LETTER

Long-term exposures to ambient PM$_1$ and NO$_2$ pollution in relation to mild cognitive impairment of male veterans in China

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Abstract

Mild cognitive impairment (MCI) is an intermediate stage of cognitive decline between normal ageing and dementia or Alzheimer's disease in the elderly. However, evidence is very limited in China for the association between air pollution and MCI. This study aims to examine the associations of long-term exposure to air pollution and MCI, using data from the Chinese Veteran Clinical Research Platform. A national investigation on mental health of veterans was conducted in 277 veteran communities in 18 cities across China. In total, 1,861 MCI cases and 3,188 controls were randomly selected using a stratified cluster sampling strategy from December 2009 to December 2011. Participants' cognitive function was first assessed using the Mini Mental State Examination and the Montreal Cognitive Assessment in the Chinese version, and then further confirmed by clinical examination. Participants' mean exposures to PM$_1$ (particulate matter with aerodynamic diameter $\leq 1 \mu m$) and NO$_2$ (nitrogen dioxide) during the 3 years before the investigation were estimated using satellite remote sensing data, meteorological variables and land use information. The association between historical exposure to air pollution and MCI was examined using Logistic regression. After controlling for individual-level and regional-level confounders, we found historical exposures to PM$_1$ and NO$_2$ significantly increased the risk of MCI. The odds ratios (ORs associated with per 10 $\mu g m^{-3}$ increase in air pollution) and 95% confidence intervals for PM$_1$ and NO$_2$ were 1.08 (1.04, 1.13) and 1.07 (1.02, 1.13), respectively. In the multi-pollutant models, higher OR for PM$_1$ while lower OR for NO$_2$ were observed compared to single-pollutant models. High levels of PM$_1$ and NO$_2$ pollution significantly increased the risk of cognitive decline among male veterans in China. Given the causal air pollution-MCI relationship, good air quality may help to reduce the burden of mental disorders among elderly veterans in China.
1. Introduction

Mild cognitive impairment (MCI) is an intermediate stage of cognitive decline between normal ageing and dementia or Alzheimer’s disease in the elderly [1]. The prevalence of MCI is 10%–20% among elderly adults (aged 65 years and older) [2], and over 50% of MCI cases develop into dementia within 5 years [3]. A wide range of factors have been recognized to increase the risk of MCI, including demographic characteristics (e.g. gender and age), vascular factors (e.g. hypertension) and psychiatric factors (e.g. depression) [4, 5]. Apart from these risk factors, recent studies have revealed the association between exposure to ambient air pollution and cognitive function in elderly people [6]. For example, a study conducted in the U.S. reported long-term exposures to particulate matter (PM) pollution was significantly in relation to cognitive decline in elderly women [7–9]. Another study in Germany also stated long-term exposure to traffic-related air pollution was associated with the impaired cognitive function in elderly women [10].

As a country with the largest population in the world, China bears huge burdens of ageing-related diseases [11, 12]. The prevalence of MCI in China was estimated to be 14.7% among elderly population (aged 60 years and older) [13]. The burden of MCI in China is expected to increase substantially in the following decades, due to the increasing trend of elderly population [14]. Although numerous studies have examined the health effects of air pollution [15, 16], few studies have been done in China focused on the association between exposure to air pollution and MCI [17, 18]. Characteristics of PM are related to its health effects, including chemical composition, total mass and size fraction [19]. In contrast to the extensively studied pollutants including PM2.5 and PM10 (particulate matter with aerodynamic diameter \( \leq 2.5 \, \mu m \) and \( \leq 10 \, \mu m \), respectively), the health effects of smaller particles (e.g. PM1 (particulate matter with aerodynamic diameter \( \leq 1 \, \mu m \))) are not clear. Due to its smaller particle size, it can be inferred that PM1 is more harmful than PM2.5 and more strongly associated with some health outcomes, which might be due to its higher efficiency of pulmonary deposition, easier penetration into the vascular system, higher surface to volume ratio and more toxic components adhered [20].

