Sex differences in Associations of Fine Particulate Matter with Non-accidental Deaths: An Ecological Time-Series Study

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Research

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Abstract

Background: Sex differences in the impact of exposure to air pollution have been reported previously and epidemiological studies indicate that fine particulate matter ($PM_{2.5}$) effects on non-accidental death are modified by sex, however, the results are not conclusive. This study aimed to investigate the sex difference in the effects of $PM_{2.5}$ on non-accidental death, considering the nonlinear exposure-response relationships between $PM_{2.5}$ and smoking and death.

Methods: Information on daily non-accidental deaths, air pollution, meteorological data, and smoking prevalence between 1 January, 2012 and 31 December, 2014 was obtained in Shanghai, China. Constrained generalized additive models were used to assess the association of interaction between sex and daily $PM_{2.5}$ concentrations with daily non-accidental deaths, adjusting for weather type and smoking rate. A two-week lag analysis was conducted as a sensitivity analysis.

Results: During the study period, the total number of non-accidental deaths in Shanghai was 336,379, with a daily mean of 163 deaths and 144 deaths for men and women, respectively. The average daily concentration of $PM_{2.5}$ in Shanghai was 55.0 μg/m^3 during the same time period. Older people and men showed a higher risk for non-accidental death (risk ratio (RR) = 1.025 per year increase in age, 95% confidence interval (CI): 1.021 – 1.029, and RR = 0.892 for women, 95% CI: 0.802 – 0.993, respectively). Compared with men, the risk for non-accidental death in relation to increasing $PM_{2.5}$ concentration was smaller in women (RR = 0.998, 95% CI: 0.996 – 1.000, per 10 μg increase in $PM_{2.5}$ concentration. The difference is consistent during the two lag weeks and more obvious when adjusting for the interaction between $PM_{2.5}$ concentration and smoking prevalence.

Conclusion: The effects of $PM_{2.5}$ on daily non-accidental death are different between men and women in Shanghai, China, and women tend to have a lower risk. The underlying mechanisms of the sex difference of $PM_{2.5}$ effects on death need further investigation.

Background

According to the latest urban air quality database, more than 80% of people living in urban areas that monitor air pollution are exposed to air quality levels with pollutants exceeding the limits of the World Health Organization (WHO). The greatest impact is among populations in low-income cities. Among the cities with a population larger than 100,000 in low- and middle-income countries, 98% do not meet WHO air quality guidelines. Even in high-income countries, the percentage is as high as 56% [1]. Air pollution has a substantial impact on human health and has become a global public health risk [2].

Fine particulate matter or particulate matter with an aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$) is a major air pollutant, which has been associated with multiple adverse effects on human health, especially on the respiratory and circulatory systems. The short-term effects of $PM_{2.5}$ on human health have been reported in numerous epidemiological studies [3-6], and the effects vary by air pollution levels, composition of $PM_{2.5}$, geographic location, as well as demographic characteristics [7].

Epidemiologic studies have provided some evidence indicating sex differences in the relationship between short-term PM2.5 exposure and various health effects [8]. There are more studies of adults reporting higher magnitude effects among women [9]. Studies of children suggest stronger effects among boys in early childhood whereas among girls in later childhood [9]. However, there is also a study suggesting that women might be more susceptible to $PM_{2.5}$ for some respiratory and cardiovascular causes [10]. Although results are not conclusive, epidemiological studies indicate that air pollution effects on health are significantly modified by sex [11, 12]. It remains however unclear whether the modifications are attributable to socially derived sex-specific exposures, sex-linked physiological differences, or both. There is a growing role for sex analysis in air pollution epidemiology, which aims to disaggregate social from biological differences between males and females, and elucidate possible sources of such differences [9].

In our previous study, we investigated the association between $PM_{2.5}$ exposure and non-accidental mortality in Shanghai, China, and found statistically significantly higher magnitude associations in women than in men when adjusting for age and age-specific smoking rate [13]. Possible reasons for such a pattern might include sex hormones which have a function in the smoking-related morbidity and mortality and women are suggested having greater risk [14]. However, in that study, we did not consider the interaction between sex and $PM_{2.5}$, and considered the associations of $PM_{2.5}$ and smoking with non-accidental deaths as linear [13]. Therefore, in this study, we applied a constrained generalized additive model (CGAM) analysis, including an interaction term between sex and $PM_{2.5}$ exposure and nonlinear exposure-response relationships between $PM_{2.5}$ and smoking and death, to further investigate the sex difference in the effects of $PM_{2.5}$ on non-accidental death.

