HHS Public Access

Author manuscript

Environ Pollut. Author manuscript; available in PMC 2021 June 01.

Published in final edited form as:

Environ Pollut. 2020 June ; 261: 114165. doi:10.1016/j.envpol.2020.114165.

Short- and intermediate- term exposure to NO_2 and mortality: a multi-county analysis in China

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Abstract

Nitrogen dioxide (NO_2) is a well-established traffic emissions tracer and has been associated with multiple adverse health outcomes. Short- and long-term exposure to NO_2 has been studied and is well-documented in existing literature, but information on intermediate-term NO_2 effects and mortality is lacking, despite biological plausibility. We obtained daily NO_2 and mortality data from 42 counties in China from 2013 to 2015. Distributed-lag non-linear models were employed to investigate the relationship between non-accidental mortality and NO_2 up to 30 days before the event, including $PM_{2.5}$, temperature, relative humidity, and holidays as covariates in a random effects meta-analysis pooling county-specific estimates. We repeated the analysis for

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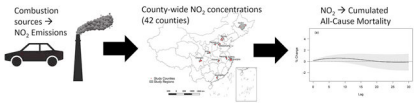
Declaration of interests

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.

cardiovascular- and respiratory-related mortality, and explored sex-stratified associations. Per 10 μg/m^3 increase in NO_2, we estimated a 0.13% (95%CI: 0.03, 0.23%), 0.57% (95%CI: −0.04, 1.18%), and −0.14% (95%CI: −1.63, 1.37%) change in non-accidental mortality for same-day and previous-day NO_2 (lag0–1 cumulated), in the preceding 7 days (lag0–7 cumulated), and in the preceding 30 days (lag0–30 cumulated), respectively. The strongest estimate was observed for respiratory-related mortality in the lag0–30 cumulated effect for women (3.12%; 95%CI: −1.66, 8.13%). We observed a trend of higher effect estimates of intermediate-term NO_2 exposure on respiratory mortality compared to that of the short-term, although the differences were not statistically significant. Our results at longer lags for all-cause and cardiovascular mortality were sensitive to modeling choices. Future work should further investigate intermediate-term air pollution exposure given their potential biological relevance, but in larger scale settings.

Graphical Abstract



Capsule:

Investigating the effects of mortality and NO_2 up to 30 days prior to exposure, we found positive, albeit insignificant, associations with respiratory mortality, with cumulated effect estimates of over 3% increase in mortality per 10 μg/m^3 increase in ambient NO_2.

Keywords

air pollution; nitrogen dioxide; epidemiology; intermediate-term effects; random-effects meta-analysis

INTRODUCTION

Ambient air pollution is one of the leading environmental problems of the 21st century. Air pollutants such as fine particulate matter (particles with aerodynamic diameter ≤ 2.5μm; $PM_{2.5}$) have been consistently linked with increases in mortality and morbidity (Di et al., 2017; Dockery et al., 1993; Guo et al., 2016; Kioumourtzoglou et al., 2015; Pope et al., 2002). The Global Burden Diseases, Injuries, and Risk Factors Study 2015 (GBD 2015) estimated that exposure to $PM_{2.5}$ caused 4.2 million deaths in 2015, representing 7.6% of total global deaths (Cohen et al., 2017). Numerous existing epidemiologic studies have also linked many other air pollutants to increased mortality, including ozone (O_3) (Bell et al., 2005; Di et al., 2017; Jerrett et al., 2009; Kinney and Özkaynak, 1991; Madrigano et al., 2015), sulfur dioxide (SO_2) (Chen et al., 2008; Kan et al., 2010; Katsouyanni et al., 1997), and also nitrogen dioxide (NO_2) (Chiusolo et al., 2017).

NO_2 is a highly reactive gas and a primary pollutant from a variety of sources, especially from the combustion of fossil fuel (Friis, 2012; Koenig, 2000). As such, it is a well-established traffic emissions tracer (Seinfeld and Pandis, 2016; U.S. Environmental Protection Agency (EPA), 2016) and a regularly monitored air pollutant around the world.