The Chinese veterans are a stable population that live in veteran communities. As they have optimal health management systems and long-term and detailed medical records, it facilitates studies on the associations between environmental factors and mental health [21]. In this study, 5,049 veterans from 277 veteran communities across China were investigated during 2009–2011. Participants’ historical exposures to PM1 and NO2 (nitrogen dioxide) were estimated using random forests models, satellite remote sensing data, and meteorological and land use information. The associations between long-term exposures to PM1 and NO2 and MCI were examined using Logistic regression.

2. Methods

2.1. Study population

Data on mental health status of veterans across China were obtained from the Chinese Veteran Clinical Research (CVCR) Platform [22]. This platform was developed by Chinese People’s Liberation Army Hospital and veterans’ hospitals that aimed to study on health status of veterans in China. Details of CVCR Platform were previously reported [21, 23]. In brief, we selected 18 cities across China as the members included in the CVCR Platform, according to the city size and economic status. They were four first-tier cities, five second-tier cities and one third-tier city in Eastern China, and eight second-tier cities in Central and Western China. For cities with more veteran communities, the sample size was 500–1000, while for cities with fewer veteran communities, the sample size was 100–300. For each selected city, veteran communities were selected according the sample size and demographic characteristics of the participants (e.g. age and educational attainment) to improve the representativeness of the sampling. In each selected veteran community, all eligible veterans were investigated. As a result of it, participants from 277 veteran communities in 18 cities were investigated, accounting for 24.36% of all veteran communities across China (figure 1). Eligible participants were veterans who met the inclusion criteria as follows: (a) aged \( \geq 60 \) years; (b) worked in the army before retirement; (c) have lived in the veteran communities for more than one month; (d) were under the management of the veteran communities and agreed to participate in CVCR Platform. Those were not included in this study who failed to meet any of the inclusion criteria. This study only included male veterans, as female veterans were very few in China and their sample size is not comparable to male veterans in this study.

2.2. Data collection and diagnosis of MCI

A two-phase investigation was performed in each veteran community for data collection and diagnosis of MCI from December 2009 to December 2011. In the first phase, participants were interviewed by trained investigators (medical staff). A standard questionnaire was used to collect information on demographic characteristics, behavioural factors and self-reported health status. If the participants were unable to respond, their caregiver or relatives were alternatively interviewed with informed consent. Disease history was extracted from medical records by research staff. Participants’ cognitive function were assessed using the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) in
Figure 1. Locations of all veteran communities across China in this study.

the Chinese version [24, 25]. For illiterate participants and those with 1–6 years and ≥7 years of educational attainment, the cut-off scores of MMSE were 20, 23 and 27, respectively. The cut-off score of MoCA was 26. Details of the cut-off scores of MMSE and MoCA were previously reported [26]. In the second phase, all participants with positive results (MMSE and MoCA scores lower than the cut-off values) in the first phase screening were further confirmed by a comprehensive neuropsychological evaluation and clinical examination including physical examination and neuroimaging scan. Based on the information collected in this two-phase investigation, the MCI cases were finally diagnosed according to recommendations from the National Institute on Ageing-Alzheimer’s Association workgroups [27].

Data on covariates were also collected, including age, educational years (<5, 5–10 or ≥10), regular physical activity (yes or not), smoking (current smoker, ex-smoker or non-smoker) and drinking (>2 times/week, ≤2 times/week, quit or never). Disease history was extracted from medical records by research staff, including hypertension, diabetes, stroke, coronary heart disease and depression.

2.3. Exposure assessment

Based on our previous works [28, 29], participants’ historical exposures to PM$_1$ and NO$_2$ were estimated using a satellite-based random forests approach and a wide range of spatial and temporal predictors, including satellite remote sensing data, meteorological conditions, land use information and day of the year. Daily ground measurements of PM$_1$ and NO$_2$ were obtained from China Atmosphere Watch Network and China National Environmental Monitoring Center, respectively. Satellite-derived moderate resolution imaging spectroradiometer (MODIS) AOD (aerosol optical depths) data (collection 6) and OMI (Ozone Monitoring Instrument) data (daily level-3 nitrogen dioxide product) were downloaded to estimate daily concentrations of PM$_1$ and NO$_2$ across China, respectively. First, based on ground measurements of PM$_1$ and NO$_2$, random forests models were developed as follows:

$$\text{Surface PM}_1 = F(AOD, \text{TEMP}, \text{WS}, \text{PRS}, \text{PREC}, \text{RHU}, \text{SRA}, \text{NDVI}, \text{Elev}, \text{Urban, DOY})$$

$$\text{Surface NO}_2 = F(\text{OMI, TEMP, WS, PRS, PREC, RHU, SRA, NDVI, Elev, Urban, DOY})$$

where surface PM$_1$ and surface NO$_2$ are daily mean levels of ground measurements at each site; AOD and OMI are satellite-derived daily AOD and OMI values; TEMP, RH, BP and WS are daily mean temperature, relative humidity, barometric pressure and wind speed, respectively; normalized difference vegetation index (NDVI) is the monthly average NDVI value; Elev is the elevation of each site. Urban is the percentage of urban cover with a buffer radius of 10 km; DOY is day of the year.

Then, predictive abilities of random forest models were examined using a 10-fold cross-validation
Table 1. Demographic characteristics of MCI cases and controls.

| Factors                                | MCI cases | Controls |
|----------------------------------------|-----------|----------|
|                                        | n        | %        | n        | %        |
| Age (mean ± SD)                         | 82.7     | 3.8      | 81       | 4.8      |
| Educational years                       |          |          |          |          |
| <5 years                                | 459      | 25%      | 551      | 17%      |
| 5–10 years                              | 836      | 45%      | 1449     | 45%      |
| ⩾10 years                               | 566      | 30%      | 1188     | 37%      |
| Regular physical activity               |          |          |          |          |
| Yes                                    | 1620     | 87%      | 2934     | 92%      |
| No                                     | 241      | 13%      | 254      | 8%       |
| Regular social activity                 |          |          |          |          |
| Yes                                    | 760      | 41%      | 1302     | 41%      |
| No                                     | 1101     | 59%      | 1886     | 59%      |
| Smoking status                          |          |          |          |          |
| Current smoker                          | 139      | 7%       | 275      | 9%       |
| Ex-smoker                               | 706      | 38%      | 1011     | 32%      |
| Non-smoker                              | 1016     | 55%      | 1902     | 60%      |
| Drinking                                |          |          |          |          |
| >2 times/week                           | 143      | 8%       | 235      | 7%       |
| ≤2 times/week                           | 454      | 24%      | 849      | 27%      |
| Quit                                    | 344      | 18%      | 443      | 14%      |
| Never                                   | 920      | 49%      | 1661     | 52%      |
| Hypertension                            |          |          |          |          |
| Yes                                    | 1282     | 69%      | 2111     | 66%      |
| No                                     | 579      | 31%      | 1077     | 34%      |
| Diabetes                                |          |          |          |          |
| Yes                                    | 529      | 28%      | 791      | 25%      |
| No                                     | 1332     | 72%      | 2397     | 75%      |
| Stroke                                  |          |          |          |          |
| Yes                                    | 407      | 22%      | 455      | 14%      |
| No                                     | 1454     | 78%      | 2733     | 86%      |
| Coronary heart disease                  |          |          |          |          |
| Yes                                    | 1367     | 73%      | 2150     | 67%      |
| No                                     | 494      | 27%      | 1038     | 33%      |
| Historical electromagnetic field exposure|          |          |          |          |
| Yes                                    | 132      | 7%       | 232      | 7%       |
| No                                     | 1729     | 93%      | 2956     | 93%      |
| Depression                              |          |          |          |          |
| Yes                                    | 60       | 3%       | 45       | 1%       |
| No                                     | 1801     | 97%      | 3143     | 99%      |
| Region                                  |          |          |          |          |
| Eastern China                           | 1452     | 78%      | 2312     | 73%      |
| Central China                           | 139      | 7%       | 337      | 11%      |
| Western China                           | 270      | 15%      | 539      | 17%      |
| Total                                   | 1861     | 100%     | 3188     | 100%     |

approach, which showed that annual averages of estimated PM$_1$ and NO$_2$ explained 75% and 72% of variabilities of ground measurement, respectively. Finally, the validated models were used to predict daily concentrations of PM$_1$ and NO$_2$ in a grid covering the entire China at a spatial resolution of 0.1 degree (≈10 km) during 2006–2011. More details of data processing, model development and validation are shown in the supplementary material (available online at stacks.iop.org/ERL/16/025013/mmedia).