Methods

Study Design and Setting

The study is an ecological time-series study using the data from a population causes of death register between January 1st, 2012 and December 31st, 2014 in Shanghai, China. Daily average $PM_{2.5}$ concentrations and meteorological conditions were also obtained during the same time period.

Shanghai is the largest and the most populous city in east China, with longitude and latitude of 121° E and 31° N, located in the Yangtze River Delta Region. It has a territory of about 6,340 km^2, an average permanent resident population of around 24.05 million, and an average local gross domestic product of approximately 2.1754 trillion Chinese Yuan during the study period [15-17].

Data collection

The data collection of the study has been described in detailed elsewhere [13, 18, 19]. In brief, hourly $PM_{2.5}$ concentrations in 2012 were obtained from the United States Consulate General in Shanghai, and daily average $PM_{2.5}$ concentrations calculated from hourly data in 2013 and 2014 were obtained from the Shanghai Meteorological Bureau. The data were collected from the same single air monitor during the study period to present the $PM_{2.5}$ level for the entire city. Daily weather meteorological data during the same period were obtained from the Shanghai Meteorological Bureau. Weather conditions were categorized into six synoptic weather types (SWT), including hot dry, warm humid, cold dry, cool dry, cool humid, and cold humid, based on the cluster analysis using 18 meteorological variables. Daily non-accidental mortality data in Shanghai during the study period were obtained from the Causes of Death Register of Shanghai (CDRS) provided by the Shanghai Municipal Center for Disease Control and Prevention (SCDC). Population level smoking rates by 5-year age groups were also obtained from SCDC. Non-accidental mortality was represented using daily death counts for non-accidental reasons. Because the total population was relatively stable during the study period, we treated it as if it remained unchanged to produce mortality rates.

Statistical Analysis

Descriptive statistical methods were used to describe the characteristics of the variables. The CGAM was used to assess the interaction of $PM_{2.5}$ exposure and sex on daily non-accidental deaths, adjusting for temperature, SWT, and time trend. In the CGAM, the logarithm was used as the link function and the Poisson distribution was the assumed probability distribution of the daily non-accidental deaths [20]. An increasing shape-restriction was used for the smooth non-linear association of $PM_{2.5}$ with daily non-accidental mortality, and smooth non-linear associations without restrictions were assumed for time and temperature. The number of knots for the smoothness was selected based on the cone information criterion (CIC) [21, 22]. The sex difference in the $PM_{2.5}$ effects on mortality was investigated by including an interaction term between sex and $PM_{2.5}$ concentration in the CGAM and presented using risk ratio (RR). The analysis was also adjusted for day of week (DOW), average age of the daily deaths, and population-standardized smoking rate. National holidays were assigned as Saturday or Sunday whichever was the nearest. An increasing shape-restriction was also used for the smooth non-linear association of smoking with daily non-accidental mortality. We also examined the interaction of sex with single-day lag and weighted moving average of $PM_{2.5}$ concentrations up to two weeks as a sensitivity analysis[23]. A nonlinear monotone increasing interaction term between smoking rate and PM2.5 concentration was also included in the models as another sensitivity analysis. To further investigate whether the interaction effect between sex and $PM_{2.5}$ was modified by age or different between causes of death, we conducted stratified analyses for age groups (<40 years, ≥40 and <60 years, ≥ 60 and <80 years, and ≥80 years) and four specific causes of deaths, including respiratory disease, cardiovascular disease, cerebrovascular disease, and other circulatory system diseases.

All statistical analyses were performed in the software R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria), and the CGAM analysis was achieved using the package *cgam* in R [20]. Two-sided statistical tests were performed, and a RR with a P-value < 0.05 was considered statistically significant.

Results

Characteristics of Non-accidental Deaths and PM2.5 Concentration

During the study period, a total of 336,379 non-accidental deaths occurred in Shanghai, with a mean of 307 daily deaths. Some 53.1% of these deaths were men and the average ages at death were 74.9 and 79.3 years for men and women, respectively (Table 1).

Table 1. Characteristics of non-accidental deaths in Shanghai, China, 2012-2014.