Existing studies conducted in North America and Europe have linked both short-term (i.e. daily) and long-term (i.e. annual) exposure to NO_2 to increased mortality (Chiusolo et al., 2017; Crouse et al., 2015; Faustini et al., 2014). In vitro studies have also reported that NO_2 is associated with cellular inflammation, bronchial hyperresponsiveness, and increased risk of infection, particularly in the respiratory system (Koenig, 2000). Furthermore, mechanistic studies have linked intermediate-term (i.e. monthly) exposure to NO_2 and black carbon (a $PM_{2.5}$ component also commonly used as a traffic emissions tracer) to sub-clinical outcomes, such as increased blood pressure and decreased lung function (Lepeule et al., 2014; Zhong et al., 2016). However, despite reported biologic plausibility, there remains a lack of epidemiologic studies exploring the relationship between intermediate-term NO_2 exposure and clinical outcomes.

China's enormous air pollution-related health burden and high greenhouse gas emissions place it squarely at the center of attention of air pollution research. As the world's most populated country with over 1.4 billion people, China is one of the fastest developing countries in the world and also one of the most impacted by the adverse health effects of air pollution (Cohen et al., 2017). While the effects of both short- and long-term exposure to NO_2 have been well-studied in Western countries, there have been relatively few studies on this topic conducted in China. Ambient air pollution levels in China are often orders of magnitudes higher than those in Western countries, and the wider exposure range fills a major gap in existing research, specifically allowing us to better characterize the exposure-response curve at a wider range of NO_2 concentrations. In addition, the distribution of potential modifiers of the NO_2-mortality association across countries, both at the population- and individual-level, are likely very different, greatly limiting the generalizability of studies from developed countries to China. To date, we are aware of only three multi-city studies that investigated the short-term associations of NO_2 on mortality in China (Chen et al., 2018, 2012; Wong et al., 2008). Furthermore, multi-city studies that investigate the association of NO_2 and mortality at longer time-scales in China, such as at the monthly or annual levels, are currently lacking. In fact, NO_2-mortality studies using exposure metrics in between daily and annual exposure are scarce in general, and we are unaware of any studies that investigates intermediate-term NO_2 exposure on cause-specific mortality around the world.

The objective of this study is to investigate the association between mortality and exposure to NO_2 up to 30 days before the event in 42 Chinese counties. Existing studies provide evidence for health effects of air pollution at the monthly scale. For example, 28-day moving average exposure to black carbon, a traffic emissions tracer like NO_2, has been linked increased blood pressure (Zhong et al., 2016). 28-day moving averages of various air pollutants, including black carbon, carbon monoxide, and NO_2, have also been linked to decreased lung function (Lepeule et al., 2014). Given that studies of sub-clinical health endpoints provide biological plausibility for different biological pathways of NO_2 at different timescales (Sandström, 1995; Steinvil et al., 2008; Ward-Caviness et al., 2016), understanding the clinical effects of monthly NO_2 exposure on mortality will not only complete the spectrum of different exposure associations for the NO_2-mortality association but also provide additional China-specific concentration-response functions that can be used to best inform China-specific regulatory actions.

METHODS

Study location

This study utilized data from 42 counties across 11 cities in China from January 2013 to December 2015. These cities include: Beijing (seven counties), Chengdu (six counties), Guangzhou (three counties), Harbin (four counties), Nanjing (three counties), Shanghai (seven counties), Shijiazhuang (four counties), Suzhou (one county), Taiyuan (two counties), Wuhan (three counties), and Xi'an (two counties). The locations of the counties are shown in Figure 1. Note that in China, counties are administrative units similar to districts, and are thus smaller than cities.

Exposure assessment

Hourly concentrations of NO_2 and $PM_{2.5}$ were obtained from the National Air Pollution Monitoring System. We calculated daily average concentrations of NO_2 and $PM_{2.5}$ in each county using the averages of the hourly reported values. In each county, NO_2 and $PM_{2.5}$ concentrations from the monitoring station closest to the county center were assigned as the exposure for that county. If there were no monitoring stations located within a county, then the closest monitoring station from a nearby county was used for exposure assessment for that county. If multiple air monitors were available for a county, the concentrations were averaged. Of the 42 counties in this study, 18 included monitoring stations within the boundaries of the county. Aside from two rural counties (Fangzheng and Yilan), where the closest monitoring station was ~200 km away, the average distance of the closest nearby monitoring station to the centroid of each county that did not have a monitoring station was 24.4 km. Daily average temperature and relative humidity of cities were obtained from the data sharing network of the China Meteorological Bureau, which were then assigned to each county that comprises the city.

