parents had N05 medications dispensed since the start date of the register. The total size of the cohort after exclusions was 896 117 individuals. We ran complete data models, meaning that individuals with missing data on any of the variables including in the models were excluded from analysis. The total size of the complete cohort was 552 221 individuals (figure 3).

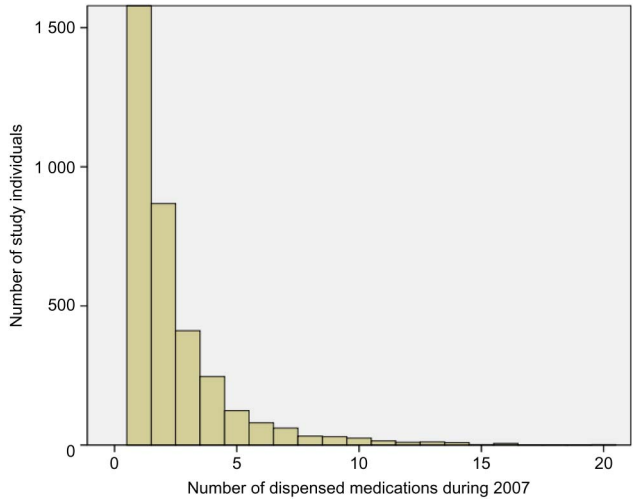

Figure 2 Histogram over the number of dispensed medications during 2007 (6647 in total, 4704=1, max=49).

Air pollution exposure assessment

The Swedish environmental research institute has developed an empirical Land Use Regression model to estimate the urban content of the contribution of nitrogen dioxide and particulate matter. The model is based on the ratio of the urban content contribution, the meteorological parameters and the population distribution. It includes the geographical distribution of the urban contribution, which means that it takes into account that the levels are not evenly distributed across a city but related to population density. This model was used together with a model for the regional background levels to calculate the exposure of NO_2 and particulates for the entire Swedish population.[40] We used three measures of exposure to air pollution as a marker of long-term exposure to air pollution, annual means of NO_2, PM_{10} and $PM_{2.5}$ for the year when the individual was included in the study (any year between 2005 and 2010). The base year of the land use regression model was 2010, and the estimation of the $PM_{2.5}$ concentrations was done by using a ratio relation between monitored $PM_{2.5}/PM_{10}$ on a yearly and geographical basis. The underlying assumptions were thus that the concentration at study inclusion was a valid marker for long-term exposure, and that the spatial contrasts in exposure during follow-up were fairly constant. In the whole country, 17 sites with measuring data were used. The urban background level of PM_{10} was estimated with modelled NO_2 and measured latitude-specific and season-specific ratios of PM_{10}/NO_2 in the model. For PM_{10}, the cross-validated explained variance ranged between 80% and 95% during the year. The model has previously been showed to have fairly good accordance with a dispersion model.[41] The spatial resolution was 1 km^2.

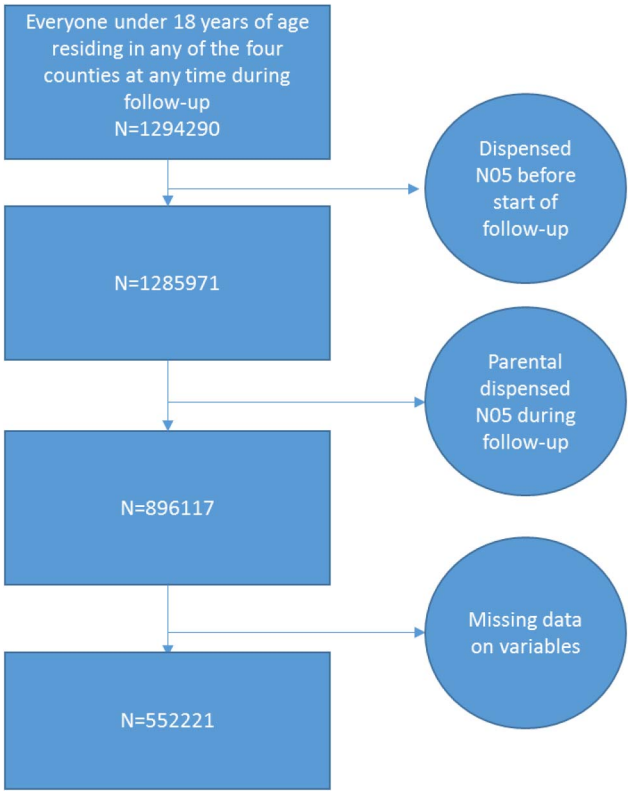

Figure 3 Flow chart.

Statistical analysis

The data were analysed with Cox regression assuming proportional hazards, with time as an underlying variable, resulting in HRs and their 95% CIs. We studied the exposure as continuous variables, as ratios associated with pollutant increases of 10 $\mu g/m^3$. Tests for proportionality were carried out by visual inspections and by formal testing confirming the assumption of proportional hazards. In the main model, we adjusted for age at the start of follow-up (continuous variable), sex, maternal and paternal education level (four categories), maternal body mass index in early pregnancy (continuous variable) and maternal smoking during early pregnancy (three categories) and for group-level education level (continuous variable). The variables were chosen on the basis of data available in the Swedish National registers. Maternal body mass index and smoking were included in the model more as indicators of socioeconomic status than as potential causes of an association. We defined a group-level variable on socioeconomic status based on data from Statistics Sweden, on Small Areas for Market Statistics (SAMS). There are 9000 SAMS areas in Sweden (6106 in our study area), and the idea is for SAMS to represent homogeneous neighbourhoods. The variable was defined as the proportion of the population in the SAMS area with three or more years of undergraduate studies in the age category 25–65 years.

In an additional analysis, we also adjusted the models for maternal and paternal income. Further, we stratified our analyses on county and sex.

Sensitivity analyses

We also ran models where NO_2 and PM_{10} were included simultaneously in the models, and a model where backward selection technique was used to identify the variables that should remain in the model. The variable inclusion criteria were: a p value <0.05 or a 20% change in the HR associated with air pollution.

In addition, we ran models where we excluded SAMS areas with <1000 inhabitants/km^2, and a threshold analysis where we only included NO_2 concentrations below 15 µg/m^3. In another sensitivity analysis, we adjusted for population density. Furthermore, we investigated effect modification with respect to age and socioeconomy (at the individual and group levels) by including cross-products of those variables with the exposure variables in the models. In another sensitivity analysis, follow-up started a year later, 1 January 2008, and individuals with a medication in the registry before that were excluded from the analysis. We also ran age-specific analyses for the age groups 0–4, 5–9, 10–14 and 15–18. Finally, we investigated if patterns of missingness among our variables were approximately the same for cases and non-cases and if they were dependent on the outcome or level of exposure. We imputed missing observations using a Markov Chain Monte Carlo approach and reran the main analyses to investigate whether our estimates changed.

SAS V.9.2 software was used to create data sets and run the analyses.

RESULTS

The HRs regarding PM_{10} and $PM_{2.5}$ were very similar. We therefore present only the results for PM_{10} and NO_2. There were in total 18 675 individuals who at least once had dispensed N05 during follow-up, with a total number of person-years followed up of 3 101 756 (table 1). The average length of follow-up was 3.5 years. The number of events per 1000 cohort members was 23 in Västra Götaland, 23 in Västerbotten, 20 in Stockholm and 20 in Skåne (table 1). The agreement between an event in 1 year and an event in subsequent years was not very high; for example, the κ statistic calculated for an event in 2007 and 2008 was 0.21, in 2007 and 2009 was 0.14, and in 2007 and 2010 was 0.11. The highest concentrations of NO_2 were found in Stockholm (yearly median: 8.3 µg/m^3) and the highest levels of PM_{10} were found in Skåne (yearly mean median: 15.8 µg/m^3; table 1). The correlation between NO_2 and PM_{10} was, due to the modelling of PM_{10}, high, and ranged between 0.83 (Västerbotten), 0.97 (Skåne) and 0.98 (Stockholm and Västra Götaland). No formal statistical testing was done of the differences between cohort members with and without an event during follow-up, but the mean concentration of NO_2 or PM_{10} did not seem to differ much between individuals with and without an event of dispensed N05 during follow-up (table 2). The age at inclusion among those who had a dispensed medication was higher than among those without an event of dispensed N05 during follow-up. Maternal body mass index was similar between the two groups, as was the group-level variable on socioeconomy (proportion with high education in the SAMS area). There were some differences with respect to maternal and paternal education levels and maternal smoking during pregnancy between individuals who dispensed medication and individuals who did not (table 2). The size and direction of the correlation coefficients between air pollution concentrations and group-level education were heterogeneous across municipalities in the study area (results not shown). Adjusting for parental income only marginally changed the results (results not shown).

The HR in association with a 10 µg/m^3 increase in NO_2 adjusted for age at the start of follow-up, sex, maternal and paternal education, maternal body mass index in early pregnancy, maternal smoking during early pregnancy and group-level education levels was 1.09 (95% CI 1.06 to 1.12; table 3). The corresponding HR associated with a 10 µg/m^3 increase in PM_{10} was 1.04 (95% CI 1.00 to 1.08). The correlation between NO_2 and PM_{10} was too high for them to be included simultaneously in the model, because NO_2 was one of the predictors of urban background PM_{10} in the PM_{10} model. When using the backward selection technique to identify what variables should be included in the model, all variables remained in the model due to their low p values, except the group-level SES variable that had a p value >0.20. The estimates with and without that variable included were very similar (results not shown). The crude HRs were close to one (no association), and the association appeared when adjusting for age. The other variables did not seem to have any substantial influence on the estimates (results not shown). The associations seemed heterogeneous across the four counties (table 3 and

Table 1 Description of the four counties in the study area

County	Events	Cohort size	Person-time (years)	Events per 1000 persons	Annual mean NO_2 50th, 5th–95th percentile (µg/m^3)	Annual mean PM_{10} 50th, 5th–95th percentile (µg/m^3)
Stockholm	7346	360 683	1 235 018	20.4	8.3 (3.7–21.5)	8.7 (3.8–21.5)
Västra Götaland	6004	270 398	948 035	22.2	7.7 (3.1–24.8)	14.2 (9.4–24.8)
Skåne	4248	218 064	758 504	19.5	7.4 (4.0–23.1)	15.8 (11.2–33.5)
Västerbotten	1077	46 972	165 599	22.9	2.3 (0.8–15.5)	5.7 (3.6–9.0)

figure 4A,B), at least for the association with PM_{10} (p=0.001). For NO_2, the p value for effect modification was 0.24. For example, the association with a 10 µg/m^3 increase in NO_2 was quite similar in Stockholm, Västra Götaland and Västerbotten (HRs of 1.13, 1.11 and 1.13, respectively), whereas there was no evident association (HR=1.03) in Skåne (table 3 and figure 4A,B). The HRs associated with a 10 µg/m^3 increase in PM_{10} were quite similar in Stockholm and Västra Götaland (1.23 and 1.18, respectively), 1.00 in Skåne and 1.89 in Västerbotten. The high estimate in Västerbotten is uncertain, a contributing factor that may be low statistical power to detect differences. The estimates seemed similar among boys and girls (table 3), and the p value for effect modification was 0.30 for NO_2 and 0.82 for PM_{10}.

Sensitivity analyses

When excluding the more rural areas (population density <1000 inhabitants/km^2), the size of the Stockholm cohort was barely affected, whereas the size of the Västra Götaland and Skåne cohorts was less than half the original size. The HRs of those three cohorts remained stable (table 3). Regarding Västerbotten, only a third of the original cohort remained, and the size of the HRs completely changed and the loss in precision was substantial (table 3). In the threshold analysis, where we excluded neighbourhoods with concentrations above 15 µg/m^3, the size of the cohorts did not change much due to the low levels of air pollution in general, and consequently neither did the HRs. However, the HR in association with the 10 µg/m^3 increase in NO_2 in Skåne was 1.16 (95% CI 1.02 to 1.33), which is different from the overall HR of 1.02. When adjusting for population density, the models did not perform very well (results not shown). There was no effect modification by age or socioeconomic status (results not shown). Starting follow-up a year later only marginally altered the effect estimates (results not shown). The age-specific HRs revealed no evident age trends (results not shown). Including the highly correlated NO_2 and PM_{10} in a two-pollutant model changed the overall estimate upwards for NO_2 to 1.18 (95% CI 1.12 to 1.24) and downwards for PM_{10} to 0.90 (95% CI 0.84 to 0.95).

The patterns of missingness among variables were approximately the same for cases and non-cases and were not dependent on the outcome or exposure level. Imputing missing data yielded similar results as the main model (results not shown).

DISCUSSION

Principal findings

In this longitudinal study of Swedish children and adolescents, neighbourhood air pollution concentration

Table 2 Descriptive statistics of explanatory variables stratified on the outcome

		Dispensed N05 during follow-up Mean (SD)	Missing N (%)	Not dispensed N05 during follow-up Mean (SD)	Missing N (%)
NO_2		9.7 (7.0)	35 (0.2)	9.8 (7.1)	7857 (0.9)
PM_{10}		13.6 (5.9)	35 (0.2)	13.7 (6.2)	7857 (0.9)
Age the start of follow-up		11.1 (6.0)	0 (0)	7.4 (5.8)	0 (0)
Maternal BMI early pregnancy		23.9 (4.3)	8467 (45.3)	23.9 (4.0)	283 811 (32.4)
Proportion with high* education level		0.22 (0.12)	1 (0)	0.23 (0.13)	154 (0)
		N (%)		N (%)	
Sex	Girls	10 068 (54)		426 669 (49)	
Maternal education level	Missing	1598 (9)		79 050 (9)	
	≤9 years	2075 (12)		79 627 (12)	
	>9 to ≤12 years	8307 (49)		351 721 (44)	
	>12 to <16 years	5137(30)		272 618 (34)	
	≥16 years	1558 (9)		94 426 (12)	
Paternal education level	Missing	2109 (11)		90 477 (10)	
	≤9 years	2775 (17)		100 911 (13)	
	>9 to ≤12 years	8248 (50)		369 703 (47)	
	>12 to <16 years	3795 (23)		209 140 (27)	
	≥16 years	1748 (11)		107 211 (14)	
Maternal smoking during pregnancy	Missing				
	Non-smokers	12 213 (79)		645 369 (89)	
	1–9 cigarettes per day	1926 (13)		54 361 (7)	
	≥10 cigarettes per day	1231 (8)		25 584 (4)	

*Proportion in SAMS (Small Areas for Market Statistics) area with three or more years of undergraduate studies in the age category 25–65 years.