Variables	Men	Women
Total numbers of non-accidental deaths during the study period (%)	178,786 (53.1%)	157,593 (46.9%)
Average population (million) during the study period (%)	12.53 (52.1%)	11.52 (47.9%)
Average daily death during the study period (SD)	163 (27)	144 (27)
Average age (years) at death (SD)	74.9 (13.0)	79.3 (11.7)
Population-standardized smoking rate of the deceased people (SD)	29.71% (15.25%)	0.92% (0.71%)

The detailed results of $PM_{2.5}$ concentrations and weather conditions during the study period were published previously [13, 19]. Overall, the average daily concentration of $PM_{2.5}$ in Shanghai was 55.0 μg/m^3, with a similar seasonal trend as the daily non-accidental deaths (i.e. high values in cold seasons and low values in warm seasons) [19].

Sex Difference in Effect of $PM_{2.5}$ on Non-accidental Mortality

When considering the nonlinear associations of $PM_{2.5}$, temperature, and smoking with non-accidental death, and adjusting weather types and day of week, older people and men showed a higher risk for non-accidental death (RR = 1.025 per year increase in age, 95% confidence interval (CI): 1.021 – 1.029, and RR = 0.892 for women, 95% CI: 0.802 – 0.993, respectively) (Table 2).

Table 2. Risk ratios of sex and its interaction with $PM_{2.5}$ for non-accidental mortality.

	Risk ratio (RR)	95% confidence interval (CI)		P-value
		Lower limit	Upper limit	
Age	1.025	1.021	1.029	<0.001
Female	0.892	0.802	0.993	0.036
Female × $PM_{2.5}$ (per 10 μg/m^3)	0.998	0.996	1.000	0.010
SWT				
Warm humid	0.996	0.980	1.012	0.596
Cold dry	0.979	0.956	1.003	0.090
Cool dry	1.006	0.988	1.025	0.486
Cool humid	1.044	1.025	1.064	<0.001
Cold humid	1.010	0.986	1.035	0.409
Day of Week				
Monday	1.017	1.004	1.030	0.009
Tuesday	1.011	0.998	1.024	0.110
Wednesday	1.013	1.000	1.026	0.050
Thursday	1.006	0.993	1.019	0.358
Friday	1.004	0.991	1.017	0.598
Saturday	0.997	0.984	1.010	0.624

SWT, synoptic weather type.

The predicted numbers of daily non-accidental deaths by day and $PM_{2.5}$ concentration, and by temperature and $PM_{2.5}$ concentration are shown in the 3D perspective plots in Figure 1. Daily non-accidental deaths fluctuated with season and increased with PM.2.5 concentration (Figure 1a), and a U-shape exposure-response relationship was observed between temperature and daily non-accidental deaths (Figure 1b). The predicted values by the CGAM indicate that 66.2% of the deviance can be explained by the model.

A low magnitude but statistically significant interaction was found between sex and $PM_{2.5}$ concentration, i.e. compared with men, the risk ratio for non-accidental death in relation to increasing $PM_{2.5}$ concentration was smaller in women (Figure 2). Per 10 μg/m^3 increase in $PM_{2.5}$ concentration, the risk ratio was 0.2% smaller (RR = 0.998, 95% CI: 0.996 – 1.000) for women, compared to men (Table 2). When including the nonlinear interaction term between smoking rate and $PM_{2.5}$ concentration in the model, although the conditional mortality rate for women was higher than that of men, the increased risk for non-accidental death per 10 μg/m^3 increase in $PM_{2.5}$ concentration for women compared to men was even lower (RR = 0.983, 95% CI: 0.979 – 0.988, P < 0.001).

Lag Struscture of Interaction between Sex and $PM_{2.5}$ Concentration

In our sensitivity analysis investigating the interaction effect of sex after applying up to 14 lag days of $PM_{2.5}$ concentration, we got consistent results. During the two lag weeks' exposure to $PM_{2.5}$, in general, the increased risk for non-accidental death is about 0.2% – 0.4% lower in women than in men, per 10 μg/m^3 increase in $PM_{2.5}$ concentration (Table 3). The results for the weighted moving average of $PM_{2.5}$ concentrations up to 14 days indicate that the risk ratio of non-accidental deaths for cumulative effects of $PM_{2.5}$ was 0.3% – 0.6% lower in women compared to men, and the results are all statistically significant and consistent throughout the 14-day time window (Table 3).

Table 3. Risk ratio of the interaction between sex and $PM_{2.5}$ (per 10 μg/m^3) for non-accidental death, after applying different lag times for exposure.