Outcome assessment

Daily mortality data for each county were obtained from the Chinese Center for Disease Control and Prevention's Disease Surveillance Point System. The International Classification of Diseases, 10^{th} revision was used to classify non-accidental mortality (A00-R99) and cause-specific mortality for each county, including for cardiovascular disease (I00-I99) and respiratory disease (J00-J99). Mortality counts were also stratified by sex.

Statistical analysis

We employed distributed-lag non-linear models (DLNMs) (Gasparrini, 2014) to investigate the relationship between non-accidental mortality and NO_2 exposure up to 30 days before the event. The distributed lag model framework allows for the adjustment of exposures on other days while still estimating the temporal trend of the association, under the assumption that it varies smoothly as a function of time (Gasparrini, 2014, 2011; Kioumourtzoglou et al., 2019; Zanobetti et al., 2000). Specifically, we utilized overdispersed county-specific Poisson regression models to evaluate the NO_2-mortality relationship. We selected the best fitting model and the appropriate degrees of freedom (*df*) for all non-linear terms included in the model based on quasi-Akaike Information Criterion (qAIC). In the model, we included

smooth functions of calendar time to adjust for seasonality and long-term trends (using natural cubic splines with 4 *df* per year), as well as indicator variables for day of the week. We assessed potential non-linearity in the exposure-response relationships using penalized splines for NO_2. We found no evidence of deviation from linearity, using the qAIC to select the best fitting linear versus non-linear models. Based on this criterion, we adopted a linear exposure-response for the NO_2-mortality relationship and used smoothing functions to model the lag constraint (natural spline, 3 *df*). We controlled for potential confounding bias due to $PM_{2.5}$ linearly, due to weather by including smoothing functions of average temperature (natural spline, 3 *df*) and relative humidity (natural spline, 3 *df*) all as 30-day distributed-lag terms, and from holidays as an indicator variable. We pooled the county-specific model results using a random effects meta-analysis (Gasparrini et al., 2017, 2012). We tested for calendar time *df* from 4 to 7 per year, and for NO_2, $PM_{2.5}$, temperature, and relative humidity, we evaluated various lag constraint structures, including polynomials and natural splines, from 3 to 6 *df*. We then repeated the analysis using both cause-specific (cardiovascular and respiratory) and sex-stratified mortality.

Finally, as a sensitivity analysis we also fit a fixed effects model using information on all counties in the same quasi-Poisson model with county-specific intercepts. We adjusted for the same variables as in the county-specific models. This model assumes the same confounding structure across all counties. However, county-specific DLNMs with 30 lags could become quite unstable, especially if the number of cases in some counties is small, and the fixed effects model using all the available information provides larger stability in the estimates.

All results are presented as percent changes per 10 $\mu g/m^3$ increase in NO_2 concentrations for comparability with other studies. All statistical analyses were performed using the R Statistical Software, version 3.5.1 (Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Table 1 shows the descriptive statistics of the variables used for the daily model. The average daily and monthly NO_2 levels for the study period across all counties were 50.2 $\mu g/m^3$ and 50.6 $\mu g/m^3$, respectively, both of which are below China's current 24-hour regulatory standard of 80 $\mu g/m^3$ (Ministry of Environmental Protection (China), 2012). The correlation between NO_2 and $PM_{2.5}$ in our data was 0.60. On average, there were around 12 non-accidental, 5 cardiovascular, and 2 respiratory deaths per county per day.