Individual’s exposures to PM$_1$ and NO$_2$ during the 3 years before diagnosis of MCI were extracted from the estimated grid data according to the location of each community (longitude and latitude) and the date of diagnosis [30].

2.4. Statistical analyses
Logistic regression was used to examine the association between exposure to air pollution and MCI. Firstly, a crude model was developed with only mean exposure to PM$_1$ or NO$_2$ as the independent variable. Then, an adjusted model was developed based on the crude model by controlling for potential confounders. According to previous studies on air pollution and MCI [6, 7], a range of potential confounders were considered including age, educational years, physical and social activities, smoking and drinking. History of hypertension, diabetes, stroke, coronary heart disease and depression were also controlled in the adjusted model, as they are risk factors of MCI and associated with long-term exposure to air.
Table 2. Participants’ mean exposures to air pollutants ($\mu g m^{-3}$) during the 3 years prior to the investigation.

| Pollutants | Quartiles | 
|------------|-----------|
|            | Mean      | Min  | 25%  | 50%  | 75%  | Max  |
| MCI cases  |           |      |      |      |      |      |
| PM$_1$     | 54.1      | 30.0 | 43.3 | 52.6 | 64.4 | 76.9 |
| NO$_2$     | 43.6      | 19.1 | 33.6 | 47.0 | 50.1 | 61.0 |
| Controls   |           |      |      |      |      |      |
| PM$_1$     | 52.2      | 23.7 | 40.0 | 49.1 | 64.2 | 76.9 |
| NO$_2$     | 42.5      | 19.1 | 34.9 | 42.2 | 49.6 | 61.0 |
| All participants | | |      |      |      |      |
| PM$_1$     | 52.9      | 23.7 | 40.7 | 50.5 | 64.4 | 76.9 |
| NO$_2$     | 42.9      | 19.1 | 34.7 | 45.3 | 49.8 | 61.0 |

Figure 2. Odds ratios of MCI (95% CIs) associated with per ten units increase in air pollutant in different models.

All statistical analyses were performed with R software (version 3.3.3, R Development Core Team 2015).

3. Results

In total, 1,861 male MCI cases and 3,188 controls with no any mental disorder were identified in this study. Demographic characteristics of cases and controls are shown in table 1. Most of participants (>70%) were from Eastern China. Male veteran cases of MCI who had less educational years and did less physical activities were more likely to develop MCI than veteran controls. In addition, veterans with stroke, coronary heart disease or depression were more probable to had MCI. Other factors were distributed evenly among cases and controls.

Participants’ mean exposures to PM$_1$ and NO$_2$ during the 3 years before diagnosis of MCI are summarized in table 2. MCI cases showed higher levels of exposures to air pollutants than the controls. Cases’ mean exposures to PM$_1$ and NO$_2$ were 54.1 $\mu g m^{-3}$ and 43.6 $\mu g m^{-3}$, respectively, while
Table 3. ORs and 95% CIs of MCI associated with PM$_1$ and NO$_2$ in stratified analyses.