Lag	Single-day			Lag	Weighted moving average		
	RR	95% CI	P-value		RR	95% CI	P-value
Lag 1	0.998	0.997 – 1.000	0.014	Lag 0-1	0.997	0.995 – 0.999	0.001
Lag 2	0.999	0.997 – 1.000	0.135	Lag 0-2	0.997	0.995 -0.999	0.001
Lag 3	0.997	0.995 – 0.998	0.000	Lag 0-3	0.997	0.995 – 0.999	0.004
Lag 4	0.996	0.995 – 0.998	0.000	Lag 0-4	0.996	0.994 – 0.999	<0.001
Lag 5	0.997	0.996 – 0.999	0.000	Lag 0-5	0.996	0.994 – 0.998	0.001
Lag 6	0.997	0.995 – 0.999	0.000	Lag 0-6	0.996	0.993 – 0.998	0.001
Lag 7	0.997	0.995 – 0.998	0.000	Lag 0-7	0.995	0.993 – 0.998	0.001
Lag 8	0.997	0.996 – 0.999	0.000	Lag 0-8	0.995	0.993 -0.998	0.001
Lag 9	0.997	0.996 – 0.999	0.000	Lag 0-9	0.996	0.993 – 0.998	0.001
Lag 10	0.997	0.995 – 0.998	0.000	Lag 0-10	0.995	0.993 – 0.998	<0.001
Lag 11	0.999	0.997 – 1.000	0.082	Lag 0-11	0.995	0.992 – 0.997	<0.001
Lag 12	0.999	0.997 – 1.000	0.084	Lag 0-12	0.995	0.992 – 0.997	<0.001
Lag 13	0.998	0.997 – 1.000	0.008	Lag 0-13	0.995	0.992 – 0.997	<0.001
Lag 14	0.998	0.996 – 1.000	0.014	Lag 0-114	0.994	0.992 – 0.997	<0.001

RR: risk ratio; CI, confidence interval.

Subgroup analysis by age groups and specific causes of death

The reduced incremental effects of PM2.5 on non-accidental deaths in women were consistent in the subgroup analyses. Although not statistically significant in the aged 40 years or younger group (might be due to the small proportion, i.e. 1.3%, of the total deaths), the risk ratio was 0.4% – 1.0% lower for women, compared to men (Table 4) Regarding the case-specific deaths, in general, the risk ratio was 0.2% – 0.8% lower for women, compared to men. However, the reduction was not statistically significant for cerebrovascular deaths (Table 4).

Table 4. Risk ratio of the interaction between sex and $PM_{2.5}$ (per 10 μg/m^3) for non-accidental death, by age groups and specific causes of death.

Subgroup	Risk ratio (RR)	95% confidence interval (CI)		P-value
		Lower limit	Upper limit	
Age (years)				
<40	0.990	0.978	1.003	0.118
≥40, <60	0.991	0.985	0.996	0.001
≥60, <80	0.996	0.994	0.999	0.008
≥80	0.996	0.994	0.998	<0.001
Causes of death				
Respiratory disease	0.992	0.987	0.997	0.001
Cardiovascular disease	0.993	0.990	0.997	<0.001
Cerebrovascular disease	0.998	0.994	1.001	0.164
Other circulatory system diseases	0.997	0.994	0.999	0.003

Discussion

In our study, we explored the interaction between sex and $PM_{2.5}$ exposure for non-accidental mortality in Shanghai, China between 2012 and 2014. Apart from the statistically significantly lower risk of non-accidental death in women and the monotone increasing nonlinear exposure-response association between $PM_{2.5}$ and mortality, we found a smaller risk increase in non-accidental death (0.2% lower), per 10 μg/m^3 increase in $PM_{2.5}$ concentration, among women compared to men. In sensitivity analysis for the lags, we noticed that the sex differences in $PM_{2.5}$ effects in lag days 2, 11 and 12 were not statistically significant (Table 3). It might be due to chance or some undetected confounding or modification, and deserves further investigation using a larger dataset. However, all the lag days show the same trend, and 11 of 14 signal-day effects and all 14 cumulative lag effects are statistically significant, which indicates the robustness of our findings. Meanwhile, we also observed statistically significantly higher mortality risk on Monday and Wednesday compared with that on Sunday, which might be attributed to the higher $PM_{2.5}$ levels in the two days (averagely, 55.7 μg/m^3 and 56.4 μg/m^3 vs. 53.6 μg/m^3). No statistically significant difference was found for other weekdays.