Table 3 HRs and their 95% CIs for an event (dispensed N05 medications during follow-up) in association with a 10 µg/m^3 increase in NO_2 and PM_{10}, adjusted for individual-level and group-level characteristics

		Number of observations in total/in analysis/events	NO_2 HR (95% CI)	PM_{10} HR (95% CI)
All cohort*		896 117/552 221/9264	1.087 (1.055 to 1.121)	1.038 (1.003 to 1.076)
Stratified by county	Stockholm	360 683/209 589/3455	1.129 (1.068 to 1.194)	1.227 (1.123 to 1.340)
	Västra Götaland	270 398/173 210/3066	1.106 (1.056 to 1.158)	1.175 (1.091 to 1.266)
	Skåne	218 064/140 385/2290	1.019 (0.945 to 1.1097)	0.995 (0.927 to 1.067)
	Västerbotten	46 972/29 500/467	1.130 (0.930 to 1.373)	1.894 (1.128 to 3.180)
Stratified by sex	Girls	436 737/268 943/4775	1.080 (1.035 to 1.127)	1.040 (0.991 to 1.093)
	Boys	459 380/283 278/4489	1.092 (1.045 to 1.141)	1.033 (0.9991 to 1.093)
Exclude SAMS areas with a population density of <1000/km^2	Stockholm	294 728/167 711/2769	1.108 (1.043 to 1.177)	1.180 (1.073 to 1.297)
	Västra Götaland	122 083/72 773/1288	1.071 (1.010 to 1.136)	1.110 (1.007 to 1.225)
	Skåne	111 000/66 235/1108	0.890 (0.808 to 0.981)	0.891 (0.812 to 0.977)
	Västerbotten	13 824/8803/142	0.853 (0.609 to 1.193)	1.127 (0.382 to 3.25)
Concentrations <15 µg/m^3	Stockholm	303 380/177 831/2919	1.179 (1.053 to 1.321)	1.401 (1.187 to 1.652)
	Västra Götaland	215 300/142 031/2494	1.107 (0.990 to 1.238)	1.194 (0.873 to 1.634)
	Skåne	179 700/119 365/1974	1.150 (1.003 to 1.319)	0.775 (0.475 to 1.266)
	Västerbotten	43 694/27 154/423	1.124 (0.891 to 1.419)	1.78 (0.889 to 3.357)

*SAMS (Small Areas for Market Statistics). The crude HR associated with a 10 µg/m^3 increase in NO_2 was 1.013 (95% CI 0.993 to 1.034) and with a 10 µg/m^3 increase in PM_{10} was 0.982 (95% CI 0.959 to1.006). The HR adjusted for individual-level, but not group-level, characteristics associated with a 10 µg/m^3 increase in NO_2 was 1.087 (95% CI 1.056 to 1.119) and with a 10 µg/m^3 increase in PM_{10} was 1.041 (95% CI 1.006 to 1.078).

was associated with dispensed medications for certain psychiatric disorders, after adjusting for individual-level and group-level characteristics. The association was present in three out of four counties within Sweden. To put our findings in perspective, the association seemed to be present even at annual levels of NO_2 lower than 15 µg/m^3, which can be compared with the WHO guideline and EU air quality standard of 40 µg/m^3. However, a finer spatial resolution would have resulted in a wider concentration range especially for NO_2. This is one of a small number of studies to consider the association between air pollution and mental health, and the first to do so in children. There are several studies suggesting associations between air pollution and autism spectrum disorders[26–32] and cognitive function in children,[23–25 33] and this study adds to evidence from them that air pollution may have detrimental effects on the brains of children and adolescents. Furthermore, this is the first study to use a whole population, and to use nationwide register-based data on dispensed medications as an indicator for mental health. Most of the existing evidence for a link between air pollution and mental health comes from short-term studies in adults, where daily fluctuations in air pollution concentrations are compared with the daily number of mental health events or symptoms.[8–16] Furthermore, associations between longer term exposure to air pollution and anxiety and stress were recently reported in two ageing cohorts.[6 7]

Limitations and strengths of the study

There are some weaknesses and strengths of the study that should be mentioned. First, any dispensed medication in the group N05 is a very crude measure of mental health. N05 consists of neuroleptics (antipsychotic medications), ataractics and sleeping pills (a broad group of sedative medications including hydroxyzine and melatonin-based medications). Furthermore, the N05 group of medications includes antipsychotic medications, which most often are used for children with acute psychosis, children who are aggressive and acting out, children with severe neuropsychiatric disorders, children with strong anxiety or children where a bipolar condition is suspected. The majority of medications dispensed in the N05 group, however, concern children with different states of anxiety and children to whom sleeping pills are prescribed. The range of mental health problems in individuals with an event during follow-up may thus vary from mild to very severe. Also, the accordance (kappa-values) between a dispensed medication consecutive years was generally low. A dispensed medication for an individual a certain year thus did not necessarily indicated a high probability to dispense a medication the following year. This may indicate that the outcome measure as a marker of general mental health could be questioned. Access to more detailed data on type of dispensed medications would have been desirable, but we did not have access to such data. Given the results of this study, we hope to be able to get access to detailed Swedish register data on dispensed medications in the future. Moreover, we decided to dichotomise the outcome, although we could have used the number of dispensed medications per year as a continuous outcome to get a better estimate of a potential dose–response association. We decided against that

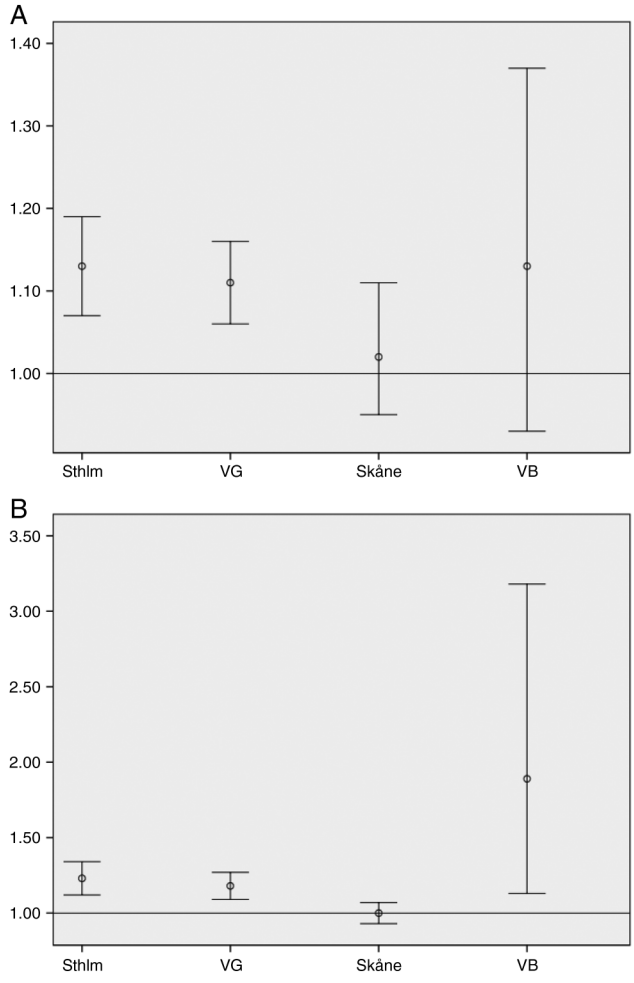

Figure 4 HRs and their 95% CIs for a dispensed N05 medication during follow-up in association with a 10 µg/m^3 increase in NO_2 (A) and PM_{10} (B) in Stockholm County (Sthlm), Västra Götaland County (VG), Skåne County (Skåne) and Västerbotten County (VB).

since the distribution of the number of dispensed medications was much skewed, with some outliers that seemed unrealistic. Despite the crude measure of mental health in this study, we consider the outcome to be an indicator for mental health in children and adolescents in general. A major strength of the data is that they cover the entire population; thus, the whole population of the study area can be seen as a cohort. We have access to register-based data, where dispensed medications of all Swedes are registered. Selection bias and recall bias therefore do not have to be considered in our setting. Another strength of this study is the longitudinal approach, which increases the validity of the results compared to cross-sectional studies. All individuals with an event 1.5 years before start of follow-up (1 January 2007) were excluded. It would have been desirable to base the exclusion criteria on the lifetime history of dispensed medications, but the register for dispensed medications did not start until 1 July 2005; thus, no data on earlier dispensed medications were available. Individuals with a dispensed medication the year and a half before start of follow-up were excluded from the analysis, but the agreement between a dispensed medication subsequent years was rather low. Therefore, an unknown proportion of the events are not incident events. The study is therefore prone to some of the limitations of a cross-sectional study; for example, reverse causation may be an explanation of our findings. However, delaying follow-up to 1 January 2008 and the sensitivity analyses restricting the sample to only urban areas do not suggest reverse causation to be a major explanation of our findings.

As expected, individuals who had been dispensed N05 during follow-up were much more likely to have parents who had been dispensed the same medication since the start date of the register (eg, 36% of the mothers compared to 22% of the mothers for individuals who had not been dispensed N05 during follow-up). We excluded children whose parents had been dispensed a medication for N05 for several reasons: (1) parental mental health problems might influence where the family resides, and therefore also the pollution levels, (2) parental inclination to dispense medication is correlated with children's dispensed medication and (3) parental mental health problems may directly influence children's mental health and an eventual association with air pollution may therefore be explained by the parental mental health status. Adjusting for parental medication for N05 is therefore not straightforward, and we decided to exclude these individuals to get 'cleaner' data, although this might have resulted in an underestimation of the true effect, as well as in a decreased generalisability. Despite that, we consider the exclusion of parents with a dispensed N05 medication to be one of the major strengths of the study.

Exposure measurement error should be considered in our study. We used neighbourhood exposure models with the resolution 1 km^2. Exposure contrasts within cities are therefore smoothed out in our data, which may have led to an underestimation of risk. However, the model has been validated, and we were able to use the same model in all four counties within Sweden, which is a major advantage. We used annual mean pollutant concentrations at the home address for the year of study inclusion as a marker for long-term exposure to air pollution. The modelled concentrations were based on the year 2010. The underlying assumption of this study is thus that spatial contrasts in pollutant concentrations were rather similar across follow-up. Another potential source of exposure measurement error is that modelled exposure is not necessarily a good marker for actual exposure.[42] It is likely that the exposure measurement error would have led to a bias towards the null, but we have not attempted to quantify that bias. In future studies, we will have access to more detailed data on exposure to air pollution, in terms of geographical and temporal resolution and in terms of source-specific exposures.

Another strength of the study is that we have enough statistical power to analyse data in the four counties

separately. The sometimes heterogeneous results between the areas raise important questions. For example, the risk estimates seemed generally close to one (no association) in Skåne, but were generally quite homogeneous in the other three counties. Excluding areas where air pollution levels >15 μg/m^3 (which basically means excluding the main city centres) resulted in a statistically significant HR associated with NO_2 in Skåne of 1.16. A possible reason for the results in Skåne is that the exposure model was not as valid in Skåne as in the other counties. For example, it is known that ozone is difficult to model in Skåne,[43] possibly due to local production of ozone in the summertime, which could skew the results. The discrepancy between Skåne and the other three counties could also be due to differences in terms of demography, immigration, heterogeneity in dispensed N05 between different socioeconomic groups or in associations between socioeconomy and residential air pollution levels, not fully accounted for in the statistical models. We have previously observed that patterns between socioeconomy and air pollution in Skåne seem to be complex,[44] but crude analyses suggest that such patterns can also be complex in other parts of the study area.

The crude HRs were close to one, but they are not meaningful unless adjusted for age. Age, in fact, seemed to be the only variable with a substantial influence on the HRs, but potential residual confounding due to socioeconomy should nevertheless be mentioned as an alternative explanation of our findings, although an additional analysis adjusting for parental income did not change the estimates. It is important to fully adjust for socioeconomy when investigating mental health outcomes in children and adolescents.[37] It should be noted that while all primary and in-patient care for children and adolescents is completely free of charge for the individual (funded by tax), medications are not free up to a certain annual amount (of around €200). Dispensation of medication is therefore more sensitive to socioeconomic status than, for example, outcomes based on hospital visits or diagnoses. Since air pollution concentrations are also associated with socioeconomic status, the importance of adjusting fully for socioeconomic status in our setting cannot be stressed enough. We used parental educational level and SAMS area educational level as main indicators for socioeconomy, and we also adjusted for body mass index and smoking during early pregnancy since those variables also capture socioeconomic status to a large extent. It would have been desirable to have other data on socioeconomy and lifestyle factors, but the data on socioeconomy are limited to what can be found in the Swedish nationwide registers. However, the HRs did not seem especially sensitive to inclusion or exclusion of the socioeconomic indicators we had access to. We therefore think that the probability for residual confounding from socioeconomy to explain our findings is rather small. Residual confounding could also be present with respect to environmental factors not accounted for in our study, for example, traffic-related noise (which hypothetically could be associated with the outcome). Unfortunately, we had no access to models on traffic-related noise, and thus could not rule out noise as an alternative explanation of our findings.

Comparison to other studies and discussion of potential mechanisms

To the best of our knowledge, this is the first study to consider the association between long-term exposure to air pollution and mental health in children. However, our findings are consistent with two prior studies of exposure to air pollution in association with anxiety,[6] and perceived stress,[7] in older citizens and with studies on short-term exposure to air pollution and mental health outcomes in the general population.[8–16] Furthermore, there is an increasing body of evidence suggesting air pollution to be associated with cognitive development in children,[23–25 33] and with autism spectrum disorder.[26–29 31 32]

The marker for mental health in this study was dispensed N05 medications, a broad group of medications where the majority of dispensed medications are sedative medications and sleeping pills, but where also medications for children and adolescents with severe mental health problems such as schizophrenia and acute psychosis are included. It is possible that the association we observed is driven by small segments in this broad group. It is therefore somewhat difficult to speculate on possible mechanisms. Furthermore, we observed associations between dispensed N05 medications and also NO_2 and PM_{10}, but it was not possible to adjust the respective pollutant estimate for the other pollutant because NO_2 was one of the predictors of urban background PM_{10} in the PM_{10} model. We therefore consider our results an indication for air pollution in general to be associated with dispensed N05 medications, and refrain from speculating on which specific component within the pollution mix might be driving the observed associations. Air pollution can cause inflammation and oxidative stress.[45–47] It has been speculated that exposure to air pollution could induce or exacerbate anxiety (which is one of the most important patient groups who dispense N05) by increasing oxidative stress and inflammation.[48] There are animal studies suggesting that oxidative stress is associated with a range of psychiatric disorders such as schizophrenia, bipolar disorder or anxiety-like behaviour,[49–51] and that systemic inflammation may be associated with depressive-like/anxiety-like behaviour and memory impairment.[51 52] Furthermore, an experimental study in mice suggests that fine particulate air pollution could cause depressive-like responses and impairments in spatial learning and memory. Mice that were exposed to fine particulate matter (PM) had an elevated hippocampal pro-inflammatory cytokine expression, whereas apical dendritic spine density and dendritic branching were decreased in the hippocampal CA1 and CA3 regions.[53] Oberdörster and Utell[2] first suggested that the brain might be vulnerable to

ultrafine ambient particulate matter. Biological components of particles such as endotoxins, mould and pollen have been linked to neurodevelopmental disorders (eg, schizophrenia, autism and mental retardation) and neurodegenerative diseases.[54] Another theory is that air pollution acts by inducing or aggravating major medical conditions, but the study design does not fully allow for a distinction between exacerbation or incident cases. We used modelled annual mean concentrations as a marker for long-term exposure to air pollution, but it is possible that only certain exposure windows are of interest. For example, fetal life may be extra sensitive.[55 56]

Conclusions and implications

In Sweden, the societal cost for mental disorders has been estimated to be 2% of Gross Domestic Product (GDP). The onset is often in adolescence or young adulthood. Remission is not always possible and for many, symptoms persist despite use of treatments. If confirmed, our findings implicate that there may be a link between exposure to air pollution and dispensed medications for certain psychiatric disorders in children and adolescents.

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Contributors All authors contributed to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work, and drafted the work or revised it critically for important intellectual content and gave their final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AO, BF and LB conceived and designed the study. AO acquired and analysed the data and drafted the manuscript. MS helped acquire data and created figure 1. DOÅ helped interpret the data for the work and with the statistical analysis of the data.

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The effects of air pollution on individual psychological distress

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ABSTRACT

This study is the first of its kind to utilize longitudinal, nationally representative panel data from the United States to assess the relationship between exposure to air pollution and reports of psychological distress. Using annual-average measures of air pollution in respondents' census blocks of residence we find that over the period 1999–2011 particulate matter 2.5 is significantly associated with increased psychological distress; this association remains even after controlling for a robust set of demographic, socioeconomic, and health-related covariates. This study suggests that public health efforts to reduce the personal and societal costs of mental illness should consider addressing not only individual characteristics and factors in the social environment, but also underexplored facets of the physical environment such as air pollution.

