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Impact of air pollution exposure on the risk of Alzheimer's disease in China: A community-based cohort study

Fan He[1], Jie Tang[2,3], Tao Zhang[1], Junfen Lin[1], Fudong Li[1], Xue Gu[1], Anthony Chen[4], Alan Nevill[2], Ruoling Chen[2]

[1] Zhejiang Provincial Center for Disease Control and Prevention, Hangzhou, Zhejiang, China

[2] Faculty of Education, Health and Wellbeing, University of Wolverhampton, UK

[3] Department of Preventive Medicine, School of Public Health, Guangzhou Medical University, Guangzhou, China

[4] Institute of Epidemiology and Health Care, University College London, UK

Correspondence: Professor Ruoling Chen, Faculty of Education, Health and Wellbeing, University of Wolverhampton, Wolverhampton, WV1 1DT, UK. T: +44 (0)1902 328622, F: +44 (0)1902 321161, E: r.chen@wlv.ac.uk

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ABSTRACT

Alzheimer's disease (AD) is the most common type of dementia. Impact of air pollution (AP) on the risk of AD is unclear. It is unknown which air pollutants are independently associated with AD and whether fish consumption mitigated the association. We carried out a community-based cohort of 6115 participants aged ≥60 years in China to examine the association of $PM_{2.5}$, PM_{10}, CO, NO_2, SO_2 and O_3 exposure with AD, and differences in the association between people with low and high consumption of fish. The participants were randomly recruited from six counties in Zhejiang province for health survey to document socio-demographic and disease risk factors in 2014, and were followed up to diagnose AD in 2019. A total of 986 cohort members were diagnosed with AD. Based on the daily mean air pollutants monitored in 2013-2015 in the counties, participants were divided into low, middle and high AP exposure groups for subsequent analysis. The multiple adjusted odds ratio (OR) of AD in participants living with the middle and high levels of $PM_{2.5}$ exposure versus the low exposure were 1.50 (95% CI 0.90-2.50) and 3.92 (2.09-7.37). The increased ORs were also with PM_{10} (1.74, 0.65-4.64; 3.00, 1.22-7.41) and CO (2.86, 1.32-6.20; 1.19, 0.45-3.18), but not with NO_2 (0.63, 0.17-2.27; 0.95, 0.28-3.19), SO_2 (0.44, 0.19-1.001; 1.21, 0.56-2.62), and O_3 (0.38, 0.20-0.74; 0.50, 0.21-1.21). There were no significant interaction effects of AP with fish consumption on AD. However, participants with low consumption of fish appeared to have higher ORs in $PM_{2.5}$ exposure (1.80, 1.39-2.33; 5.18, 3.93-6.82) than those high consumption (1.38, 0.78-2.47; 2.89, 1.50-5.59). Our findings of $PM_{2.5}$ and PM_{10} exposure significantly increased the risk of AD and the potential mitigating effect of fish consumption on the association provide evidence for developing effective strategies for AD reduction and air pollution control.

Keywords: Air pollutants; Alzheimer's disease; Fish intake; Cohort study; China

Introduction

Ambient air pollution (AP) is an important global environmental concern (WHO, 2019), and has been recognized as a major risk factor for many chronic diseases (Yusuf et al., 2020), contributing to one in nine deaths worldwide (Cohen et al., 2017). Exposure to AP increases the risk of cardiovascular disease (Shah et al. 2013), stroke (Shah et al. 2015), diabetes (Bowe et al. 2018) and depression (Fan et al. 2020), which may be through multiple biological mechanism, including inflammation, oxidative stress, DNA damage, chromosome damage and DNA methylation (Seaton et al., 1995; Yang et al., 2017). However, it remains unknown whether AP was significantly associated with increased risk of Alzheimer's disease (AD) - the most common type of dementia. We have considered that chronic exposure of the small blood vessels of the brain to biological microparticles leads to local inflammation and microhaemorrhages at the blood brain barrier, and episodic release of biologic micro-particles from pollution-induced lung inflammation caused secondary inflammation in the blood-brain barrier and cerebral micro bleeds, culminating over time in cognitive impairment and then causing dementia (Seaton et al., 2020). But there has been lack of research on the association of AP with AD in the population. Our systematic literature conducted in 2016 (Clifford et al, 2016) showed only one study in the area. Over the past five years, a limited number of studies were published examining the association of AP with AD (Fu et al., 2020), and the findings are inconsistent; some showed a positive association (Oudin et al., 2016; Cacciottolo et al., 2017; Chen et al., 2017; Carey et al., 2018) whilst others did not (Jung et al., 2015; Andersson et al., 2018). Most studies did not adjust for enough important confounders (e.g., depression, fish intake) (Fu et al., 2020) to examine the independent association of AP with AD. Few studies have examined the associations of different air pollutants with AD simultaneously and assessed which air pollutant played mostly role in the association (Cerza et al., 2019). Furthermore, the current knowledge of the association between AP and AD is predominantly derived from