The effects of ambient $PM_{2.5}$ on mortality have been widely studied at global and national levels [5, 24-26]. $PM_{2.5}$ pollution is ranked as the 6th leading cause of mortality and disability-adjusted life-years (DALYs) globally, and is estimated to contribute to 4.24 million deaths and 103.1 million DALYs in the Global Burden of Diseases project [27]. Men and women exhibit different health responses to air pollution. Sex-related differences in the relationship between air pollutants and adverse health outcomes, such as asthma [28], type 2 diabetes [29], cardinal symptoms [30], and declined cognition [10, 31], have been observed in earlier studies. The literature is however far from consistent. For example, a previous study indicated that women might be at greater risk of fatal coronary heart disease as a result of exposure to particulate matter (PM), than men. The authors suspected that PM deposits differently and perhaps more harmfully in women's lungs compared to men's lungs [32]. However, a meta-analysis indicated that the association of $PM_{2.5}$ with lung cancer was stronger for men than for women [33], which was later confirmed by a 10-year time-series study [34]. Analyses of sex differences are more common in occupational epidemiology than in environmental health, because persistent job stratification by sex has produced marked differences in occupational exposures to chemical agents, ergonomic demands, injury, and psychosocial stressors [9, 35]. So far, few studies investigating the sex-related exposure-response difference in the effects of $PM_{2.5}$ on all-cause non-accidental mortality, by adjusting for sex in analysis [36] or stratifying the analysis by sex [37].

The weaker association between $PM_{2.5}$ and non-accidental mortality in women, compared to men, as found in our study might be due to different reasons. One possibility is that $PM_{2.5}$ interacts with male-specific factors that are known to be associated with increased risk of the causes of non-accidental deaths, including male hormones [38], lifestyle factors [39], occupational exposures [27, 40], etc. For instance, in China, the prevalence of smoking is 47.2% among men whereas 2.7% among women [41]. An interaction between smoking and $PM_{2.5}$ has been proposed earlier for different chronic diseases, including cardiovascular mortality [42] and depression [43]. Another possibility is the misclassification of real exposure to $PM_{2.5}$. For instance, in China, women are more likely to wear face masks and on average spend less time outdoors, compared to men [44]. This might have resulted in an attenuated effect of $PM_{2 \cdot 5}$ in women, compared to men.

Except for the known advantages of ecological studies as have been discussed extensively [45-47], the major advantage of our study is the application of CGAM in analysis. Generalized additive models (GAM) have been widely implemented in time-series studies to explore the relationship between environmental factors and health outcomes because they can control for seasonal trends and nonlinear modification effects of multiple variables, adding to the fact that they are more maneuverable than full-parameter alternatives, generalized linear models [48, 49]. However, the traditional GAM only assumes the smoothness of the nonlinear associations and cannot restrict their shape. In CGAM, however, we may specify the shapes of the smooth functions, including smooth or isotonic, as well as increasing, decreasing, convex or concave. The constraints allow us to model the nonlinear relationships more in line with reality, such as the known monotonic increasing relationship of $PM_{2.5}$ with mortality and concave relationship of temperature with mortality, capturing therefore the sex-related difference more accurately. This study has several limitations. First, as an ecological study, exposure to $PM_{2.5}$ was assessed at the population level, which might have led to aggregation bias. Second, personal demographics such as occupation and lifestyle factors (e.g. amount of time spent outdoors) are not available for the analysis and might have affected personal exposures to $PM_{2.5}$. Third, although we adjusted for population smoking prevalence and its interaction with $PM_{2.5}$ in the analysis, this information is not on an individual level. Other than smoking, we had little information on other potential factors. Fourth, we only analyzed the short-term (up to two weeks) effects in the current study, however, when we look at all non-accidental deaths only a subset of diseases would be influenced by the particulate matter. Therefore, a further cause-specific analysis deserves in the future. In addition, this study was conducted in Shanghai, one of the most developed cities with the highest life expectancy in China, which limits the generalizability of the findings to other parts of China.

Conclusion

Compared to men, exposure to $PM_{2.5}$ pollution was associated with a smaller risk increase in non-accidental mortality in women, in Shanghai, China, after adjusting for weather types, population level smoking prevalence, and interaction between the smoking prevalence and $PM_{2.5}$ exposure. The underlying mechanisms of the sex difference of $PM_{2.5}$ on death need further investigation.