1. Introduction

It is widely established in the public and environmental health literatures that exposure to air pollution is hazardous to human health (Mosley, 2014). Past research has largely focused on physical health effects: the association of air pollution with various adverse respiratory and cardiovascular disease outcomes has been particularly well documented (Brunekreef and Holgate, 2002; Seaton et al., 1995). However, recent epidemiological and animal toxicology studies also suggest a plausible connection between air pollution and psychological health.

This is an important avenue of investigation since mental illnesses are common in the United States (US) and account for a sizable share of the burden of disease (Murray and Lopez, 1996). According to findings from the 2014 National Survey on Drug Use and Health (NSDUH), nearly one in five Americans ages 18 and older (18.1% or 43.6 million adults) had a mental illness in the past year and 4.1% (9.8 million adults) had a serious mental illness. This has profound implications for individual and population health (Moussavi et al., 2007), mental health care systems, and the economy (Chisholm et al., 2016). Nevertheless, the environmental determinants of mental illness remain only partially understood.

New evidence has emerged regarding the impact of air pollution on the brain and in the pathogenesis of mental illness. Of interest are animal (e.g., rodent and feral dog) and human studies suggesting that air pollution exposure may lead to neuroinflammation, oxidative stress, cerebrovascular damage, and neurodegenerative pathology via several cellular and molecular pathways (Block and Calderón-Garcidueñas, 2009). A separate but related line of research has further implicated neuroinflammation and cerebrovascular damage in the risk and/or exacerbation of certain mental illnesses (e.g., depression) (Anisman and Hayley, 2012; Dantzer et al., 2008; Krishnadas and Cavanagh, 2012; Sneed and Culang-Reinlieb, 2011).

Air pollution has also been associated with the more proximal behavioral determinants of psychological health. In particular, in areas with higher levels of air pollution, people tend to reduce the amount of time they spend outdoors (Bresnahan et al., 1997). Such averting behavior introduces a number of indirect pathways through which air pollution may further induce or worsen psychological distress, including limited exposure to sunlight and subsequent vitamin D deficiency (Wilkins et al., 2006; Anglin et al., 2013), reduced physical activity and/or exercise (Goodwin, 2003; Abu-Omar et al., 2004; Motl et al., 2004), reduced contact with parks and other green space (Sugiyama et al., 2008; Cohen-Cline et al., 2015; Bratman et al., 2015), and social isolation (Broadhead et al., 1983; Biegel et al., 1985; George et al., 1989).

Despite growing empirical justification for investigating the effects of air pollution on psychological health, relatively few studies have done so explicitly. The small body of research in this area has examined

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the association of air pollution with depressive symptoms (Wang et al., 2014; Lim et al., 2012), anxiety (Power et al., 2015), suicide risk (Kim et al., 2010), and associated emergency department visits (Szyszkowicz et al., 2010a, 2010b; Szyszkowicz, 2007). Findings from this work are promising but not conclusive, as many of these studies tend to rely on small samples, utilize inconsistent measures and methodologies (Zijlema et al., 2016), or are limited in demographic (Lim et al., 2012; Power et al., 2015; Kioumourtzoglou et al., 2017), geographic (Wang et al., 2014; Kim et al., 2016; Cho et al., 2014), and/or temporal (Kim et al., 2010) scope. Of the few studies conducted in the US, one found no association between air pollution and depressive symptoms among older adults (Wang et al., 2014), while two others reported pollution effects on anxiety symptoms (Power et al., 2015) and depression (Kioumourtzoglou et al., 2017).

The present study is among the first to assess the impact of air pollution on psychological distress, a global rather than disorder-specific indicator of mental health problems which encompasses depression, anxiety, and other mood disorders, among US adults. Psychological distress can interfere with social functioning and activities of daily living (Drapeau et al., 2012), and has been associated with increased risks of chronic disease and mortality (Weissman et al., 2015; Forman-Hoffman et al., 2014; Russ et al., 2012). We extend past research by utilizing over a decade of nationally-representative data on individual respondents merged with highly resolved temporal and spatial measures of fine particulate matter ($PM_{2.5}$), a mixture of solid particles and liquid droplets that are 2.5 micrometers in diameter and smaller, in respondents' neighborhoods. Given the ubiquitous but often modifiable nature of air pollution exposure, even associations with psychological distress that are of relatively small magnitude have the potential to greatly impact the personal and societal burdens of mental illness.

2. Data and methods

We use individual-level data from the 1999–2011 waves of the Panel Study of Income Dynamics (PSID), a longitudinal, replenishing survey of Americans which began in 1968 as a national probability sample of over 18,000 individuals in approximately 4800 families. As of 2011, the PSID had expanded to include information on the demographic characteristics, socioeconomic position, and health of over 24,000 individuals in nearly 9000 families.

2.1. Sample

The analytic sample for this study comprises 6006 PSID respondents who were interviewed at least once and up to 6 times (mean=3) between 1999 and 2011, years that correspond with our data on psychological distress and air pollution exposure (psychological distress was not assessed in the PSID in 2005). We organize this information into a series of person-period observations, with each observation referring to the two-year period between PSID interviews. In total, respondents contributed 17,974 person-period observations.

2.2. Independent variable

To this dataset, we attach annual-average concentrations of $PM_{2.5}$ in respondents' neighborhoods using the PSID's supplemental Geospatial Match File. $PM_{2.5}$ is defined by particulate size and is derived primarily from combustion: fireplaces or wood stoves, car engines, and coal- or natural gas-fired power plants are all major sources. Between 1999 and 2011, respondents resided in blocks in which the concentration of $PM_{2.5}$ was, on average, 11.34 micrograms per cubic meter ($\mu g/m^3$), with a range of 2.16–24.23 $\mu g/m^3$. For reference, the Environmental Protection Agency's (EPA) annual national safety standard for $PM_{2.5}$ is 12 $\mu g/m^3$. Consistent with nationwide trends, $PM_{2.5}$ in respondents' neighborhoods declined from an average of 13.23 $\mu g/m^3$ to 9.46 $\mu g/m^3$ during our observation window (Fig. 1).

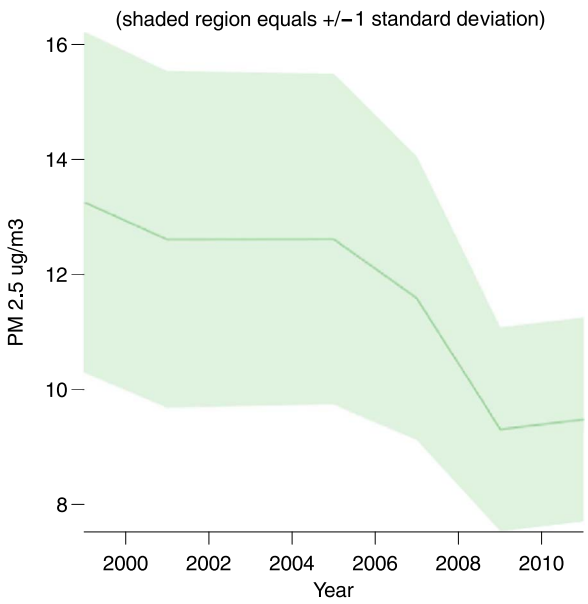

Fig. 1. Mean PM 2.5 decline over time in data sample.

Our measures of neighborhood $PM_{2.5}$ exposure are derived from the EPA's Air Quality System, a database which contains ambient air pollution measurements collected from a nationwide network of monitoring stations. Because these monitoring stations are unevenly distributed across the US and vary across time, we used a combination of land-use regression (LUR) and universal kriging to spatially interpolate reliable air pollution estimates in respondents' neighborhoods. This strategy is described in detail elsewhere (Sampson et al., 2013). In brief, the LUR was based on a database of over 265 geographic covariates, including: population density, total emissions of criteria air pollutants, land use, the normalized difference vegetation index (NDVI), measures of impervious surfaces, distance to and length of major road ways, and distance to commercial zones, airports, railroads, and the like. These variables were measured using a variety of buffer sizes of various radii ranging from 50 m to 30 km. Given such a large number of multicollinear variables, partial least squares (PLS) techniques were used to select only a subset of relevant covariates.

The nation was then divided into three regions – (1) East, (2) Mountain West, and (3) West Coast – and $PM_{2.5}$ prediction models using universal kriging for spatial smoothing were run separately in each region for each year. These models showed high cross-validated R^2, with a national R^2 of 0.88, and well-calibrated predictive intervals. This approach has also been applied in several recent epidemiologic studies of air pollution and health (Chi et al., 2016; Liu et al., 2016; Reding et al., 2015; Chan et al., 2015; Young et al., 2014). In this study, for each interview year, predictions were made at the census block centroid of respondents' census blocks of residence, the smallest unit of geography available in the PSID.

2.3. Dependent variable

Psychological distress is measured with the Kessler 6 (K6) Non-Specific Psychological Distress Scale (Kessler et al., 2003a), a composite instrument of 6 items assessing how often an individual felt sad, nervous, restless, hopeless, worthless, or "that everything was an effort" during the past 30 days. Each item is scored from 0 ("none of the time") to 4 ("all of the time"). Combined scores from the 6 items on this scale range from 0 to 24. According to past research, values of 5–12 may be indicative of moderate mental distress (Prochaska et al., 2012), while scores of 13 and higher have been shown in clinical calibration studies

Table 1
Data sample descriptives.

	Median	Range	Mean ± SD
K6	2	0–24	3.71 ± 4.13
PM 2.5 μg/m^3	11.234	2.16–24.23	11.35 ± 2.93
Age	42	15–97	43.72 ± 15.57
Years of Education	12	0–14	13.03 ± 2.37
Family Income ($1000 s)	$40.00	-$73.50–$1657.51	$55.59 ± $66.15
Family Size	2	1–14	2.7 ± 1.5
BMI	26.75	12.8–69.00	28.08 ± 6.4
Neighborhood Poverty Rate	0.15	0.00–0.86	0.18 ± 0.12
	N (Observations)	N (Unique Individuals)	Percentage
Married/Cohabitating	9422	3425	52.42%
Homeowner	10,205	3381	56.78%
White	11,468	3753	63.80%
Black	5801	1999	32.27%
Latino/a	705	254	3.92%
Male	6049	2176	33.65%
Female	11,925	3830	66.35%
Unemployed	3872	2116	21.54%
Employed	12,118	4669	67.42%
Student	287	248	1.60%
Retired	1697	757	9.44%
Active (Low)	6140	3252	34.16%
Active (Moderate)	6628	3816	36.88%
Active (High)	5206	3043	28.96%
Never Smoked	8504	3026	47.31%
Quit Smoking	4936	1896	27.46%
Smoker	4534	1899	25.23%
Never Drink	7652	3208	42.57%
Drinker (Low)	4765	2600	26.51%
Drinker (Moderate)	4760	2535	26.48%
Drinker (High)	797	568	4.43%
Asthma	2354	927	13.10%
Lung Disease	1621	654	9.02%
Hypertension	5774	2083	32.12%
Heart Disease	1595	576	8.87%
Heart Attack	700	273	3.89%
Diabetes	1869	713	10.40%

Note: 17,974 observations for 6006 unique individuals.

to be associated with serious mental illness (Kessler et al., 2010). Notably, however, no clear standards have yet emerged for optimal K6 scoring (Russ et al., 2012). The mean K6 score was 3.71 across person-periods in our sample (range: 0–24), with no noticeable year-to-year variation over the study period. Moreover, *t*-tests of seasonal variation in mean K6 scores were not statistically significant. As such, we do not adjust for temporal trends in our analyses.

2.4. Covariates

We also considered a number of potentially confounding covariates. Sociodemographic covariates included: age, race (non-Hispanic white, non-Hispanic black, Latino), gender (male, female), marital/cohabitation status (unpartnered, married/cohabitating), years of education, homeownership (rent, own), employment status (unemployed, employed, student, retired), family size, and household income. Health-related covariates included: smoking status (never smoked, current smoker, past smoker), body mass index (BMI), physical activity, alcohol use, and chronic conditions. We measured physical activity level by adding together the number of times per week an individual participated in light and heavy activity. Tertiles were created based on the distribution of all person-period observations with low activity categorized as anything below 3.23 times per week, medium activity between 3.23 and 8 times per week, and high activity as anything over 8 times per week. Alcohol consumption categories were defined a priori, adhering as closely as possible to the National Institute on Alcohol Abuse and Alcoholism's definitions of drinking behavior. As such, low drinking was defined as less than 1 drink per day, moderate drinking as 1–4 drinks per day, and high drinking as five or more drinks per day (versus no drinking). Chronic disease status was assessed with respect to asthma, lung disease, hypertension, heart disease, heart attack, and diabetes using the question: "Has a doctor ever told you that you have or had [said condition]?" Lastly, we measured neighborhood poverty as the poverty rate of the census tracts in which respondents resided at each survey wave using U.S. Census data.

2.5. Analytical strategy

To estimate the effects of air pollution on psychological distress, we fit a series of linear regression models to our pooled dataset.[1] We calculated robust standard errors to account for the non-independence of person-period observations related to the same individual. Model 1

[1] While the distribution of the K6 is not normal (there is clustering at or near zero), comparable negative binomial models produced substantively equivalent results to the pooled linear regressions reported. Given the ease of interpreting OLS coefficients, the linear models were selected over the negative binomial models for final presentation.

Table 2
Linear regression of PM 2.5 on K6 psychological distress.

	Dependent variable: Psychological distress - continuous (0 - 24)			
	Bivariate (1)	Demographics (2)	Health Behaviors/Diagnoses (3)	Neighborhood Poverty (4)
PM 2.5 (5 μg/m^3)	0.457*** (0.351, 0.564)	0.180*** (0.073, 0.288)	0.192*** (0.087, 0.298)	0.185*** (0.079, 0.290)
Age		0.019 (−0.005, 0.043)	−0.015 (−0.039, 0.009)	−0.015 (−0.038, 0.009)
Age Squared		−0.0004*** (−0.001, −0.0002)	0.0002* (−0.0005, 0.00004)	0.0002* (−0.0005, 0.00004)
Coupled		−0.451*** (−0.613, −0.289)	−0.356*** (−0.517, −0.196)	−0.356*** (−0.517, −0.196)
Years of education		−0.171*** (−0.201, −0.140)	−0.125*** (−0.156, −0.094)	−0.124*** (−0.155, −0.093)
Homeowner		−0.518*** (−0.675, −0.361)	−0.376*** (−0.530, −0.222)	−0.365*** (−0.521, −0.210)
Black		−0.216** (−0.383, −0.049)	−0.287*** (−0.456, −0.118)	−0.325*** (−0.508, −0.143)
Latino/a		−0.571*** (−0.926, −0.216)	−0.447** (−0.796, −0.099)	−0.471*** (−0.821, −0.121)
Female		0.355*** (0.230, 0.481)	0.415*** (0.287, 0.543)	0.410*** (0.282, 0.538)
Employed		−1.685*** (−1.875, −1.495)	−1.435*** (−1.638, −1.268)	−1.448*** (−1.632, −1.263)
Student		−0.563* (−1.174, 0.047)	−0.448 (−1.051, −0.155)	−0.449 (−1.051, 0.153)
Retired		−1.010*** (−1.315, −0.706)	−1.056*** (−1.353, −0.758)	−1.051*** (−1.348, −0.753)
Family Size		−0.013 (−0.065, 0.039)	−0.012 (−0.063, 0.040)	−0.013 (−0.064, 0.038)
Family income ($1000 s)		−0.002*** (−0.003, −0.001)	−0.002*** (−0.003, −0.001)	−0.002*** (−0.002, −0.001)
Active (Moderate)			−0.207*** (−0.355, −0.060)	−0.207*** (−0.355, −0.060)
Active (High)			−0.161** (−0.319, −0.004)	−0.163** (−0.320, −0.005)
Quit Smoking			0.181** (0.040, 0.321)	0.180** (0.039, 0.320)
Smoker			0.914*** (0.745, 1.083)	0.909*** (0.740, 1.078)
Drinker (Low)			0.111 (−0.040, 0.262)	0.119 (−0.033, 0.271)
Drinker (Moderate)			0.070 (−0.090, 0.229)	0.075 (−0.085, 0.234)
Drinker (High)			0.367** (0.032, 0.703)	0.367** (0.032, 0.702)
BMI			0.020*** (0.009, 0.031)	0.020*** (0.009, 0.031)
Asthma			0.535*** (0.329, 0.740)	0.535*** (0.329, 0.740)
Heart Attack			0.300 (−0.107, 0.707)	0.296 (−0.111, 0.703)
Heart Disease			0.748*** (0.467, 1.029)	0.749*** (0.468, 1.029)
Hypertension			0.573*** (0.417, 0.730)	0.570*** (0.414, 0.726)
Lung Disease			0.769*** (0.509, 1.029)	0.768*** (0.508, 1.028)
Diabetes			0.619*** (0.378, 0.859)	0.617*** (0.377, 0.858)
Neighborhood Poverty Rate				0.402 (−0.204, 1.009)
Constant	2.512*** (2.270, 2.755)	7.268*** (6.567, 7.970)	6.045*** (5.293, 6.797)	5.980*** (5.221, 6.739)
Observations	17,974	17,974	17,974	17,974
R^2	0.004	0.081	0.113	0.113
Adjusted R^2	0.004	0.08	0.112	0.112
Residual Std. Error	4.119	3.958	3.89	3.89
F Statistic	76.042***	113.037***	81.565***	78.824***

Note:
* p < 0.1.
** p < 0.05.
*** p < 0.01.

focused on bivariate associations between psychological distress and $PM_{2.5}$ measured in the previous period. We used a one-year lagged measure of pollution to reflect the temporal ordering of our focal relationship and because we expected the effects of air pollution to be lagged or cumulative rather than instantaneous. Moreover, given the lack of evidence to support a specific lag period, we conceptualized a one-year lag as a proxy for longer-term exposure, as previous studies have also done (Power et al., 2016).