Figures 2a, 2b, and 2c show the 30-day lag-specific cumulated mortality effect estimates per 10 $\mu g/m^3$ increase in NO_2 for non-accidental, cardiovascular-, and respiratory-related mortality, respectively. Sex-stratified lag-specific cumulated estimates and lag-specific non-cumulated effect estimates are presented in the supplemental materials (Figures S1–S3). Specifically, we estimated an increase of 0.13% (95%CI: 0.03, 0.23%) in non-accidental mortality for same-day and previous day NO_2 (lag0–1 cumulated), and an overall decrease of 0.14% (95%CI: −1.63, 1.37%) for the lag-specific cumulated effect of NO_2 30-days before the event (lag0–30 cumulated). For cardiovascular mortality, we observed an increase of 0.10% (95%CI: −0.06, 0.25%) for lag0–1 cumulated NO_2, and a decrease of 0.87%

(95%CI: −3.26, 1.58%) for lag0–30 cumulated NO_2. For respiratory mortality, we observed an increase of 0.03% (95%CI: −0.23, 0.30%) for lag0–1 cumulated NO_2, and an increase of 2.13% (95%CI: −1.21, 5.58%) for lag0–30 cumulated NO_2.

In the sex-stratified analyses, effect estimates for women were generally higher than those of men at lag0–1 cumulated and at lag0–30 cumulated (Figure S2 and S3). In women, a 10 $\mu g/m^3$ increase in 30-day cumulated NO_2 resulted in a 0.83% (95%CI: −1.23, 2.93%) increase in non-accidental mortality. In comparison, for men, a 10 $\mu g/m^3$ increase in 30-day cumulated NO_2 resulted in a 1.10% (95%CI: −2.82, 0.65%) decrease in non-accidental mortality. Similar trends were observed for both cardiovascular and respiratory-related mortality, although the confidence intervals overlapped for sex-stratified results (Figure S3). Figure S4 presents the county-specific and pooled cumulated effect estimates for lag0–1, lag0–7, and lag0–30.

In sensitivity analyses we observed that these results were sensitive to modeling choices. Specifically, in the fixed effects analysis we found similar effect estimates at lag0–1 and statistically significant positive cumulated lag0–30 effect estimates (Figure S5). In general, while lag-specific effect estimates from the meta-analysis displayed the same trend, they resulted in attenuated estimates compared to the fixed effects analysis (Figure S6).

DISCUSSION

Using data from 42 counties spanning from northern to southern China, we investigated the association between NO_2 and mortality for up to 30 days exposure before the event. We found increases in non-accidental mortality across China for up to 7 days exposure before the event, as well as higher albeit insignificant effect estimates for respiratory mortality for up to 30 days exposure before the event. To our best knowledge, this is the first study to investigate the association between intermediate-term NO_2 exposure and mortality, and it adds to the already rich database of research looking at similar relationships between short-term NO_2 exposure and mortality (Burnett et al., 2004; Chen et al., 2018, 2012; Chiusolo et al., 2017; Faustini et al., 2014; Wong et al., 2008).

Our results for the estimated effects of short-term NO_2 exposure are smaller in magnitude compared to existing studies conducted in North America and Europe. In their single-pollutant models, Chiusolo and colleagues found a 2.09% (95%CI: 0.96, 3.24%) increase in all-natural mortality, a 2.63% (95%CI: 1.53, 3.75%) increase in cardiac mortality, and a 3.48% (95%CI: 0.75, 6.29%) increase in respiratory mortality per 10 $\mu g/m^3$ increase in NO_2 (Chiusolo et al., 2017). Crouse and colleagues reported a 5.2% (95%CI: 4.5, 5.9%) increase in non-accidental mortality, a 4.1% (95%CI: 2.8, 5.3%) increase in cardiovascular mortality, and a 3.6% (95%CI: 1.2, 6.1%) increase in diseases of the respiratory system per 8.1ppb increase in NO_2 (Crouse et al., 2015). We believe that these smaller effect estimates may be explained by a plateauing exposure-response relationship. A recent study by Burnett et al. found that the long-term $PM_{2.5}$-mortality relationship levels off at higher concentrations of $PM_{2.5}$ (Burnett et al., 2018), and a similar phenomenon may be observed here in NO_2 as well. Please note that this would not contradict our findings of a linear association in the NO_2 concentration range included in our analyses. It is possible that we are only able to