Declarations

Ethics approval and consent to participate: This study is an ecological and observational study, based on the data from population-based registers in Shanghai. No personal identification was disclosed in our data. The study was approved by the Ethical Review Committee of the SCDC (approval number: SCDC2016-08).

Consent for publication: Not applicable.

Availability of data and material: The use of the data was under the agreement between the Institute of Environmental Medicine, Karolinska Institutet, Sweden and the Shanghai Municipal Center for Disease Control and Prevention within a bilateral collaboration framework. The data were not publicly available but may be available upon reasonable request and with permission of the SCDC (xiatian@scdc.sh.cn).

Competing Interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The funding body was not involved in the design of the study, data collection and analysis, interpretation of results, or writing the manuscript. The authors declare no conflict of interest.

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Figures

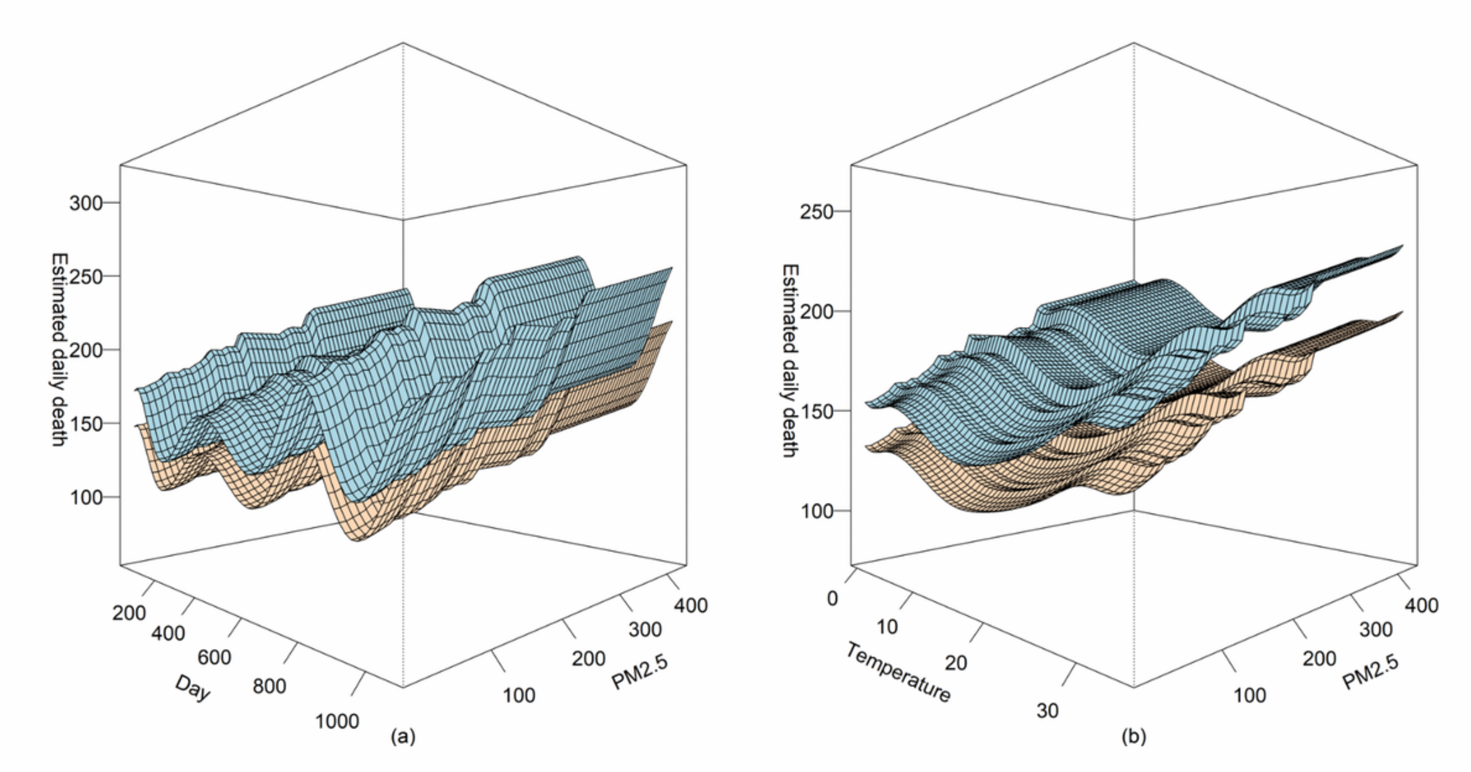

Figure 1

Predicted daily non-accidental deaths by (a) day and PM2.5 concentration (μg/m3), and (b) temperature (℃) and PM2.5 concentration (μg/m3). * Blue surface, men; khaki surface, women.