Our second model adjusted for age, race, gender, marital/cohabitation status, years of education, homeownership, employment status, family size, and household income. Model 3 adjusted for a number of health behavioral characteristics and chronic conditions, including physical activity, BMI, smoking status, drinking behavior, asthma, lung disease, diabetes, and various indicators of heart disease, in addition to the sociodemographic variables just listed. Model 4 added an additional control for neighborhood poverty. We also ran analogous logistic regression models for the dichotomous version of the K6 score (< 13 vs. ≥ 13). These results are largely consistent with those for the continuous measure and are available in the Supplemental materials (Appendix A).

3. Results

Table 1 presents summary statistics for our key independent and dependent variables, along with the sociodemographic, health-related, and neighborhood covariates. The variables in the top panel were measured continuously and are accompanied by ranges, grand means, and standard deviations. The variables in the bottom panel were coded dichotomously (1 if applicable, 0 otherwise) and are therefore presented as percentages of the sample. The total number of person-period observations and the corresponding number of individual respondents are presented with each variable.

Our analyses reveal a statistically significant association between $PM_{2.5}$ and psychological health before as well as after adjustment for relevant covariates (Table 2). In the bivariate analysis (**Model 1**), K6 scores were greater (worse) among respondents who resided in blocks with higher concentrations of $PM_{2.5}$ (b= 0.46; 95% CI= 0.35–0.56). Consistent with conventions in the environmental health literature, coefficient estimates are expressed throughout as change in respondents' K6 score per a 5 unit change in $PM_{2.5}$.

In multivariate analyses adjusted for sociodemographic, health-related, and neighborhood covariates, the relationship between $PM_{2.5}$ and psychological distress remained statistically significant, albeit attenuated by just over half in the fully-adjusted model (**Model 4**). The addition of sociodemographic covariates accounted for the largest share of this reduction, with years of education, household income, marital/cohabitation status, and race playing the largest explanatory roles. The addition of health behavioral and chronic disease covariates (**Model 3**), however, increased the magnitude of the $PM_{2.5}$ coefficient, likely due to their potential moderating effects on psychological distress.

Table 3
Race and gender stratified linear regressions of PM 2.5 on K6.

	Dependent variable: Psychological distress - continuous (0 - 24)					
	White Males (1)	White Females (2)	Black Males (3)	Black Females (4)	Latino Males (5)	Latina Females (6)
PM 2.5 (5 μg/m3)	0.001 (−0.007, 0.008)	0.009** (0.001, 0.018)	0.017* (−0.002, 0.036)	0.002 (−0.013, 0.017)	0.002 (−0.019, 0.023)	−0.009 (−0.045, 0.028)
Age	0.001 (−0.002, 0.003)	0.004*** (0.003, 0.006)	0.003 (−0.001, 0.007)	0.00004 (−0.003, 0.003)	−0.002 (−0.015, 0.011)	0.009** (0.001, 0.018)
Age Squared	−0.00001 (−0.00003, 0.00002)	−0.0001*** (−0.0001, −0.00004)	−0.00004 (−0.0001, 0.00001)	−0.00001 (−0.00004, 0.00003)	0.00002 (−0.0001, 0.0002)	−0.0001*** (−0.0002, −0.00004)
Coupled	0.006 (−0.009, 0.022)	−0.018*** (−0.031, −0.005)	0.014 (−0.015, 0.043)	−0.016 (−0.036, 0.003)	−0.023 (−0.082, 0.036)	0.006 (−0.060, 0.071)
Years of Education	−0.003** (−0.006, −0.001)	−0.005*** (−0.008, −0.002)	−0.004* (−0.009, 0.001)	−0.002 (−0.007, 0.002)	−0.003 (−0.012, 0.005)	−0.005 (−0.017, 0.008)
Homeowner	0.006 (−0.022, 0.009)	−0.010 (−0.023, 0.003)	−0.001 (−0.024, 0.022)	−0.021** (−0.039, −0.004)	0.027 (−0.026, 0.080)	0.070* (−0.007, 0.147)
Employed	−0.076*** (−0.108, −0.044)	−0.052*** (−0.068, −0.037)	−0.060*** (−0.089, −0.030)	−0.069*** (−0.089, −0.050)	0.0001 (−0.034, 0.034)	−0.056 (−0.132, 0.019)
Student	−0.039 (−0.129, 0.051)	−0.031 (−0.076, 0.015)	−0.027 (−0.127, 0.073)	0.017 (−0.054, 0.089)	0.031 (−0.029, 0.091)	−0.075* (−0.156, 0.006)
Retired	−0.074*** (−0.111, −0.038)	−0.031*** (−0.053, −0.009)	0.004 (−0.063, 0.071)	−0.056** (−0.102, −0.010)	0.129 (−0.050, 0.308)	−0.025 (−0.133, 0.082)
Family Size	−0.002 (−0.007, 0.003)	−0.003 (−0.008, 0.001)	0.001 (−0.008, 0.010)	0.003 (−0.003, 0.009)	−0.006 (−0.014, 0.003)	−0.008 (−0.024, 0.008)
Family income ($1000 s)	−0.00003* (−0.0001, 0.00000)	−0.00004 (−0.0001, 0.00002)	−0.0002 (−0.0005, 0.0001)	−0.0001 (−0.0004, 0.0003)	0.001 (−0.0003, 0.002)	−0.001 (−0.002, 0.0004)
Active (Moderate)	−0.012* (−0.024, 0.001)	−0.010* (−0.022, 0.001)	−0.005 (−0.031, 0.020)	−0.019** (−0.037, −0.001)	−0.009 (−0.062, 0.044)	−0.014 (−0.073, 0.045)
Active (High)	−0.014** (−0.027, −0.0004)	−0.004 (−0.016, 0.009)	−0.019 (−0.043, 0.004)	−0.019 (−0.039, 0.001)	−0.020 (−0.077, 0.036)	0.007 (−0.069, 0.084)
Quit Smoking	−0.010** (−0.019, −0.0003)	0.00003 (−0.010, 0.010)	−0.006 (−0.030, 0.018)	0.017 (−0.004, 0.038)	−0.006 (−0.046, 0.034)	0.051 (−0.028, 0.129)
Smoker	0.027*** (0.012, 0.043)	0.019** (0.004, 0.034)	0.010 (−0.013, 0.034)	0.033*** (0.012, 0.054)	0.015 (−0.030, 0.060)	−0.047 (−0.111, 0.017)
Drinker (Low)	−0.002 (−0.016, 0.012)	−0.008 (−0.020, 0.003)	0.007 (−0.021, 0.034)	0.008 (−0.012, 0.028)	−0.049* (−0.104, 0.007)	0.063 (−0.031, 0.157)
Drinker (Moderate)	−0.009 (−0.022, 0.003)	−0.009 (−0.022, 0.004)	0.017 (−0.007, 0.040)	0.003 (−0.018, 0.024)	−0.026 (−0.077, 0.024)	−0.003 (−0.077, 0.071)
Drinker (High)	0.008 (−0.020, 0.035)	−0.002 (−0.038, 0.034)	0.041 (−0.008, 0.090)	−0.004 (−0.070, 0.062)	−0.043* (−0.090, 0.005)	−0.106* (−0.216, 0.004)
BMI	−0.001 (−0.002, 0.001)	0.0001 (−0.001, 0.001)	−0.0001 (−0.002, 0.002)	0.001* (−0.00002, 0.002)	−0.003 (−0.007, 0.001)	0.001 (−0.005, 0.006)
Asthma	0.014 (−0.008, 0.035)	0.023** (0.005, 0.041)	0.003 (−0.032, 0.038)	0.007 (−0.018, 0.033)	0.010 (−0.054, 0.073)	0.023 (−0.094, 0.141)
Heart Attack	0.036** (0.005, 0.067)	0.011 (−0.032, 0.054)	−0.023 (−0.085, 0.039)	−0.003 (−0.065, 0.059)	0.352 (−0.177, 0.880)	0.028 (−0.171, 0.227)
Heart Disease	0.002 (−0.018, 0.022)	0.028** (0.004, 0.052)	0.025 (−0.037, 0.087)	0.040* (−0.001, 0.081)	−0.085 (−0.243, 0.073)	0.131 (−0.061, 0.324)
Hypertension	0.013* (−0.00004, 0.026)	0.019*** (0.006, 0.032)	0.012 (−0.014, 0.039)	0.021** (0.001, 0.040)	0.034 (−0.037, 0.104)	0.054 (−0.024, 0.132)
Lung Disease	−0.011 (−0.034, 0.011)	0.039*** (0.015, 0.063)	0.011 (−0.042, 0.064)	0.044*** (0.011, 0.077)	−0.026 (−0.063, 0.011)	0.002 (−0.154, 0.158)
Diabetes	0.023* (−0.004, 0.050)	0.037*** (0.013, 0.061)	0.030 (−0.010, 0.070)	0.006 (−0.021, 0.033)	0.001 (−0.089, 0.091)	0.002 (−0.085, 0.089)
Neighborhood Poverty Rate	0.055 (−0.011, 0.120)	0.059** (0.002, 0.116)	−0.100**** (−0.174, −0.025)	−0.081*** (−0.142, −0.020)	−0.090 (−0.238, 0.058)	0.159 (−0.083, 0.401)
Constant	0.147*** (0.074, 0.220)	0.068** (0.006, 0.129)	0.060 (−0.056, 0.175)	0.110** (0.017, 0.203)	0.222 (−0.084, 0.528)	−0.040 (−0.292, 0.211)
Observations	4002	7466	1732	4069	315	390
R^2	0.061	0.061	0.042	0.05	0.17	0.109
Adjusted R^2	0.055	0.058	0.028	0.044	0.095	0.046
Residual Std. Error	0.148	0.195	0.194	0.237	0.159	0.248
F Statistic	9.934***	18.706***	2.888***	8.219***	2.274***	1.715**

Note:
* $p < 0.1$.
** $p < 0.05$.
*** $p < 0.01$.

Given well-documented differences in psychological distress by gender (Drapeau et al., 2010) and racial-ethnic group (Bratter and Eschbach, 2005) , we also performed a combined gender- and race-stratified analysis using the final, fully-adjusted model (Table 3). In these stratified models, white women were the only gender-race group in which a statistically significant relationship between $PM_{2.5}$ and psychological distress remained. Additionally, the magnitude of this relationship was twice that observed in the pooled analysis. It should be noted, however, that in a race- and gender-stratified analysis using the dichotomous version of the K6 (Appendix B), a sizable and significant positive association for black men was found, while the significance for white women was only marginal ($p < 0.1$).

4. Discussion

Most past research on the health repercussions of air pollution has focused on adverse respiratory (Young et al., 2014) and cardiovascular disease outcomes (Chi et al., 2016; Chan et al., 2015). Only a handful of studies have examined the association of air pollution with psychological health, despite growing evidence elucidating possible mechanisms to support such a relationship. Those studies that have considered the air pollution-psychological health link tend to rely on demographically- (Lim et al., 2012; Power et al., 2015; Kioumourtzoglou et al., 2017) and geographically-limited (Wang et al., 2014; Kim et al., 2016; Cho et al., 2014) samples at a single cross-section in time, and often utilize relatively crude measures of air pollution exposure (Wang et al., 2014) or mental health (Szyszkowicz et al., 2010a, 2010b, 2007).

This study extends the emerging research in this area. Specifically, using longitudinal data for a nationally-representative sample of individuals, merged with robust annual-average measures of air pollution in respondents' census blocks of residence, we show that even after adjustment for various sociodemographic, health-related, and neighborhood covariates, higher concentrations of $PM_{2.5}$ are associated with an increased risk of psychological distress.

In addition, when stratified by race and gender, we find differential impacts of $PM_{2.5}$ on psychological distress. Specifically, the overall association between $PM_{2.5}$ and distress (measured as a continuous K6 score) appears to be driven by the effect among white women. However, the positive and significant finding for black men in supplementary analyses using the dichotomous version of the K6 suggests that further investigation into the intersecting roles of race and gender in the relationship between $PM_{2.5}$ and psychological distress is warranted.

Notably, however, additional analyses (Appendices C and D) examining other indicators of air pollution, including nitrogen dioxide (NO_2) and coarse particulate matter (PM_{10}), did not show statistically significant effects on psychological distress beyond the simple bivariate associations. These null findings point to the need for future research assessing variations in the effects of the physical environment across different pollutants and health outcomes.

4.1. Study limitations

These findings should be interpreted in the context of several study limitations. First, although our observation window spans over a decade from 1999 to 2011, we examine psychological health as a function of air pollution measured solely in the prior time period (versus a cumulative measure better able to capture chronic exposure). However, past research on human health generally (Liu et al., 2016) and at least one animal toxicologic study of depressive symptoms more specifically (Fonken et al., 2011) suggest that longer-term exposure to air pollution may be more detrimental than single point in time measurements. Future research examining both the physical and psychological health effects of longer durations of air pollution exposure will be valuable.

Second, we relied on self-reports of psychological distress. Although the K6 is a validated instrument for use in community-based samples (Kessler et al., 2002, 2003b), the items that make up the scale were specifically selected to minimize variation in reports across gender and racial-ethnic groups. Given potential asymmetries in social experiences, including air pollution exposure, by gender and race (e.g., the social context of disadvantage is not the same experience for whites as it is for African Americans due to racial residential segregation), the K6 may mask variation in reports of psychological distress, perhaps especially among women and/or people of color (Roxburgh, 2009; Brown, 2003). The use of gender- and race-stratified models in our study addresses, in part, such concerns; however, additional research examining the validity of mental health scales such as the K6 across gender and race, as well as their intersection, is critical.