observe the linear portion at the high NO_2 levels of the full non-linear exposure-response curve. In comparison, our results were more similar to those of studies from China. Wong and colleagues using data from three cities in China found a 1.19% (95%CI: 0.71, 1.66%) increase in natural mortality, a 1.32% (95%CI: 0.79, 1.86%) increase in cardiovascular mortality, and a 1.63% (95%CI: 0.62, 2.64%) increase in respiratory mortality per 10 $\mu g/m^3$ increase in NO_2 (Wong et al., 2008). In a more recent paper, Chen and colleagues conducted a nationwide time-series across 272 Chinese cities and found a 0.9% (95%PI: 0.7, 1.1%) increase in non-accidental mortality, a 0.9% (95%PI: 0.7, 1.2%) increase in cardiovascular mortality, and a 1.2% (95%PI: 0.9, 1.5%) increase in respiratory mortality per 10 $\mu g/m^3$ increase in 2-day average concentrations of NO_2 (Chen et al., 2018).

In our sex-stratified analysis, we observed stronger effect estimates in women than in men for lag0–30 cumulated exposure and all-cause mortality, albeit with overlapping confidence intervals. Stronger effect estimates in women have been reported previously in air pollution research (Clougherty, 2010). While the exact reason remains unclear, existing research has linked this disparity to sex differences in toxicity, metabolic rate, and sex steroid hormones (Butter, 2006; Cabello et al., 2015). Additional research is necessary to elucidate the biological mechanisms behind this phenomenon. Nonetheless, these differences in our analyses were not statistically significant and could be due to chance.

As mentioned earlier, to our best knowledge, this is the first study that investigated the association between intermediate-term NO_2 exposure and mortality. Numerous biomarker studies have provided biological plausibility for different biological pathways of NO_2 sub-clinical effects at different timescales (Sandström, 1995; Steinvil et al., 2008; Ward-Caviness et al., 2016). In terms of short-term exposure, one generally accepted mechanism is that air pollution is linked to pulmonary inflammation, which then results in the production of local inflammatory mediators that can then lead to systemic inflammation. As mentioned previously, intermediate-term (e.g. 28-day moving average) exposure to black carbon, a traffic emissions tracer like NO_2, has been linked increased blood pressure (Zhong et al., 2016). 28-day moving averages of various air pollutants, including black carbon, carbon monoxide, and NO_2, have also been linked to decreased lung function (Lepeule et al., 2014). Long-term (e.g. annual) exposure to air pollution, on the other hand, have been linked to DNA damage, epigenetic alterations, and biological aging (Ward-Caviness et al., 2016). For NO_2 specifically, some of the major proposed mechanisms of toxicity include lipid peroxidation in cell membranes and reactions of free radicals on both structural and functional molecules (Sandström, 1995). Depending on the molecules of interest, the time it takes for a reaction to occur may differ drastically. However, despite strong biological plausibility, we did not observe elevated cumulated lag0–30 NO_2 effect estimates for mortality, with the exception of respiratory mortality. Given the reported biological plausibility and the limited evidence for intermediate-term exposures, it is therefore of interest for time-series studies to look at the effect of exposures beyond that of the short- and long-term on clinical outcomes.

Although the effect estimates for short-term exposures are similar in our main and sensitivity analyses, we obtained different results for the cumulated lag0–30 exposures in the random effects meta-analysis vs. the fixed effects analysis. Specifically, we observed null

associations when we ran county-specific models and then pooled in a meta-analysis and significantly positive associations in the fixed effects models. This discrepancy in results could indicate that the assumption of a similar confounding structure across counties in the fixed effects model may not be valid. However, it is also likely that the county-specific DLNMs with 30 lags, especially in some of the smaller counties in our analyses, may not have been stable enough to accommodate the high NO_2 day-to-day autocorrelation. This is evident by the highly sensitive lag structure to the change in *df* observed in our sensitivity analysis. We are therefore not confident in our reported cumulated lag0–30 results and further research in settings with longer study periods is warranted. Nonetheless, we observed good agreement in the cumulated lag0–1 and lag0–7 effect estimates in both the main and sensitivity analyses.