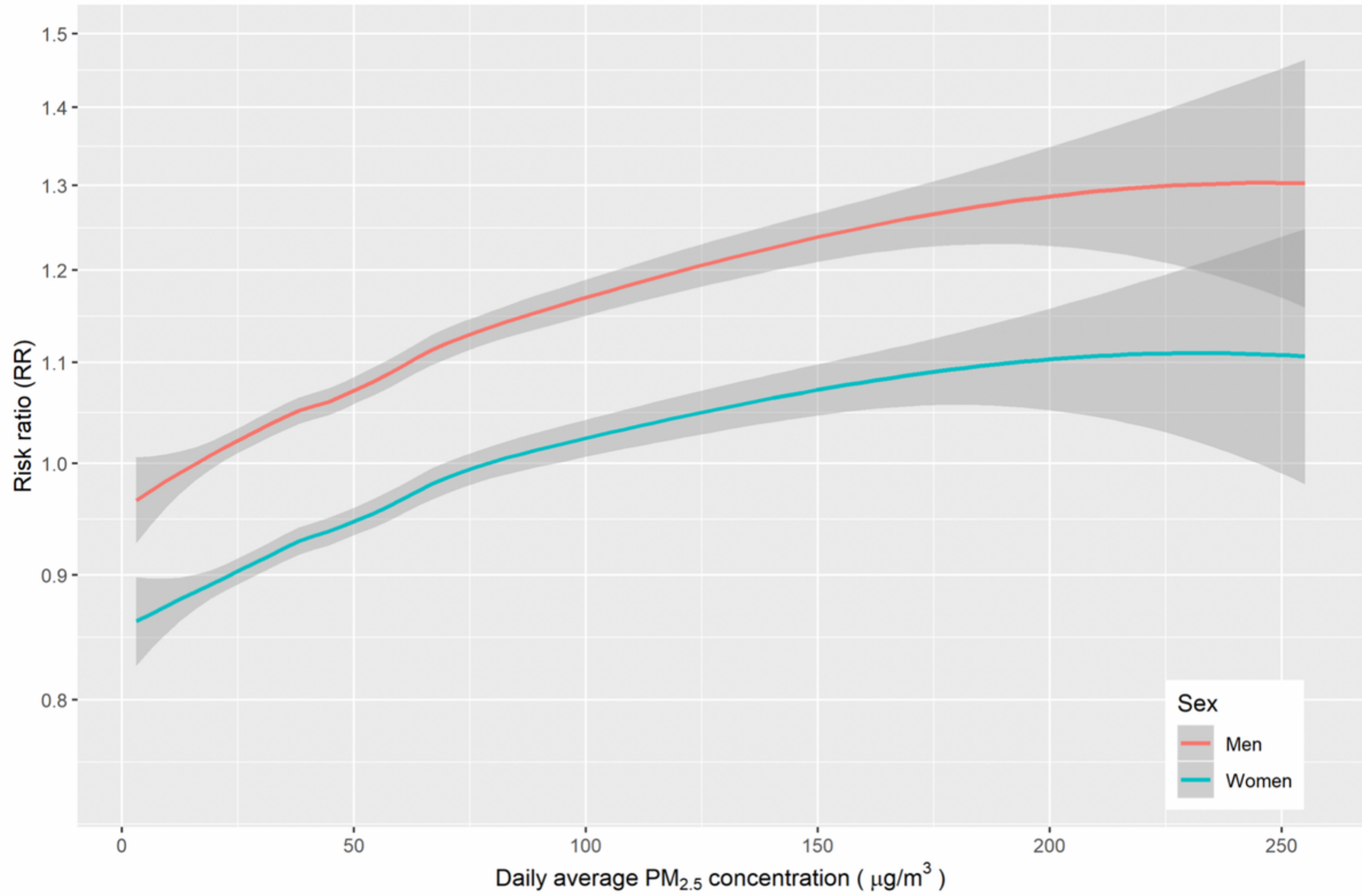

Figure 2

Risk ratios for non-accidental death by PM2.5 concentrations in men and women.