Finally, although our models include a number of demographic, socioeconomic, and health-related covariates to control for possible confounding, the potential for residual and unmeasured confounding is always a limitation in observational studies. Furthermore, theory and past research suggest that many of the covariates we consider confounders may in fact be on the causal pathway between air pollution exposure and psychological distress (e.g., physical activity level). A fuller examination of the direct and indirect mechanisms through which air pollution operates on psychological health, however, was beyond the scope of the present study. Future research in this area would benefit from explicit assessments of the more proximal determinants linking air pollution and psychological distress, including various physiological and (mal)adaptive behavioral responses to environmental hazards, especially among racial/ethnic minority groups and other vulnerable populations who are disproportionately exposed to air pollution (Kravitz-Wirtz et al., 2016; Pais et al., 2014).

4.2. Public health implications

Nonetheless, this study suggests that public health efforts to reduce the personal and societal costs of mental illness should consider addressing not only individual characteristics and factors in the social environment, but also underexplored facets of the physical environment such as air pollution. Although nationwide levels of air pollution have declined over the last several decades (US EPA, 2017), past research indicates that even exposure to relatively low levels of air pollution, including at levels below EPA safety standards, may be associated with adverse health effects (Olmo et al., 2011).

Moreover, given the ubiquitous nature of air pollution across the US, even the relatively modest adverse association we observed may be related to considerable population attributable psychological health risks. Fortunately, air pollution is also readily modifiable through local, state, and national policies and practices directed at curbing vehicle and industrial sources of pollution. The political context and environmental regulations associated with the more recent declines in pollution, however, may shift with electoral changes in political administration, making ongoing research and action on the environmental determinants of psychological health even more critical.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.healthplace.2017.09.006.

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Air Pollution and Suicide in 10 Cities in Northeast Asia: A Time-Stratified Case-Crossover Analysis

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Background: There is growing evidence suggesting an association between air pollution and suicide. However, previous findings varied depending on the type of air pollutant and study location.

Objectives: We examined the association between air pollutants and suicide in 10 large cities in South Korea, Japan, and Taiwan.

Methods: We used a two-stage meta-analysis. First, we conducted a time-stratified case-crossover analysis to estimate the short-term association between nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and particulate matter [aerodynamic diameter $\leq$10 μm (PM_{10}), aerodynamic diameter $\leq$2.5 μm ($PM_{2.5}$), and $PM_{10-2.5}$] and suicide, adjusted for weather factors, day-of-week, long-term time trends, and season. Then, we conducted a meta-analysis to combine the city-specific effect estimates for NO_2, SO_2, and PM_{10} across 10 cities and for $PM_{2.5}$ and $PM_{10-2.5}$ across 3 cities. We first fitted single-pollutant models, followed by two-pollutant models to examine the robustness of the associations.

Results: Higher risk of suicide was associated with higher levels of NO_2, SO_2, PM_{10}, and $PM_{10-2.5}$ over multiple days. The combined relative risks (RRs) were 1.019 for NO_2 (95% confidence interval [CI]: 0.999, 1.039), 1.020 for SO_2 (95% CI: 1.005, 1.036), 1.016 for PM_{10} (95% CI: 1.004, 1.029), and 1.019 for $PM_{10-2.5}$ (95% CI: 1.005, 1.033) per interquartile range (IQR) increase in the 0–1 d average level of each pollutant. We found no evidence of an association for $PM_{2.5}$. Some of the associations, particularly for SO_2 and NO_2, were attenuated after adjusting for a second pollutant.

Conclusions: Our findings suggest that higher levels of air pollution may be associated with suicide, and further research is merited to understand the underlying mechanisms. https://doi.org/10.1289/EHP2223

Introduction

Suicide is a significant public health concern. An estimated 804,000 people worldwide died by suicide in 2012, accounting for 1.4% of all deaths; suicide constitutes the 15th most common cause of death (WHO 2014). Among a broad range of contributing factors to suicide, attention has been given to environmental factors that may be associated with suicide (Sinyor et al. 2017). Numerous studies have reported evidence of a seasonal peak in suicide in spring and early summer (Christodoulou et al. 2012; Coimbra et al. 2016). Some studies have investigated the association between weather and suicide, suggesting that increases in ambient temperature are associated with increased risk of suicide (Deisenhammer 2003; Kim et al. 2016; Likhvar et al. 2011; Page et al. 2007). In addition, the association with sunlight or sunshine hours has been studied (Vyssoki et al. 2014; White et al. 2015), although it remains controversial because the association was attenuated after adjusting for the seasonality of suicide (White et al. 2015).

Emerging evidence suggests that air pollution may be another potential environmental factor associated with suicide. Several epidemiological studies have reported that higher levels of air pollutants, such as particulate matter with aerodynamic diameter $\leq$10 μm (PM_{10}) and $\leq$2.5 μm ($PM_{2.5}$), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and carbon monoxide (CO), are associated with suicide (Kim et al. 2010, Bakian et al. 2015, Lin et al. 2016, Ng et al. 2016) and with suicide attempts (Szyszkowicz et al. 2010). These studies used time-stratified case-crossover analysis, which is widely used to examine short-term associations between air pollution and health; this method is also considered the least biased method in the case-crossover design (Janes et al. 2005).

However, previous findings varied depending on the type of air pollutant and on the study location. For example, there were consistent findings of positive associations for $PM_{2.5}$ and NO_2 in three studies (Bakian et al. 2015; Kim et al. 2010; Lin et al. 2016). Other pollutants, such as PM_{10} and SO_2, were found to be associated with suicide in two of the studies (Kim et al. 2010; Lin et al. 2016) but not in the third (Bakian et al. 2015). This discrepancy may be attributed to geographical variations (e.g., the sources and components of air pollution, climate conditions, cultural backgrounds, socioeconomic factors, and suicidal behaviors). Moreover, different modeling strategies make it difficult to compare results across studies. To gain a better understanding of air pollution and suicide, a study to investigate multiple locations with a unified modeling strategy is merited.

In the present study, we examined the association between air pollution and suicide in 10 large cities in three countries in Northeast Asia: South Korea, Japan, and Taiwan. The three countries share, in part, traditional cultural backgrounds, and have recorded relatively high suicide rates (31.0, 24.0, and 17.6 per 100,000 population in 2009 in South Korea, Japan, and Taiwan, respectively, compared with the global rate of 11.2 per 100,000

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population in 2010) (Chen et al. 2012; WHO 2017). We conducted a two-stage analysis to examine the city-specific association and the combined association. To our knowledge, this is the first study of the association between air pollution and suicide comparing multiple cities in multiple countries using a unified analytical framework.

Methods

Data

We collected the data on suicide, air pollutants (NO_2, SO_2, and PM_{10}) and weather in four cities in South Korea from 1 January 2001 to 31 December 2010 (10 y), in three cities in Japan from 1 April 1979 to 31 March 2009 (30 y), and in three cities in Taiwan from 1 January 1994 to 31 December 2007 (14 y) (Figure 1). All cities are considered large because the populations were >2,000,000 in 2010 (see Table S1). The study area in Tokyo covers the 23 special wards that comprise the most populous part of the metropolis. The data on $PM_{2.5}$ levels covered a shorter period and were limited to three cities: Seoul, between 1 January 2002 and 31 December 2010 (8 y); Tokyo, between 1 December 2001 and 31 January 2008 (6 y, 2 mo); and Taipei, between 1 January 2006 and 31 December 2007 (2 y).

We extracted suicide cases, defined as intentional self-poisoning and self-harm based on the *International Statistical Classification of Diseases and Related Health Problems* (ICD) [E950.0–E958.9 for ICD-9 (WHO 1978) and X60–X84 for ICD-10 (WHO 2016)] from national death registries (Statistics Korea, Ministry of Strategy and Finance in South Korea, written communication, December 2011; Ministry of Health, Labour and Welfare in Japan, written communication, December 2011; Department of Statistics, Ministry of Health and Welfare in Taiwan, written communication, June 2008). The city-specific suicide data included information on sex, age, and method of suicide. We categorized age into three groups: 10–24 y (adolescents and young adults), 25–64 y, and ≥65 years (older adults). We also dichotomized the method of suicide into violent (E950.0–E952.9 for ICD-9 and X60–X69 for ICD-10) and nonviolent (E953.0–E958.9 for ICD-9 and X70–X84 for ICD-10). The suicide reporting systems have been described in detail elsewhere (Hendin et al. 2008).

The data on the daily mean levels of NO_2, SO_2, PM_{10}, and $PM_{2.5}$ were obtained from the Research Institute of Public Health and Environment in South Korea (written communication, January 2012), the National Institute for Environmental Studies

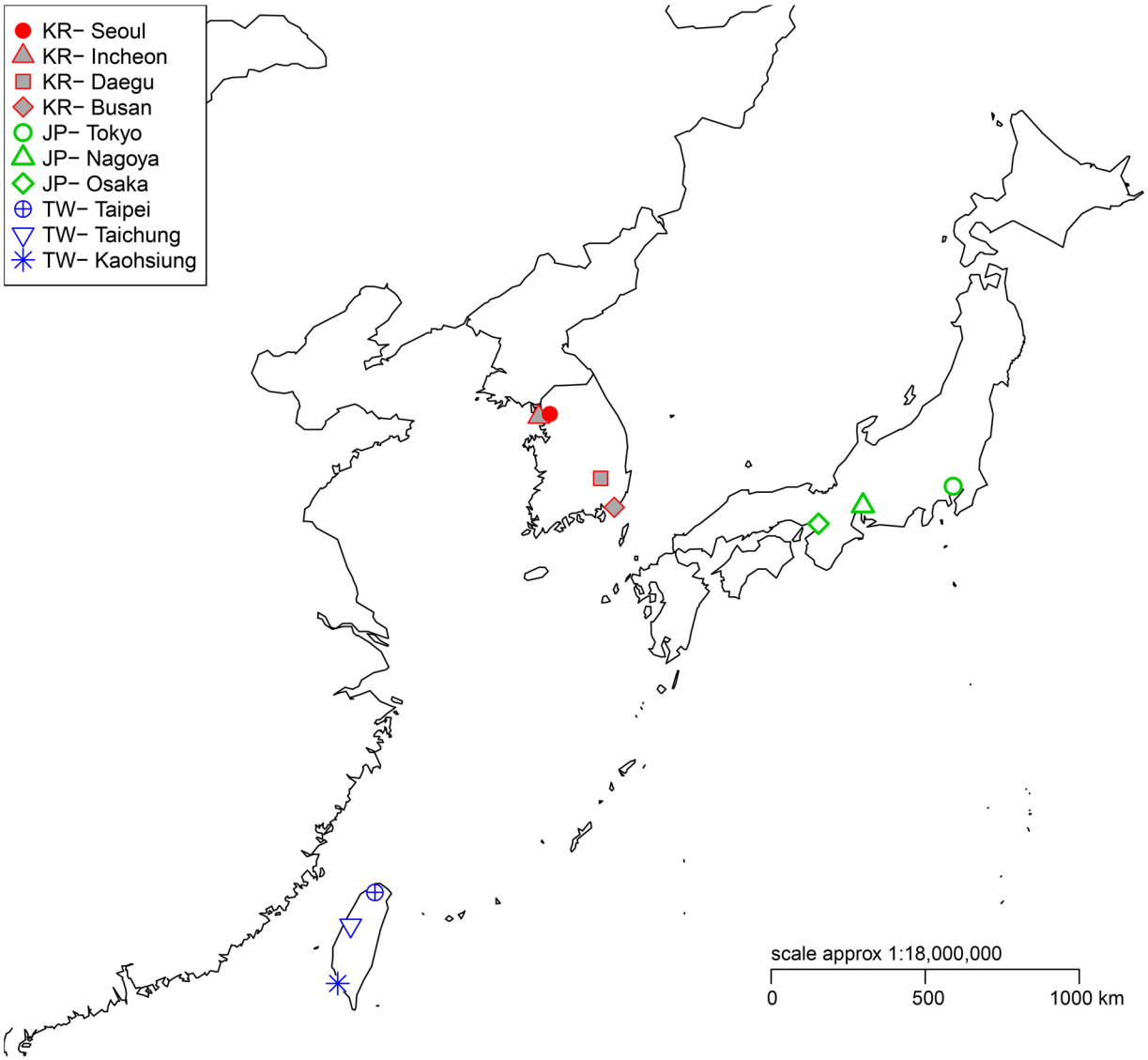

Figure 1. Study location of 10 cities in South Korea (KR), Japan (JP), and Taiwan (TW).

in Japan (written communication, April 2011), and the Taiwan Environmental Protection Administration in Taiwan (https://taqm.epa.gov.tw/taqm/en/default.aspx). The data originally included hourly concentrations of each pollutant measured by multiple monitoring stations in each city. We first calculated hourly means across the stations and from these values, we calculated the daily 24-h average concentrations in each city. Daily levels of coarse particles ($PM_{10-2.5}$) were obtained by subtracting daily concentrations of $PM_{2.5}$ from those of PM_{10}. For four cities in Korea, we identified extremely high concentrations of PM_{10} and $PM_{2.5}$, that is to say, daily mean PM_{10} levels $>400\,\mu g/m^3$ (6 d in Seoul, 5 d in Incheon, and 4 d in Busan and Daegu) and the daily mean $PM_{2.5}$ for the same 6 d in Seoul (on average, $226.2\,\mu g/m^3$). These values are considered outliers according to the Asian dust warning system (advisory) of the Korea Meteorological Administration (KMA 2016). Air pollution data were unavailable for some days; the missing rates were $\leq 0.33\%$ for NO_2 and SO_2, $\leq 0.44\%$ for PM_{10}, and $\leq 0.40\%$ for $PM_{2.5}$ over the study periods.

Weather data were obtained from the KMA (written communication, September 2012), the Japan Meteorological Agency (http://www.jma.go.jp), and the Taiwan Central Weather Bureau (written communication, May 2012). We collected daily mean ambient temperature (°C); daily sum of sunshine hours, defined as hours with direct sunlight $\geq 120\,W/m^2$ (WMO 2014); daily mean relative humidity (%); daily mean sea-level atmospheric pressure (hPa); and daily total precipitation (mm). The missing rates were $\leq 0.03\%$ for temperature, $\leq 0.05\%$ for sunshine duration, $\leq 0.11\%$ for humidity, $\leq 0.04\%$ for atmospheric pressure, and $\leq 11.5\%$ for precipitation over the study periods.

Statistical Analyses

A two-stage meta-analysis was conducted to analyze the multicity time-series data. In the first stage, we used a time-stratified case-crossover analysis to estimate the short-term association between suicide and air pollutants for each city. In the second stage, we used a meta-analysis to combine the city-specific estimates. We used R (version 3.2.3; R Development Core Team) with the packages "gnm" and "dlnm" for the time-stratified case-crossover analysis and "metafor" for the meta-analysis.

First-Stage Modeling

We used a time-stratified case-crossover design for comparing exposure levels between case and control days matched within a stratum. We defined a stratum as a combination of year, month, and day-of-week; each case was matched to controls on the same day-of-week in the same month and year (i.e., 1:3 or 1:4 matching depending on the length of a month). This design allows for the adjustment of long-term time trend, seasonality, and day-of-week, and it assumes that unmeasured time-varying confounders are constant within a stratum (Lu et al. 2008).

We fitted a conditional Poisson regression model with quasi-Poisson family to accommodate an over-dispersion (Armstrong et al. 2014). We assumed a linear association between air pollutants and suicide upon confirming by an *F*-test that nonlinearity is unnecessary. To examine a delayed effect of the association, we used an average exposure of air pollutant levels over multiple days from the current day up to 9 preceding days (i.e., 0–1 to 0–9 lag days) and estimated associations across different lengths of exposure. We included potential time-varying confounders (temperature and sunshine hours) and an indicator of public holidays (except on Saturday and Sunday) in the model. The weather factors were incorporated as distributed lag nonlinear functions with a maximum lag of 5 d. Specifically, we used a natural cubic spline with three internal knots placed at the 25th, 50th, and 75th percentiles of exposure distribution and the same spline for lags with an intercept and two equally spaced internal knots in the log scale.