| Factors                  | PM$_1$          | NO$_2$          |
|--------------------------|-----------------|-----------------|
| Age                      |                 |                 |
| <85                      | 1.08 (1.02, 1.13) | 1.07 (1.01, 1.14) |
| ≥85                      | 1.09 (1.01, 1.19) | 1.08 (0.97, 1.20) |
| Educational years        |                 |                 |
| <10                      | 1.10 (1.05, 1.16) | 1.11 (1.04, 1.18) |
| ≥10                      | 1.04 (0.96, 1.13) | 1.00 (0.91, 1.11) |
| Smoking                  |                 |                 |
| Smoker                   | 1.08 (1.01, 1.15) | 1.06 (0.98, 1.14) |
| Non-smoker               | 1.08 (1.02, 1.15) | 1.08 (1.01, 1.16) |
| Drinking                 |                 |                 |
| Drink every week         | 1.05 (0.97, 1.13) | 1.03 (0.94, 1.13) |
| Quit or Never drink      | 1.10 (1.05, 1.16) | 1.09 (1.02, 1.16) |
| Regular physical activity|                 |                 |
| Yes                      | 1.08 (1.03, 1.13) | 1.07 (1.01, 1.13) |
| No                       | 1.08 (0.95, 1.23) | 1.09 (0.93, 1.28) |
| Regular social activity  |                 |                 |
| Yes                      | 0.95 (0.88, 1.02) | 0.94 (0.87, 1.02) |
| No                       | 1.17 (1.11, 1.24) | 1.16 (1.09, 1.25) |

Figure 3. The results of adjusted models using different exposure periods.

The results for controls were 52.2 μg m$^{-3}$ and 42.5 μg m$^{-3}$, respectively. Participants’ mean exposures to PM$_1$ and NO$_2$ during the 1 year or 2 years before the investigation are shown in tables S2–S3 in the supplementary material. The mean levels of exposures to PM$_1$ and NO$_2$ were highly correlated ($r = 0.87$, $p < 0.01$).

The results of crude, adjusted and multi-pollutant models are present in figure 2. Illustrated by the crude models, exposures to ambient PM$_1$ and NO$_2$ pollution significantly increased the risk of MCI and the ORs (95% CI) were 1.10 (1.06, 1.15) and 1.09 (1.04, 1.15), respectively. After controlling for potential confounders (all variables shown in table 1), the ORs (95% CI) for PM$_1$ and NO$_2$ were 1.08 (1.04, 1.13) and 1.07 (1.02, 1.13), respectively. In the multi-pollutant models, higher OR for PM$_1$ while lower OR for NO$_2$ were observed compared to single-pollutant models.

The results of stratified analyses are shown in table 3. Higher ORs of PM$_1$ and NO$_2$ were observed among veterans who had less educational years and less alcohol consumption, and those who did fewer social activities. The results of sensitivity analyses are shown in figure 3. The significant associations between MCI and air pollution were also observed during other exposure periods prior to the investigation including single year and two year average exposures. It showed our results were robust to different exposure periods.
4. Discussion

In this study, mental health status of male veterans was investigated in 18 cities in China and their past exposures to PM$_{1}$ and NO$_{2}$ pollution were estimated using satellite remote sensing data and a random forests approach. The relationships between ambient air pollution and cognitive function of male veterans were examined. According to our study, historical exposures to PM$_{1}$ and NO$_{2}$ pollutant significantly increased the risk of MCI. To the best of our knowledge, this is the first study on ambient pollution and cognitive function in elderly population in China. Our study population are male elderly veterans in China. The health information of veterans is well managed and recorded, which facilitates studies on patterns of chronic disease and their associations with environmental factors. The veterans in this study have no mobility, and their socioeconomic factors are more comparable than the general population, which may reduce the confounding effects of these factors on the results. The findings of this study can provide valuable information for multidisciplinary studies based on the CVCR platform in the future.

Currently most of the studies in China on health effects of air pollution are focused on cardiovascular and respiratory diseases and birth outcomes [34–36], but very few studies have ever examined mental health outcomes. On the other hand, compared to the short-term effects, the long-term health effects of air pollution in China is less known due to unavailability of long-term ground monitoring data and health data [37]. Some cohort studies in Europe and North American have examine the long-term health effects of air pollution on health outcomes (mortality, cardiovascular disease and cancer) [38–40], however, those findings may not directly apply to China, considering the differences in characteristics of air pollutants, population and environment.