studies conducted in high income countries/regions (HICs) (Fu et al., 2020) and their findings may not be generalizable to those in low- and middle-income countries (LMICs), where the levels of the AP exposure and AD risk are higher (Brauer et al., 2016; Chen et al. 2011; Renata et al., 2009).

Previous studies showed that the consumption of fish reduced the risk of AD (Bakre et al., 2018). Fish comprises of ample amounts of a protein called β-parvalbumin, which forms amyloid structures that readily inhibits the amyloid formation of human amyloidogenic protein (e.g., α-synuclein) (Werner T et al., 2018). Fatty acids from fish are important constituents for proper brain functioning; the omega-3 fatty acid in particular is a major component of neuronal membranes, with anti-inflammatory, anti-oxidant, anti-atherogenic and anti-amyloid properties (Connor WL and Connor SL, 2007; Calder 2006; lnnis SM, 2007; Uauy and Dangour, 2006). These components, including anti-inflammatory property could help reduce the impact of AP on dementia since AP exposure increased the risk of dementia mainly through inflammatory pathways (Seaton et al., 2020). We have considered that the inflammation may be carried by blood from organ to organ by biologic micro-particles derived from cell membranes, and ultimately by incomplete repair and accumulation of amyloid, this increases the risk of dementia and AD (Seaton et al., 2020). Neuro-inflammation has been proposed as a major mechanism in both the development and progression of AD (Wyss-Coray & Rogers, 2012). Thus, increased consumption of fish in older people living in high AP areas may mitigate the association between AP exposure and increased risk of AD. However, no study has been conducted to investigate whether fish intake could mitigate the association of AP with AD. In this study, we examined data of a community-based cohort study from rural and suburban China to determine the associations of each individual air pollutants ($PM_{2.5}$, PM_{10}, CO, NO_2, SO_2, and O_3) at baseline with AD identified in the follow-up. We also examined differences in the impact of AP on AD between people with low and high levels of fish intake.

Material and Methods

Study design and population

Study populations were derived from the Zhejiang Major Public Health Surveillance (ZJMPHS) Program, a prospective study which aimed to monitor health conditions and their determinants among older people. The methods of the ZJMPHS cohort study have been fully described in previous publications (Li et al., 2016; He et al., 2020a; He et al., 2020b). Briefly, in 2014 we randomly selected six counties (Changshan, Haishu, Jingning, Tongxiang,Yuecheng, Yuhuan) from 90 in Zhejiang province, China as study fields. In each county we selected one town, and through the town residential registration list we randomly recruited no fewer than 1,500 permanent residents aged ≥60 years for the ZJMPHS. A total of 9,353 older people took part in the baseline survey, with a response rate of 89.6%. They were interviewed by local community general practitioners (GP) in the community hospital or at home, to record socio-demographic, lifestyles, disease histories, disease risk factors and dietary intakes. In the interview we asked each participant whether she or he attended any school or not. If answered with 'yes', she or he would be asked to specify either (1) primary school, (2) secondary school, (3) high secondary school/professional school, (4) college or (5) university or higher. Those without any formal school attainment were defined as illiterate. The participant was asked to report her/his economic status and provide the answer with (1) very rich, (2) relatively rich, (3) average, (4) relatively difficult, or (5) difficult for perception financial situation in comparison to those in other households in the local residential area. Each participant was asked for the frequencies of consumptions of fish (including shrimp and crab), vegetables and other dietary intakes over the past year, at (1) *daily*, (2) *weekly,* (3) *monthly,* (4) *yearly* or (5) *never eat*, and if any consumed s/he put how many times of eating in the frequency selected. They provided the answer '*yes*' or '*no*' relating to environmental tobacco smoke (ETS) exposure via passive smoking questionnaire (He et al., 2020a). Depressive symptom was determined using the