We started with a single-pollutant model to estimate marginal association, followed by a two-pollutant model adjusting for a second pollutant to assess the robustness of the association. To obtain comparable results between the two models, we fitted the single-pollutant model using a subset of data without any missing second pollutant. In the two-pollutant model, we examined possible multicollinearity based on the variance inflation factor (VIF) (O'brien 2007).

We analyzed the total population and conducted subgroup analyses by sex, age, and method of suicide using single-pollutant models. All city-specific analyses were performed without the missing values described above. We excluded the days with extreme PM_{10} and $PM_{2.5}$ levels in the Korean cities from the analysis.

Second-Stage Modeling

To combine the city-specific results estimated from the first-stage modeling, we performed a meta-analysis based on a random-effect model (Borenstein et al. 2009; Viechtbauer 2010). To investigate the heterogeneity, we calculated I^2 and tested the uncertainty of the heterogeneity using a chi-squared test for Cochran's *Q* statistic (Borenstein et al. 2009; Higgins et al. 2003).

Sensitivity Analysis

We performed several sensitivity analyses to evaluate the robustness of our results. First, as an alternative to the distributed lag nonlinear function, we adjusted for temperature and sunshine duration using the natural cubic splines of their average of 0–5 lag days with four degrees of freedom. Second, we added other weather variables—relative humidity, atmospheric pressure, and precipitation—one at a time to the final model. We used the distributed lag nonlinear function with the same specifications as temperature or sunshine duration to humidity and pressure, and with different knot placement (at the 80th, 90th, and 99th percentiles) to precipitation after natural log transformation because of the skewness. Third, we redefined the stratum from the original year, month, and day-of-week combination to every 2 or 3 wk matched by day-of-week to assess whether our length of stratum was sufficiently short to control for seasonality in the time-stratified case-crossover design (Guo and Barnett 2015). Finally, we performed the same analysis including the days with extremely high concentrations of particulate matter (PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$) in Korean cities.

Results

Table 1 shows summary statistics for suicide, air pollutants, and weather variables. The total number of suicides ranged from 3,352 in Taichung to 46,519 in Tokyo during the study periods. The daily mean suicide count was the highest in Seoul at 5.3 ± 2.9 [mean $\pm$ SD (standard deviation)] and the lowest in Taichung at 0.7 ± 0.8). Air pollution levels varied depending on pollutant and location. NO_2 levels were higher in larger cities, such as Seoul and Tokyo (capital cities) and Osaka (the second-largest city in Japan). SO_2 levels were higher in Kaohsiung and Osaka. The PM_{10} level was highest in Kaohsiung, which is located in Taiwan's industrial area. Among the three capital cities, the $PM_{2.5}$ level was lowest in Tokyo. The cities in Taiwan had smaller variations in temperature and humidity given its location in the subtropical zone, with a warmer and more humid climate than Korea and Japan (Table 1; see also Table S1).

Association between Suicide and Air Pollutants

We found evidence of short-term associations between suicide and air pollutants (NO_2, SO_2, PM_{10} and $PM_{10-2.5}$), estimated as the

Table 1. Summary statistics of suicide (daily mean and standard deviation), air pollutants and weather factors (median and interquartile range) for each city.

Country	City	Total number of suicide	Daily mean suicide counts	NO_2 (ppb)	SO_2 (ppb)	PM_{10} ($\mu g/m^3$)	$PM_{2.5}$ ($\mu g/m^3$)	$PM_{10-2.5}$ ($\mu g/m^3$)	Temperature (°C)	Sunshine duration (hour)
South Korea	Seoul	19,218	5.3 ± 2.9	35.0 ± 18.1	4.7 ± 2.7	53.0 ± 38.3	26.0 ± 20.0	25.0 ± 18.9	14.4 ± 17.8	5.4 ± 7.1
	Busan	8,971	2.5 ± 1.7	22.8 ± 12.5	5.6 ± 3.2	49.9 ± 28.8	—	—	15.7 ± 12.9	7.0 ± 6.9
	Incheon	6,204	1.7 ± 1.4	27.1 ± 15.1	6.6 ± 3.2	53.2 ± 34.2	—	—	13.9 ± 16.9	6.8 ± 7.0
	Daegu	5,420	1.5 ± 1.3	22.8 ± 13.4	5.2 ± 3.2	50.4 ± 30.8	—	—	15.7 ± 16.3	6.9 ± 6.7
Japan	Tokyo[a]	46,519	4.2 ± 2.3	30.3 ± 14.8	6.7 ± 7.1	40.2 ± 32.4	17.8 ± 11.9	11.1 ± 10.5	16.5 ± 13.4	5.6 ± 8.0
	Nagoya	11,685	1.1 ± 1.1	26.2 ± 13.1	6.2 ± 4.9	40.1 ± 30.9	—	—	16.3 ± 15.0	6.4 ± 7.4
	Osaka	18,911	1.7 ± 1.4	31.7 ± 15.9	7.3 ± 6.1	38.6 ± 30.6	—	—	17.2 ± 14.8	5.9 ± 6.9
Taiwan	Taipei	9,481	1.9 ± 1.6	26.9 ± 10.0	4.6 ± 3.7	47.6 ± 29.7	25.8 ± 18.8	20.5 ± 9.9	23.8 ± 8.6	3.4 ± 7.1
	Taichung	3,352	0.7 ± 0.8	22.3 ± 11.2	3.7 ± 2.6	56.2 ± 41.7	—	—	24.8 ± 7.6	6.5 ± 6.2
	Kaohsiung	5,050	1.0 ± 1.1	24.5 ± 17.1	9.3 ± 5.9	80.6 ± 66.8	—	—	26.3 ± 5.8	6.8 ± 5.5

Note: —, data unavailable; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with aerodynamic diameter ≤10 μm; $PM_{10-2.5}$, coarse particulate matter; SO_2, sulfur dioxide. Study period varies by city: 10 years in Korean cities, 30 years in Japanese cities, and 14 years in Taiwanese cities. The data on $PM_{2.5}$ and $PM_{10-2.5}$ were limited to 8 years in Seoul; 6 years, 2 months in Tokyo; and 2 years in Taipei. The summary statistics of the particulate matter were calculated after excluding extremely high concentrations.
[a]23 special wards covering the most populous area of Tokyo.

relative risk (RR) per interquartile range (IQR) increase in the average of each pollutant at varying lag periods from the current day to lag 0–5 d. (Figure 2; see also Figure S1). Statistical significance was determined if the 95% CI for the RR excluded 1. The combined RR was the highest at the lags of 0–1 d for NO_2 [RR = 1.019 (95% CI: 0.999, 1.039)], 0–3 d for SO_2 [RR = 1.026 (95% CI: 1.008, 1.044)], and 0–2 d for PM_{10} [RR = 1.020 (95% CI: 1.007, 1.033)] and $PM_{10-2.5}$ [RR = 1.023 (95% CI: 1.007, 1.038)]. We found no evidence of an association for $PM_{2.5}$ on any of the lag days.

Figure 3 shows the city-specific effect estimates from the first-stage modeling at a lag of 0–1 d. Although the variability across cities was small in general, some cities had stronger signals than others (e.g., Tokyo for NO_2, SO_2, and PM_{10}; Osaka for SO_2). Among the capital cities, there was evidence of elevated RRs for $PM_{2.5}$ and $PM_{10-2.5}$ in Taipei and Seoul, respectively.

In two-pollutant models, some associations observed in the single-pollutant models were attenuated after adjusting for a second pollutant (Table 2). In particular, the association between SO_2 and suicide weakened substantially after adding NO_2 into the model. The combined RR for SO_2 also decreased after adjusting for PM_{10}. Similarly, the estimates for NO_2 decreased after adjusting for either SO_2 or PM_{10}, and the 95% CIs became wider. The association for PM_{10} weakened after adjusting for NO_2 but remained significant after adjusting for SO_2. The estimated association for $PM_{10-2.5}$ varied slightly after adjusting for NO_2 or SO_2. The VIFs were <10 in all the two-pollutant models.

The chi-squared test for Cochran's Q statistic showed no evidence of strong heterogeneity across cities based on the estimates from the single- or the two-pollutant models ($p > 0.10$) with I^2 values ranging from 0 to 61.0%, except for $PM_{2.5}$ (p for Cochran's Q test = 0.03 and $I^2 = 77.9\%$ at lag 0).

In subgroup analyses, there was no clear pattern of effect modification by sex, age, or method of suicide (Figure 4; see also Figures S2–S4). The confidence intervals among the subgroups largely overlapped covering the point estimates, suggesting that large uncertainty exists when comparing estimates across the groups. Nevertheless, we found some differences by age group in some cities (see Figure S3). Based on the city-specific results estimated from the first-stage modeling at a lag of 0–1 d, the associations for NO_2, SO_2, and PM_{10} were higher in the young age group (10–24 y) in Tokyo and Taipei.

Sensitivity Analysis

The effect estimates for NO_2, SO_2, and PM_{10} were generally larger when we used the simpler functional form (moving average)

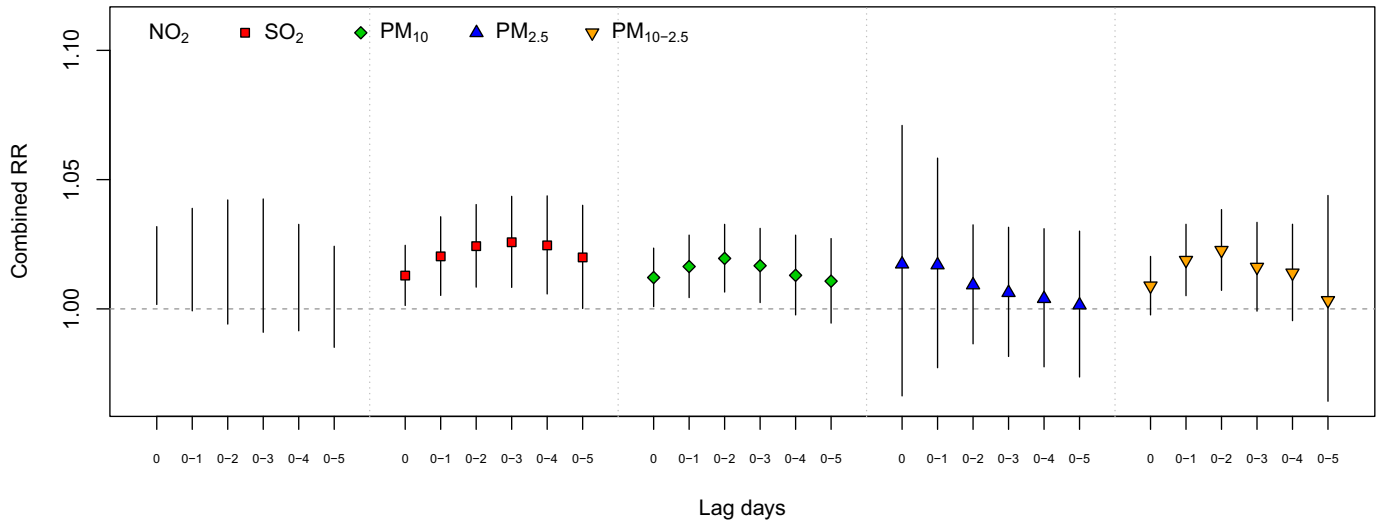

Figure 2. Lag structure of combined relative risks (RRs) and 95% confidence intervals of suicide per interquartile range increase in the concentration of nitrogen dioxide (NO_2), sulfur dioxide (SO_2), particulate matter with aerodynamic diameter ≤10 μm (PM_{10}), particulate matter with aerodynamic diameter ≤2.5 μm; ($PM_{2.5}$), and coarse particulate matter ($PM_{10-2.5}$) averaged across the cities after adjusting for potential confounders (i.e., ambient temperature, sunshine duration, day-of-week, public holiday, seasonality, and long-term time trend) in single-pollutant models.

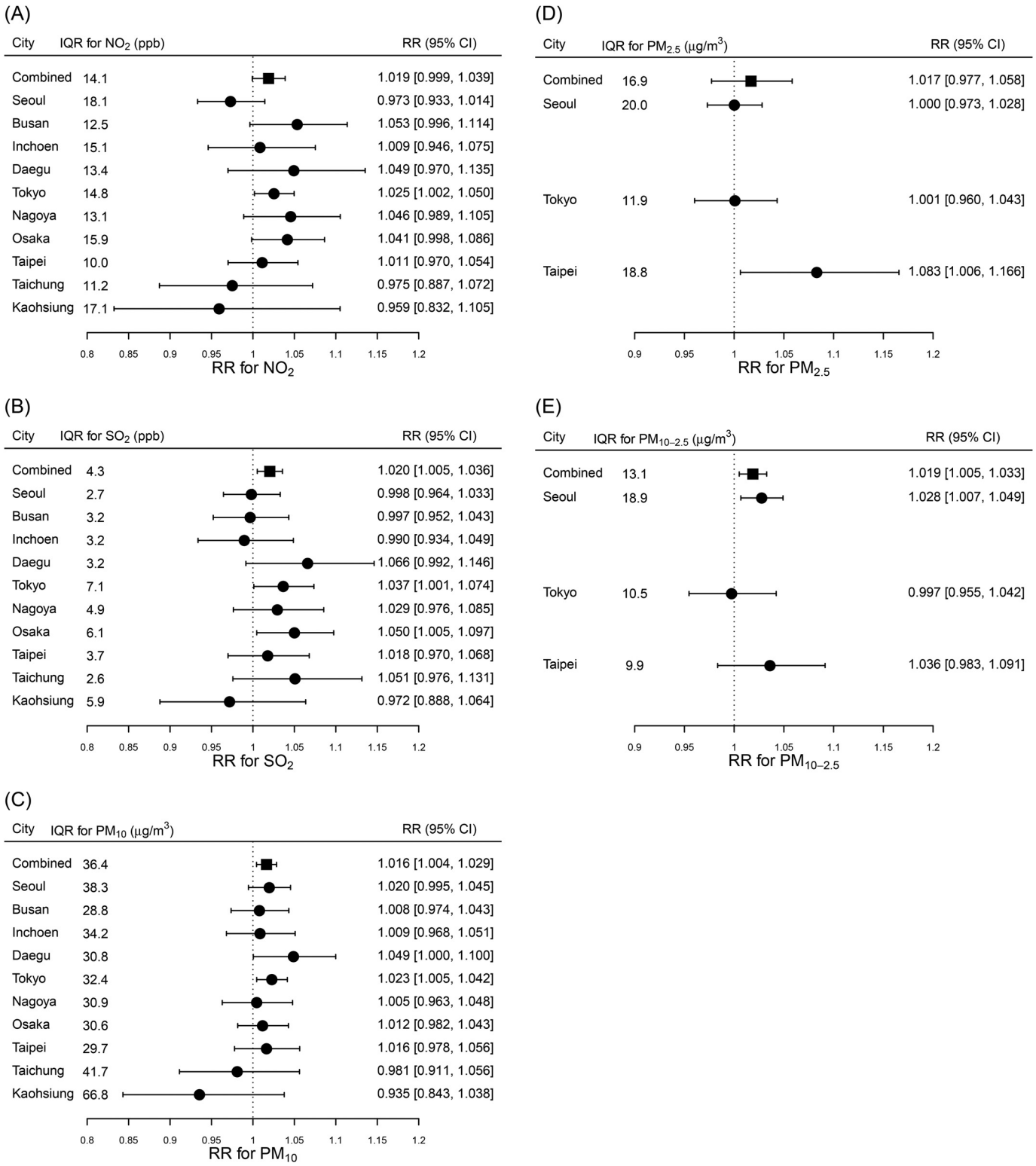

Figure 3. Interquartile range (IQR), combined and city-specific relative risks (RRs), and 95% confidence intervals of suicide per IQR increase in the average 0–1 d concentration of (*A*) nitrogen dioxide (NO_2), (*B*) sulfur dioxide (SO_2), (*C*) particulate matter with aerodynamic diameter $\leq$10 μm (PM_{10}), (*D*) particulate matter with aerodynamic diameter $\leq$2.5 μm ($PM_{2.5}$), and (*E*) coarse particulate matter ($PM_{10-2.5}$) after adjusting for potential confounders (i.e., ambient temperature, sunshine duration, day-of-week, public holiday, seasonality, and long-term time trend) in single-pollutant models.

of temperature and sunshine duration for adjustment instead of the distributed lag nonlinear models (see Figure S5). This finding implies that a simpler form of adjustment for weather variables may lead to bias in the estimates (Gasparrini 2016), and we relied on the latter approach in reporting our main results.