Ambient air quality has been regulated in China since 1982, and NO_2 is one of the originally regulated air pollutants. Since then, the standards have been revised three times, with the most recent standards released in 2012 (GB 3095–2012) that took effect in 2016. Under current standards, annual, 24-hour, and hourly limits for NO_2 are set at 40, 80, and 200 $\mu g/m^3$, respectively (Ministry of Environmental Protection (China), 2012). In addition to the ambient air quality standards, China's twelfth Five-Year Plan (2011–2015) specifically set a goal of reducing national emissions of nitrogen oxides (NO_x) by 10% relative to 2010 levels (de Foy et al., 2016). The most recent thirteenth Five-Year Plan (2016–2020) further tightened air quality regulations, requiring prefecture-level and larger cities to have an air quality index of 100 or below in at least 80% of the days per year (State Council of the People's Republic of China, 2016). Combined with China's concerted effort in reducing traffic in major urban areas through road space rationing (such as the even-odd license plate policy) and the drastic expansion of the public transportation system, NO_x reduction will remain one of China's top priorities over the next several years. We recommend that future policies should formally incorporate the health effects of different time-metrics of air pollution exposure as considered criteria. Specifically, given the current lack of existing standards for NO_2 levels between daily and annual time-metrics, we believe that it is important to consider additional NO_2 standards at more intermediate timescales, such as the monthly level. It is possible that NO_2 concentrations slightly lower than the daily standard—i.e., in compliance with existing standards—are observed on multiple days within a month. However, neither the daily nor the annual standards would address this issue, highlighting the need to also consider intermediate-term standards.

Our study has numerous strengths. First, this is the first study on the intermediate-term associations of NO_2 on mortality to date. Second, our dataset has coverage over 42 counties in 11 cities from northern to southern China, and provides a representative sample of China's urban population in some of its most densely populated cities. Third, the use of DLNMs allows us to simultaneously evaluate short-term and longer-term NO_2-mortality associations. Compared to a monthly-only model (i.e. average monthly exposure, aggregated monthly outcomes), the distributed lag models allow us to be more confident that the estimated intermediate-term effect is actually an intermediate-term effect, and not just an aggregate of short-term effects or an indicator for long-term effects. Lastly, this work coincides with priorities in China's recent Five-Year Plans, and adds to the growing body of literature that policy makers can reference when formulating future regulations.

Our study also has a few limitations. First, although the existing dataset provides a representative spatial coverage of China, it is lacking in temporal coverage and only includes the time period of 2013 to 2015. Although this relatively short time period does not provide us with enough statistical power to explore longer-term associations of NO_2 (e.g. annual exposures), the already large sample size allows us to be confident with all of our existing conclusions. Second, NO_2 exposure data are obtained from the National Air Pollution Monitoring System, which provides hourly NO_2 concentrations for each county and may be prone to measurement error since point estimates from monitors are used to represent county-level ambient concentrations. Third, we only had three years of data in each county, potentially limiting our power for the county-specific DLNMs and the stability of our results at longer lags. Lastly, there are a number of counties that did not have monitoring stations within its vicinity, and the closest monitoring station from a nearby county had to be used as the exposure assignment, which is another potential source of measurement error. However, only two counties were assigned monitors that were ~200 km away—their exclusion from the meta-analysis did not impact our results—and the centroids of the remaining 16 counties without a monitoring station were on average < 25 km away from the assigned monitoring station. A sensitivity analysis comparing the meta-analysis of all counties versus the meta-analysis of a subset of counties that only contained monitoring stations within its vicinity did not show significant differences. There is no reason, furthermore, to believe that the above errors would be differential, and non-differential exposure measurement error in time series studies has been shown to bias estimates towards the null (Dominici et al., 2000; Zeger et al., 2000), making the results of our study more likely to be conservative.

CONCLUSION

While China has rapidly expanded the number of air monitoring stations over the past few years, relatively few monitors exist in western China, which is traditionally less populated and less urbanized than eastern China. Most existing air pollution epidemiological studies in China are therefore better representations of urban China rather than China as a whole. As the number of air monitors in China continue to increase or predictions from highly spatiotemporally resolved NO_2 models become available, more work needs to explore the air pollution-mortality relationship in understudied regions, such as Qinghai province, Xinjiang Autonomous Region, and Tibet Autonomous Region. As this is a county-level analysis, future studies in China should also explore intermediate- and long-term effects of air pollution on mortality and morbidity at the individual level, preferably using dedicated air pollution cohorts.