Weuve et al [7] found in the U.S. that long-term exposures to high levels of PM$_{2.5}$ and PM$_{2.5-10}$ (particulate matter with aerodynamic diameter 2.5–10 $\mu$m) were significantly associated with 0.18 and 0.2 global scores of cognitive decline, respectively. Tzivian et al [6] also reported exposure to PM$_{2.5}$ significantly increased the risk of MCI with the IQR (interquartile range increase) OR and 95% CI of 1.16 (1.05, 1.27). Different from those studies, our study is focused on cognitive function among male veterans, which is a susceptible population to mental disorders. Veterans may experience high stress during their military service and they are vulnerable to some mental health problems [41, 42]. Veterans may also occupationally expose to electromagnetic field due to working with military facilities, which is a known risk factor of mental disorders [43]. In addition, our study examined the association between PM$_{1}$ pollution and MCI. Numerous studies revealed the adverse health effects of PM$_{2.5}$, however little is known its specific size fractions [20, 44]. Thus, our study provides valuable information on health effects of air pollution on mental health in developing countries and indicates a research perspective on smaller particles.

Although some studies indicated components of air pollutants can reach human brain and have impacts on central nervous system disease, the mechanism and pathway have not been thoroughly studied [45]. There are several potential biological mechanisms for the air pollution-MCI association. First, the PM induced systemic inflammation have impacts on blood-brain barrier, which results in chronic oxidative stress involving neural-immune interaction [10]. Secondly, study indicated inhalation of air pollutants caused changes of olfactory bulb pathologically and these changes were linked with progress of Alzheimer’s disease [46]. Finally, long-term exposure to air pollution is associated with a wide range of health outcomes and some of them are established risk factors of MCI, including hypertension, stroke and diabetes [47–49]. Smoking and drinking are known risk factors of cognitive decline in the elderly [50, 51]. In our stratified analysis, higher ORs were observed among non-drinkers than drinkers. This may due to competing risks of drinking and air pollution and selection bias [52].

MCI represents the early stage of dementia and Alzheimer disease [53]. Mental disorder among elderly population, e.g. dementia, has been recognized as a major problem of public health since decades ago [54], especially in China with the huge and increasing ageing population. Currently, China is experiencing almost the worst air pollution in the world, as a downside of rapid economic development and urbanization [37]. PM$_{1}$ originates from either direct emissions during combustion process or from formation of particles in the air from gaseous precursors [55, 56]. NO$_{2}$ is mainly emitted from combustion related sources including traffic and industry emissions [57]. Results of Source appointment studies showed that coal and combustion, secondary aerosol and crustal sources were main contributors to PM$_{1}$ [58], and NO$_{2}$ were mainly attributed to transportation fuels, fossil fuel burning in power plants, and industrial facilities [39]. Considering that both ambient PM$_{1}$ and NO$_{2}$ pollution are mainly from combustion related sources, more effective policies should be made to govern transportation industry development in urban China. Given the causal air pollution-MCI association, improving air quality may help with better cognitive function among elderly population and further reduce the burden of mental disorders in China. Moreover, evidence for adverse health effects of PM$_{1}$ is limited. No guidelines of PM$_{1}$ have been made in China or elsewhere in the world. In future, more studies should explore the short-term and long-term association between PM$_{1}$ and various health outcomes. These studies will provide valuable
information to make guidelines and standards for curbing PM$_1$ pollution.

Several limitations of our study should be notified. Previous study reported body mass index (BMI) in midlife was in relation to cognitive decline in late life [60]. However, accurate information on participants’ BMI in midlife was not available, as they were over 60 years old when investigated. Additionally, there are two types of MCI, amnestic and nonamnestic [1]. As we have no access to the clinical information regarding subtypes of MCI in this study, it is not clear whether air pollution showed different effects on these two types of MCI and more studies are needed focusing this issue in future. Finally, the exact disease onset date of each MCI case was not available in our study. This information will help improve the accuracy of exposure assessment.

5. Conclusion

In our study, we found higher levels of PM$_1$ and NO$_2$ pollution were associated with increased risk of cognitive decline among male veterans in China. Currently, evidence for the association between air pollution and mental health is very limited in China. More studies should explore the long-term health effects of air pollution, especially for smaller particles. If causal relationship between air pollution and cognitive decline exists, tough action and effective policy curbing air pollution will reduce the burden of mental disorders among elderly Chinese.

Data availability statement

All data that support the findings of this study are included within the article (and any supplementary files).

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