In other analyses, the effect estimates were fairly robust to the adjustment of additional weather variables (relative humidity, atmospheric pressure, and precipitation) (see Figure S6). The results showed no clear pattern of possible bias in the air pollution–suicide associations attributable to the longer stratum (see Figure S7),

Table 2. Combined relative risks and 95% confidence intervals in single- and two-pollutant models.

Primary exposure	Adjustment of another pollutant	RR[a] (95% CI)
NO_2	No adjustment	1.019 (0.999, 1.039)
	SO_2	1.014 (0.990, 1.040)
	PM_{10}	1.015 (0.986, 1.045)
SO_2	No adjustment	1.020 (1.006, 1.035)
	NO_2	1.012 (0.995, 1.029)
	PM_{10}	1.014 (0.995, 1.034)
PM_{10}	No adjustment	1.016 (1.004, 1.029)
	NO_2	1.011 (0.995, 1.026)
	SO_2	1.014 (1.000, 1.029)
$PM_{2.5}$	No adjustment	1.017 (0.977 1.058)
	NO_2	1.022 (0.970, 1.078)
	SO_2	1.012 (0.986, 1.037)
$PM_{10-2.5}$	No adjustment	1.019 (1.005, 1.033)
	NO_2	1.020 (0.999, 1.043)
	SO_2	1.022 (1.007, 1.036)

Note: CI, confidence interval; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 μm; PM_{10}, particulate matter with aerodynamic diameter ≤ 10 μm; $PM_{10-2.5}$, coarse particulate matter; RR, relative risk; SO_2, sulfur dioxide. In single-pollutant models, a subset of data without any missing copollutants was used to ensure comparability.

[a]Combined RRs of suicide per interquartile range (IQR) increase in the average 0–1 day concentration across the cities (14.1 ppb for NO_2, 4.3 ppb for SO_2, 36.4 $\mu g/m^3$ for PM_{10}, 16.9 $\mu g/m^3$ for $PM_{2.5}$, and 13.1 $\mu g/m^3$ for $PM_{10-2.5}$), after adjusting for potential confounders (i.e., ambient temperature, sunshine duration, day-of-week, public holiday, seasonality, and long-term time trend).

although their 95% CIs became wider in the narrower stratum, most likely because of a lack of control days matched to a case.

When including the days with extremely high PM concentrations in the Korean cities, the combined RRs for PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ were generally weaker (see Figure S8). This finding suggests that the association with PM becomes attenuated at extreme levels.

Discussion

We found that higher levels of NO_2, SO_2, PM_{10}, and $PM_{10-2.5}$ were associated with increased risk of suicide in 10 large cities in three northeast Asian countries. These associations were found at shorter delayed exposure lasting a few days and were generally consistent across the cities. We also found weak evidence of effect modification by age group in some cities in the stratification analysis. Some of the associations in the single-pollutant model weakened after adjusting for a second pollutant.

Our findings from the single-pollutant model are in part consistent with previous epidemiological studies, which found that higher levels of air pollutants were associated with increased suicides. Lin et al. (2016) reported an association between suicide and higher levels of PM_{10}, NO_2, and SO_2 in a single-pollutant analysis for Guangzhou, China. Kim et al. (2010) reported associations between PM_{10} and $PM_{2.5}$ and suicide cases in a subpopulation with cardiovascular diseases in seven cities in South Korea. The latter study used data from 2004, and our study confirmed this evidence using a longer period of data and in the entire population. Another study, undertaken in Salt Lake County, Utah, also based on a single-pollutant model, reported positive associations between NO_2 and $PM_{2.5}$ levels and suicide but found no association for SO_2 or PM_{10} (Bakian et al. 2015). The associations for $PM_{2.5}$ reported by the previous studies in South Korea (Kim et al. 2010) and in the United States (Bakian et al. 2015) were based on single-lag estimates, but these associations weakened when including multiple lag days to estimate the effects of cumulative exposure. Similar to our findings, all the previous evidence of associations suggested short exposure periods lasting one day (current day) to an average of 0–3 d.

A previous study conducted in Tokyo reported little evidence for the association of NO_2, SO_2, $PM_{2.5}$, and suspended particulate matter with total suicides based on both the single- and two-pollutant models (Ng et al. 2016). Their finding of a lack of associations between air pollutants and total suicide is inconsistent with our significant findings from the single-pollutant model; this discrepancy may be due to the differences in the study design, such as the study period and the geographical boundary of Tokyo, which render the results not directly comparable. For example, we used data from central Tokyo, which is smaller than the metropolitan Tokyo in Ng et al. (2016). Our study period spanned 30 y (April 1979 to March 2009), whereas Ng et al. (2016) investigated a shorter and more recent period (from 2001 to 2011).

In our study, some of the air pollution–suicide associations from the single-pollutant model were attenuated after adjusting for a second pollutant. For example, the association for SO_2 was largely reduced after adjusting for NO_2 or for PM_{10}. These reductions may be due to high correlations among the pollutants. The mean values of Pearson's correlation coefficient across cities were 0.65 between NO_2 and SO_2, 0.64 between NO_2 and PM_{10}, and 0.60 between PM_{10} and SO_2 (see Table S2). A notable finding is that the association between PM_{10} and suicide remained significant after adjusting for SO_2, although we observed that the association for SO_2 decreased considerably after adjusting for PM_{10} or for NO_2. This finding suggests that SO_2 may act as a proxy for PM_{10} or for NO_2 in unadjusted models, and its effect on suicide should therefore be interpreted with caution. It is also noteworthy that the concentrations of SO_2 were generally low in our study area (ranging between 3.7 and 7.3 ppb, with the exception of Kaohsiung, where the concentration was 9.3 ppb) and have decreased over time in Japanese and Taiwanese cities (data not shown). The observed SO_2 levels were lower than those recommended by World Health Organization air quality guidelines (24-h mean of 20 $\mu g/m^3$; approximately 7.6 ppb) (Krzyzanowski and Cohen 2008; WHO 2006).

We observed a higher risk of suicide mortality associated with air pollution (NO_2, SO_2, and PM_{10}) in the young age group (10–24 y) than in the older age groups in some cities, although subsequently, the combined RRs provided weak evidence of an effect modification. A few previous studies have reported a similar tendency. Lin et al. (2016) reported higher risks for NO_2 and SO_2 in a population <65 y old in Guangzhou, China. Kim et al. (2010) reported a higher risk for PM_{10} in a population 36–64 y old in seven cities in South Korea. In Tokyo, there was evidence of an association for NO_2 in the population <30 y of age, although the association was not reported for the total population (Ng et al. 2016).

Mechanisms for why increases in air pollutants may be associated with suicide are unknown. Previous researchers have hypothesized that higher levels of air pollution induce proinflammatory cytokines that may lead to a neuroinflammatory effect on the brain (e.g., dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis and changes in neurotransmitter levels) by direct and indirect pathways and that these pathways, in turn, may be involved in the development of depression, suicidal behavior, or both (Bakian et al. 2015; Kim and Cho 2016; Ng et al. 2016). Some studies have suggested that air pollutants can reach the brain through multiple pathways and may cause neuroinflammation related to neurodegenerative diseases such as Parkinson disease (Block and Calderón-Garcidueñas 2009; Levesque et al. 2011). A cohort study has indicated potential links between oxidative stress, inflammation, and anxiety related to air pollution (Power et al. 2015). Previous evidence has mainly supported the chronic effect of air pollution on the brain, whereas our study demonstrates a short-term association between air pollution and suicide, suggesting that higher levels of air pollutants, playing a role as neurotoxins,

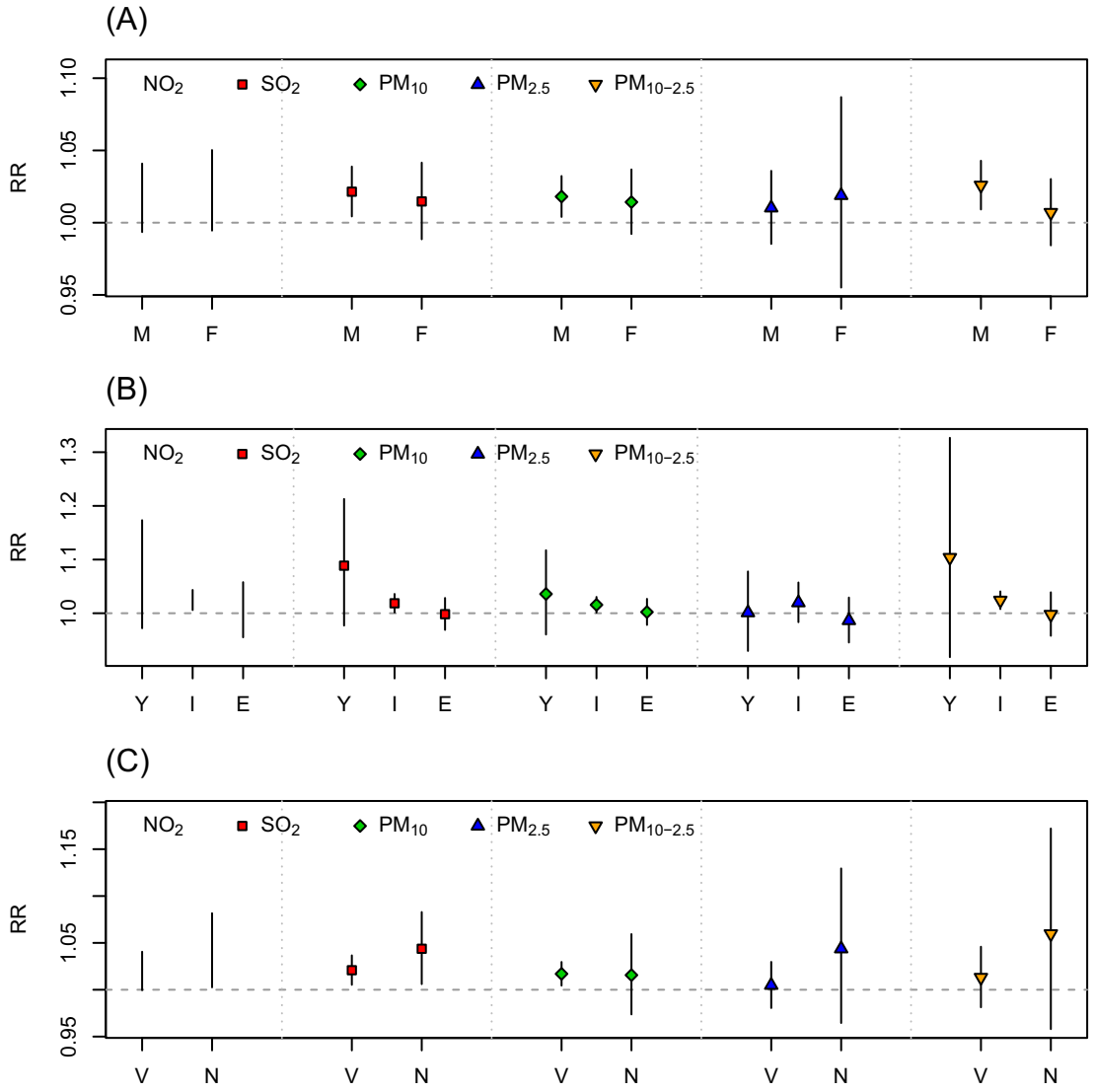

Figure 4. Combined relative risks (RRs) and 95% confidence intervals of suicide stratified by (*A*) sex (M, males; F, females), (*B*) age groups (Y, 10–24 y; I, 25–64 y; E, ≥65 years), and (*C*) method of suicide (V, violent suicide; N, nonviolent suicide) per interquartile range increase in the average 0–1 d concentration of nitrogen dioxide (NO_2), sulfur dioxide (SO_2), particulate matter with aerodynamic diameter ≤10 μm; (PM_{10}), particulate matter with aerodynamic diameter ≤2.5 μm ($PM_{2.5}$), and coarse particulate matter ($PM_{10-2.5}$) after adjusting for potential confounders (i.e., ambient temperature, sunshine duration, day-of-week, public holiday, seasonality, and long-term time trend) in single-pollutant models.

might provoke predisposed susceptible people to die by suicide. However, this supposition is premature and lacks support because suicide is a complex behavior linked to a number of psychosocial factors. Further research evaluating the neurophysiological response to air pollutants is needed to help understand the impact of air pollution on suicide.

One of our sensitivity analyses comparing two different approaches to control for temperature and sunshine duration showed that the effect estimates for the air pollution–suicide association were consistently higher in models that employed moving averages of the variables for adjustment, as opposed to the distributed lag nonlinear model. Our results suggest the importance of appropriate adjustment for weather factors, particularly temperature, in air pollution–suicide studies. This issue has been described in a simulation study by Gasparrini (2016), which suggested more flexible approaches. Because the temperature–suicide association was positive and strong in our study, the use of moving averages might have led to overestimation of the air pollution–suicide association. However, this should be evaluated further in a controlled setting.

This study has several limitations. First, it is possible that we did not consider other unmeasured time-varying factors that may be associated with suicide, and these remained as residual confounders. However, as we adjusted for day-of-week, seasonality, and long-term time trend using the time-stratified case-crossover design, such confounding may be negligible because it is unlikely that those factors change within a stratum. Second, suicide data may be underreported by misclassification, such that the cause of death is recorded as undetermined or accidental (Chan et al. 2015; Chang et al. 2010). However, such misclassification has become less likely in recent years. In Korea, death statistics have become more accurate because multisource databases are linked (Chan et al. 2015). Japan has had few misclassified suicide statistics over at least the past two decades (Chan et al. 2015). In addition, there is no reason to believe that the underreported cases have biased our findings substantially because the extent of misclassification is not likely to be associated with exposure levels (air pollution). Third, we used ambient air pollutant level as a surrogate for individual-level exposure. This measurement error, known as Berkson's error, could cause more uncertainty for the estimated

association, but little or no bias (Armstrong 1998). Finally, we assumed that the association is constant over time, but it may vary over time. It would be interesting to investigate whether a time-varying association exists in future studies using more flexible statistical approaches.

Conclusion

Our study suggests that higher levels of air pollution may be associated with suicide. These findings contribute to a better understanding of suicide associated with environmental factors. Further study is required to identify the underlying mechanisms for the short-term association between air pollution and suicide.

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Air Pollution and Suicide: Exploring a Potential Risk Factor

Nate Seltenrich

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Could air pollution be a trigger for suicide? Researchers first began asking this question less than a decade ago.[1,2,3] Accumulated evidence from around the world now suggests there may well be a connection,[4,5,6] although the nature of such a connection is still unknown. The authors of a study in *Environmental Health Perspectives* add to the evidence for this link, drawing upon a robust data set of pollution and suicide figures.[7]

The researchers examined the relationship between daily suicide deaths and daily mean levels of nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and categories of particulate matter (PM_{10}, $PM_{10–2.5}$, $PM_{2.5}$) in 10 large Northeast Asian cities. The data covered one to three decades, depending on the country. The team controlled for variables such as hours of daylight, day of week, and ambient temperature, which can potentially affect the risk of suicide.[8,9,10]

On a city-by-city basis, higher levels of air pollution were not always associated with higher suicide risk; in some cities, the association was even reversed, with increases in air pollution associated with lower risks of suicide. But when up to 30 years of information for PM_{10}, NO_2, and SO_2 was combined across all 10 cities, higher average exposures on the same day and over the previous 1–3 days were associated with a higher daily suicide risk. Combined estimates for PM_{10} and $PM_{10–2.5}$ across three cities with two to eight years of data also suggested an increased risk of suicide with higher exposures. However, these estimates were less precise, particularly for $PM_{2.5}$.