In conclusion, we investigated the association between mortality and NO_2 exposure up to 30 days before the event and found significant cumulated associations up to seven days for non-accidental mortality, as well as an increase (albeit insignificant) of over 3% in respiratory mortality per 10 $\mu g/m^3$ increase in ambient NO_2 for cumulated lag0–30. Our all-cause and cardiovascular mortality cumulated lag0–30 effect estimates, however, were sensitive to modeling choices. Given the above and the established biological relevance, we believe that there is still a need to investigate intermediate-term exposure to air pollutants using data available for longer periods as these become available, and we would recommend

sufficiently powered studies that are interested in intermediate-term health effects to further explore this topic.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This study was partially supported by the National Institutes of Health Institutional Research T32 Training Grant (T32 ES023770), the National Institute of Environmental Health Sciences (NIEHS) Individual Fellowship Grant (F31 ES029372) and Center Core Grant (P30 ES009089), the Columbia Global Policy Initiative Faculty Grant, and the Columbia Weatherhead East Asian Institute Sasakawa Young Leaders Fellowship Fund.

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Highlights

- We found non-linear NO_2-mortality associations across lag time
- Effect estimates are generally stronger in women than in men
- Observed short-term effect estimates were robust to modeling choices
- Cumulated intermediate-term results were sensitive to modeling choices