The estimated increases in suicide risk were small but consistent. For example, each 4.3-ppb increase in average daily exposure to SO_2 was associated with a 2.0% increase in estimated suicide risk on the same day, while each increase of 36.4 mg/m^3 in PM_{10} was associated with a 1.6% increase in estimated risk.

"Previous studies have considered [data for] maybe a decade or so, but having up to thirty years is a unique contribution," says University of Utah professor of psychiatry Amanda Bakian, who was not affiliated with the study. "There's growing evidence to suggest an association between ambient air pollution and suicide risk in diverse populations from around the world."

Japan, South Korea, and Taiwan share more than just the waters of the East China Sea. They all have above-average suicide rates, with South Korea ranking fourth worldwide in 2016 with 26.9 deaths per 100,000 people and Japan fourteenth with 18.5.[11] Taiwan's rate of 16 per 100,000 in 2016 also significantly exceeded

Hikers scale Geumjeongsan, a mountain overlooking the city of Busan, South Korea. In 2015, South Korea had the seventh highest average $PM_{2.5}$ levels of all developed countries and the third highest levels in East Asia, behind China and North Korea.[14] Image: © MiriamPolito/iStock.

the global average of 10.6.[12] Worldwide, roughly 800,000 people die from suicide every year.[13]

One major unanswered question is exactly how specific pollutants, or air pollution in general, might influence suicide risk. The young line of inquiry has yet to provide any answers, although some studies have suggested that neuroinflammation may be involved.[4,6] The authors note that suicide is a complex behavior linked to a number of psychosocial factors. Geographical differences such as cultural backgrounds, socioeconomic factors, and sources and components of air pollution all deserve consideration, they write.

"From my perspective, the broader take-home message relates to how we think about preventing suicide," says Sunnybrook Research Institute's Mark Sinyor, a psychiatrist and expert in mood disorders and suicide prevention, who was not affiliated with the study. "Any effort to make an enduring dent in suicide rates must address broader social problems and, as the evidence increasingly suggests, environmental problems such as air pollution as well. That may seem daunting, but at least there is a confluence of agendas—efforts to protect and improve our world are also likely to lead to fewer suicide deaths."

Nate Seltenrich covers science and the environment from the San Francisco Bay Area. His work on subjects including energy, ecology, and environmental health has appeared in a wide variety of regional, national, and international publications.

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Occupational diesel exhaust exposure as a risk factor for COPD

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Abstract

Purpose of Review—Chronic obstructive pulmonary disease (COPD) is a major source of morbidity and mortality worldwide. Although cigarette smoking is the major cause of COPD, occupational exposures have emerged as an important risk factor, especially in nonsmokers. In this review we assess the state of the literature on the association of COPD with a specific occupational exposure, diesel exhaust.

Recent Findings—A large body of literature links general occupational exposures to dust and fumes with an increased risk of COPD, particularly in nonsmokers. Few studies, however, have explicitly examined the role of occupational diesel exhaust exposures to COPD risk. Suggestive recent findings link occupational diesel exposures to an increased risk of COPD,

Summary—The available literature directly examining the effects of occupational diesel exhaust on risk of COPD is quite small, but does suggest that increasing exposures are associated with increasing risk. Additional research, with more advanced exposure metrics is needed to fully elucidate this association.

Keywords

chronic obstructive pulmonary disease (COPD); occupation; diesel exhaust; fumes

Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease that results in considerable morbidity and mortality in the United States and worldwide. Its clinical course is characterized by acute exacerbations resulting in large numbers of physician and hospital outpatient visits (~8 million), emergency department visits (~1.5 million), and hospitalizations (~726,000) in the US (1). COPD was the underlying cause in approximately 1 in 20 deaths in the US in 2006 and was the fourth leading cause of death worldwide in 2008 (1–3).

Occupational exposures, especially to dust and fumes, have been identified as potentially significant risk factors for COPD (4). Since 1989 a number of review articles have

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synthesized the association of occupation on risk of COPD and determined that it is an important risk factor (5–15). Numerous studies have attempted to determine the population attributable risk percent to account for the percentage of COPD due specifically to work-related factors. Estimates of this percentage for the general population range from 0–37%, with a median value of 15% (4). Higher percentages were reported for non-smokers (12–53%)(16–20). In a recent analysis, an 8.8% reduction in occupational exposures to dust/gases/fumes would result in an estimated 20% reduction in the prevalence of COPD worldwide (21). All of these reviews have highlighted the importance of exploring occupational risk factors for COPD.

Recent attention has focused specifically on diesel exhaust exposure as an important occupational risk factor. Diesel exhaust is a complex mixture of particulate matter (PM) and gases, and includes particles <1.0 μm diameter with mutagenic and polycyclic aromatic hydrocarbon (PAH) carcinogenic compounds adsorbed to a carbon core and ultrafine particles made up of condensed organics (22). Individuals in a variety of occupations, including transportation (railroads, trucks, buses), construction, mining and maintenance, are routinely exposed to diesel exhaust. There is no one accepted measure specific to diesel exhaust. However, work in an exposed job, as determined by industrial hygiene assessment or expert review; or self- reported exposure to occupational dust and fumes or specifically to diesel exhaust, have been used in the epidemiologic literature to assess associations with COPD.

The goal of this review is to assess the body of literature on the association of occupational diesel exhaust exposure and risk of COPD incidence and mortality. Results from observational epidemiology studies are presented, with emphasis on more recent publications. They are organized by specificity of exposure assessment for diesel exhaust.

Occupations with Likely Diesel Exhaust Exposure and COPD Risk

One of the most comprehensive studies of occupations with exposure to diesel exhaust and COPD was based on data from the US Third National Health and Nutrition Examination Study (NHANES III). Using data on occupation and industry collected as part of the standardized interview, the association between 25 *a priori* selected occupational categories and COPD defined based on lung function testing was examined (18). After adjustment for age, sex, race/ethnicity, body mass index, smoking (status and pack-years), educational level and socioeconomic status, elevated odds ratios (OR) were observed for industries with likely diesel exhaust exposure, such as, construction (OR 1.3, 95% confidence interval (95%CI) 0.8–2.3) and transportation and trucking (OR 1.2, 95%CI: 0.8–2.0), Figure 1. The odds ratios were higher in never smokers (construction OR 3.5; 95%CI 0.9–14.0, transportation and trucking OR 2.0; 95%CI 0.3–15.0). Odds ratios were also elevated when the analysis was performed by occupation, with ORs for occupations such as vehicle mechanics, transportation, construction workers, and motor vehicle operators ranging from 1.2 to 2.0 in the total sample and 2.1 to 3.4 in never smokers.

In a cohort study (23) of workers in the US railroad industry, worker job histories were classified into years of work in different job categories with varying levels of exposure to diesel exhaust from locomotives. After adjusting for age, calendar year and time since leaving work, each additional year of work in a job with locomotive exposure was associated with a 2.5% (95%CI 0.9%-4.2%) increased risk of COPD mortality. These associations were robust to indirect control for cigarette smoking. These were similar to findings from an earlier case-control study in the same industry, where increasing years of work were associated with an OR1.02 (95%CI 1.01–1.04) (24).

Diesel Exhaust Exposure and COPD Risk

Few studies have had the ability to examine the effects of diesel exhaust specifically on the risk of COPD (25). However, in a recent case-control study of participants in the Kaiser Permanente Northwest health maintenance organization, COPD cases and controls completed a questionnaire with information on demographics, family history, and a detailed work history (26). As part of the job history, individuals reported routine (weekly) exposures to diesel exhaust. In addition, industrial hygienists assessed the potential for diesel exhaust exposure based on a review of the jobs and industries each individual reported. In logistic regression models adjusted for age and sex, individuals with any diesel exhaust had an OR of 1.9 (95%CI 1.3–3.0) compared to those with no exposure. The risk was higher among never-smokers (OR 6.4, 95%CI 1.3–31.6) and among those rated by the industrial hygienists to have moderate exposure.

Occupational Dust/Fume Exposure and COPD Risk

There are hundreds of studies looking at occupational dust and/or fume exposure. Excellent summaries of the literature were conducted by the American Thoracic Society in 2003 (27) and again in 2010 (28*). In both cases they concluded that occupational exposures were important risk factors for COPD. Diesel exhaust may be one of the fumes being referred to; however, this specificity is often not available.

Five recent studies have examined the effects of general occupational gas, dust, or fume exposure. In a US population based case-control study, two methods were used to assess exposure to vapors, gases, dust, and fumes: a question asking specifically if each job involved exposure to any of these four entities, and a job exposure matrix (JEM) based on an occupational history and expert review (29). The OR for COPD with self-reported exposure was 2.1 (95%CI 1.4–3.0) and with high likelihood of exposure from the JEM was 1.2 (95%CI 0.6–2.3), after adjustment for age, sex, race/ethnicity and smoking status.

In a South-African hospital based case-control study, exposure to dust, gas, and fume exposure was determined from both self-reports and a JEM derived from occupational histories taken from each participant (30*). After adjustment for age, sex, smoking status, and history of tuberculosis, self reported chemical, gas, and fume exposure years were associated with an OR of 2.9 (95%CI 1.3–6.3) for low exposure and 3.6 (95%CI 1.6–7.9) for high exposure. The equivalent measures from the JEM were associated with an OR of 2.2 (95%CI 1.1–4.7) for low exposure and 1.8 (95%CI 0.8–3.9) for high exposure.

Risk factors for COPD were examined among 4,291 never smokers participating in Burden of Obstructive Lung Disease (BOLD) from 14 different countries (31*). As part of the standardized questionnaire, participants were asked if they had worked for longer than 3 months in a list of occupations previously associated with risk of COPD (for gases/fumes/vapors: welding, fire fighting, chemical or plastic manufacturing, public transportation, or dry cleaning). In multivariable models, 10 or more years of work in a job with gas/fume/vapor exposure was associated with an OR of 1.54 (95%CI 0.71–3.34) in males, and no association in females.

In a population-based study in the north of England, questionnaires were sent to a randomly selected subsample of the population (32*). The questionnaire specifically asked if each individual had prior occupational exposure to a variety of substances, including asbestos, welding, and dust/fumes. Among respondents who also underwent lung function testing, any occupational exposure was associated with an OR of 3.0 (95%CI 1.3–6.9), adjusted for age, gender, hay fever, cigarette smoking, and the interaction between gender and occupational exposures.

Among a series of 185 male patients with COPD at a large hospital in Spain, information was obtained on employment status and lifetime occupational history (33). A JEM was constructed to determine the levels (none, low, high) of three exposures, biological dust, mineral dust, and gases and/or fumes. Among those with any work ever in a job with a high level of gas and/or fume exposure, the relative risk (RR) of having an FEV1 less than 30% predicted (compared to >70% predicted) was 11.4 (95%CI 1.4–95.0) and each additional 10 years of work in such a job was associated with a RR of 1.9 (95%CI 1.0–3.7).

Conclusion

The available literature directly examining the effects of occupational diesel exhaust on risk of COPD is quite small. However, these investigations, along with a large body of literature exploring general occupational exposures to dust and fumes suggest a role of occupational diesel exhaust exposure on risk of COPD. Additional research, with more advanced exposure metrics is needed to fully elucidate this association.

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Summary

- A large body of literature links general occupational exposures to dust and fumes with an increased risk of COPD, particularly in nonsmokers.
- The available literature directly examining the effects of occupational diesel exhaust on risk of COPD is quite small, but does suggest that increasing exposures are associated with increasing risk.
- Additional research, with more advanced exposure metrics is needed to fully elucidate the impact of occupational diesel exposure on COPD risk.

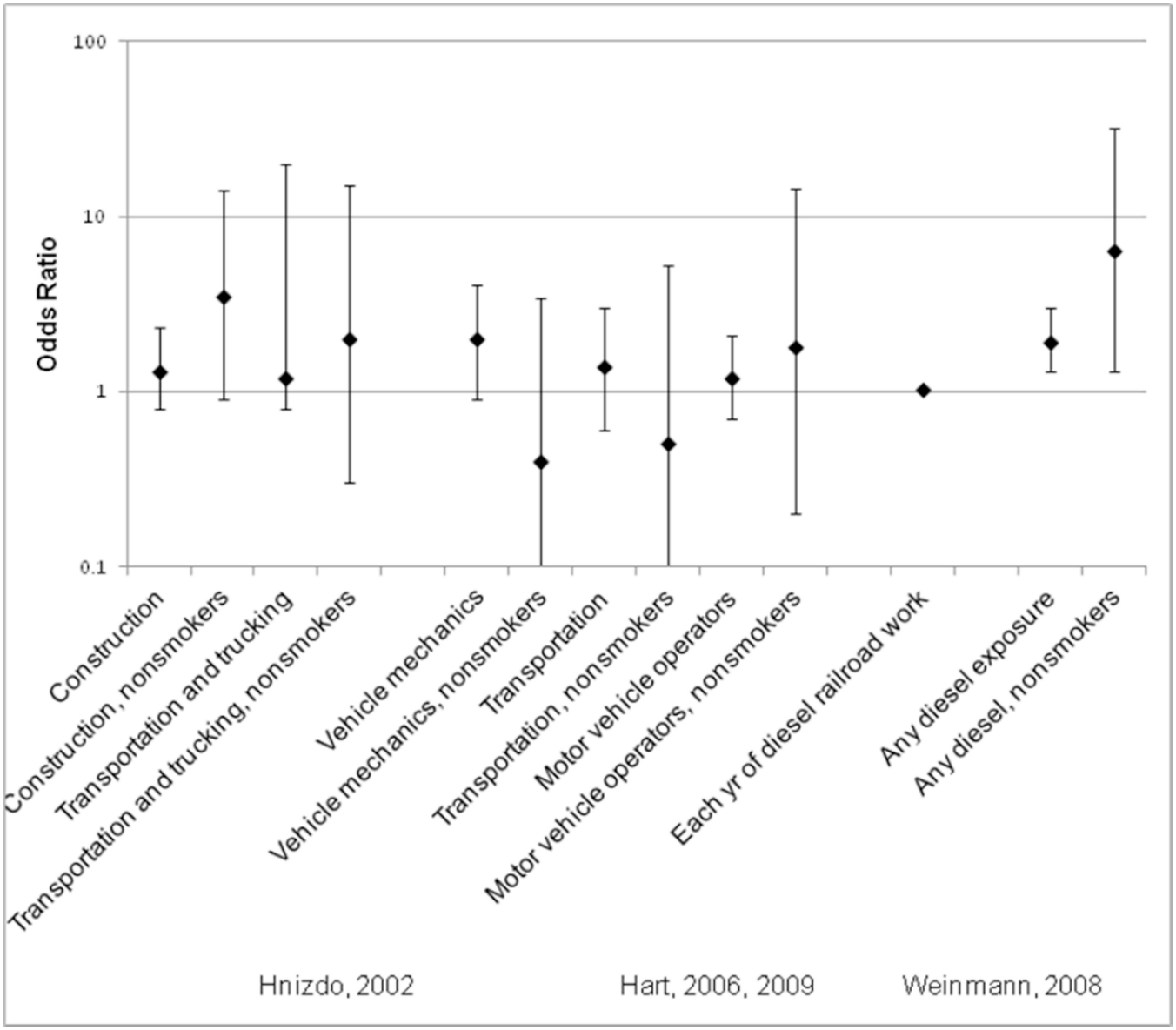

Figure 1.
COPD odds ratios and 95% confidence intervals for various occupational diesel exhaust exposures