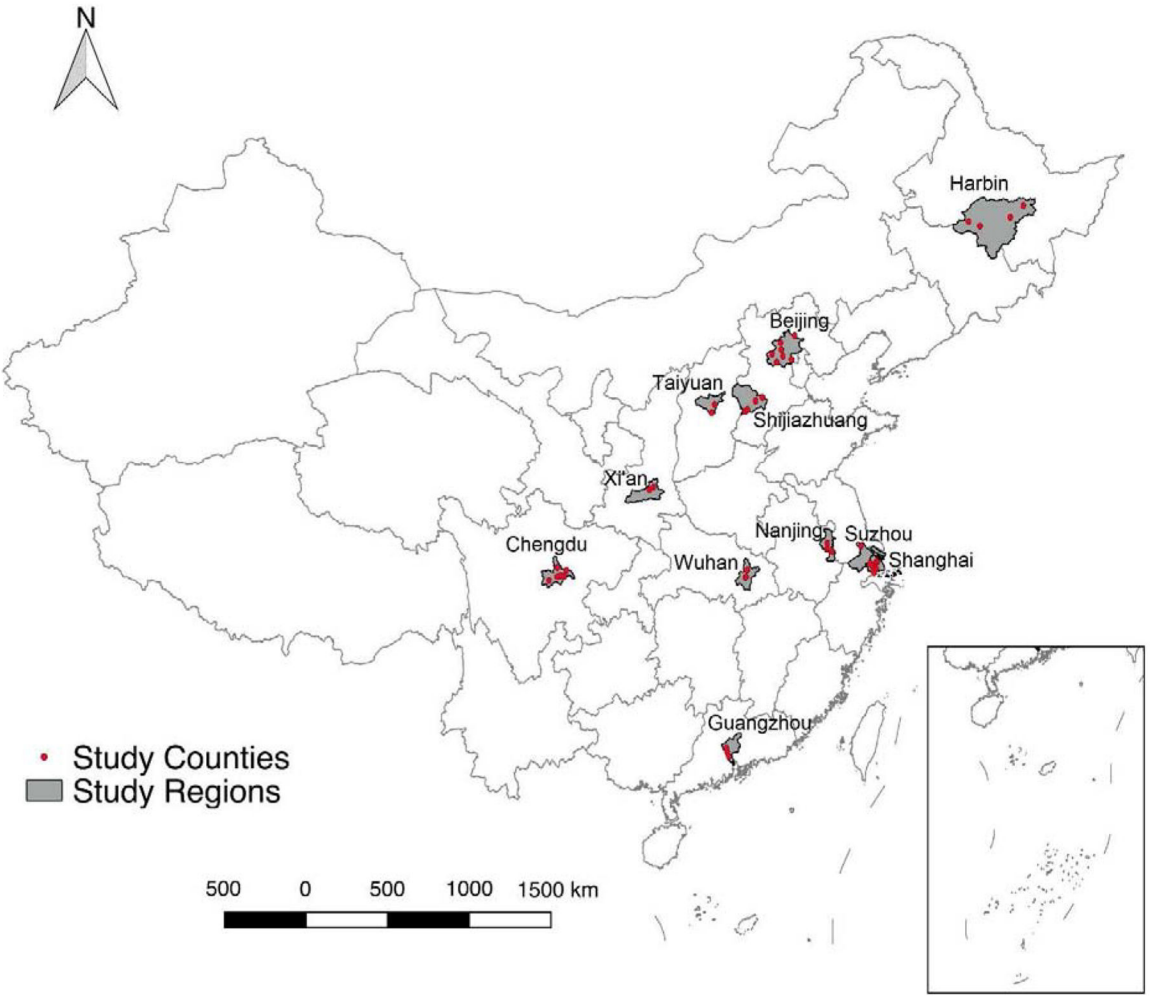

Figure 1.
Geographic distribution of study counties.

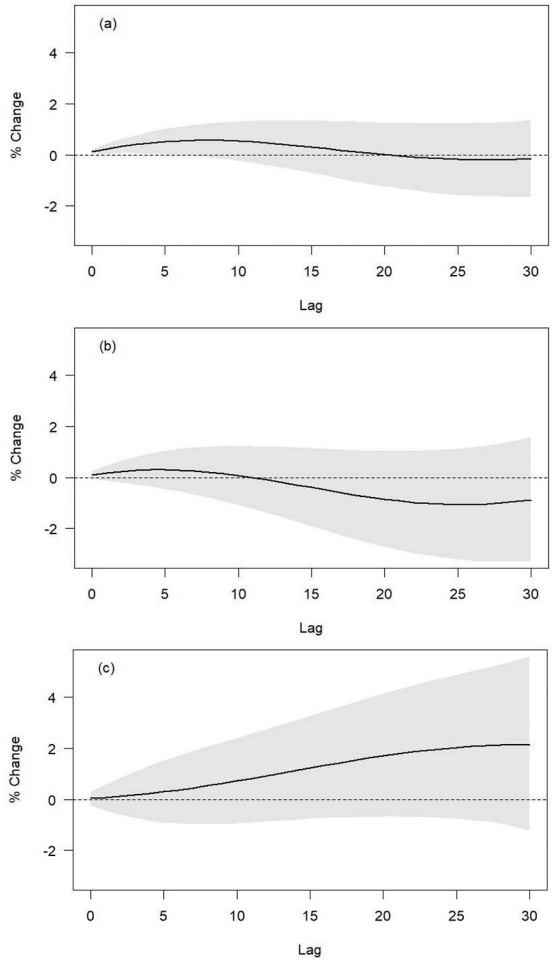

Figure 2.

30-day lag-specific cumulated effect estimates per 10 μg/m^3 NO_2 increase for a) non-accidental mortality; b) cardiovascular mortality; and c) respiratory mortality.

Table 1.

Pollutant, confounder, and outcome descriptive statistics (2013–2015; N = 42,248 days)

Variable	Mean	Min	25%	50%	75%	Max
NO_2 (μg/m^3)	50.2	0.8	32.0	46.0	63.4	327.8
$PM_{2.5}$ (μg/m^3)	73.1	3.1	33.4	55.1	92.0	1009.6
Mean Temperature (°C)	15.3	−25.7	7.4	17.6	23.9	35.5
Relative Humidity (%)	66.8	2.1	56.0	71.0	81.0	100.0
Daily Mortality Counts						
Non-accidental	11.5	0.0	6.0	10.0	15.0	53.0
Cardiovascular	5.0	0.0	3.0	4.0	7.0	36.0
Respiratory	1.5	0.0	0.0	1.0	2.0	19.0