Patient Health Questionnaire-9 scale (PHQ-9) (Li et al., 2016). The family histories of dementia were given to those who had any dementia recorded from parents or siblings in the questionnaire. According to the standard procedures, the GPs took blood pressure, heart rate, physical measurements for each participant. Her/his body mass index (BMI) was calculated based on body weight and height in a formula of kg/m^2. All participants completed a Chinese version of the Mini-Mental State Examination (MMSE) to assess cognitive impairment (CI) using the validated education specific cut-off points of the Chinese version MMSE. A total of 1406 participants were identified to have CI (He et al., 2020b). In 2015 and 2016, 8,598 cohort participants were re-interviewed using the same questionnaires as those at baseline (He et al., 2020b).

Air pollution measurement

In each county where the participants lived, daily concentrations of air pollution were measured, including $PM_{2.5}$ ($\mu g/m^3$), PM_{10} ($\mu g/m^3$), NO_2($\mu g/m^3$), CO (mg/m^3), SO_2 ($\mu g/m^3$) and O_3(µg/m3). We obtained these data of atmospheric environmental monitoring of 2013, 2014 and 2015, from Department of Ecology and Environment of Zhejiang Province. The daily mean of air pollutants within the same county was assigned to ZJMPHS participants who lived in the same county. We took AP measurements of three years of 2013, 2014 and 2015 as average AP exposure at baseline for analysis (He et al., 2020).

The Follow-up of Cohort

In 2019, after excluding 832 deaths and 1012 lost to follow up we re-interview 6,115 surviving cohort members, using the same questionnaires as before in 2014. Participants with CI were further examined by the general practitioners or neurologists to diagnose AD and other types of dementia using Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association-Alzheimer's Criteria (NINCDS-

ADRDA). In total, 986 cohort members were diagnosed as having AD.

The ZJMPHS program was approved by the Ethics Committee of the Zhejiang Provincial Center for Disease Control and Prevention, and written informed consent was obtained from each participant before the enrolment.

Statistical Analysis

The characteristics of participants were described using mean and standard deviation (SD) for continuous variables and percentage (%) for categorical variables. Differences in the characteristics between participants with and without AD were examined by t-tests for continuous variables and χ^2 tests for categorical variables.

Multilevel binary logistic regression models were employed to calculate odds ratio (OR) and its 95% confidence intervals (CIs) of AD in relation to each air pollutant. We divided participants into three groups at low, middle, and high levels of air pollutant exposure for categorical data analysis of air pollution according to our previous study (He et al., 2020b), some of which were around the criteria for "good, moderate and poor" air quality in China and in USA (http://www.cnblogs.com/tiandi/p/6158576.html). In the models, we adjusted for age, sex, education, financial situation, smoking, ETS, drinking, exercise, fish consumption, vegetable consumption, BMI, hypertension, hyperlipidemia, diabetes, coronary heart disease, stroke, Parkinson's disease, depression and family history of dementia. We tested the interaction effect of AP with fish consumption on the risk of AD in these models (multiplicative interaction effect), and examined differences in the impact of AP on AD between participants with low and high consumption of fish (additive interaction effect). We computed ratio of ORs in two groups using the methods in our previous studies (Bakre et al., 2018, Chen et al., 2014) and tested the differences in the ORs using a one-side $p < 0.05$ as our test of significance since the impact of AP might be stronger in participants with low consumption of fish than in their counterparts. All analyses were performed using SAS software version 9.4.

Results

The average baseline age of 6,155 participants was 68.0 years (SD 6.6), 49.9% were women, 48.0% were illiterate, and 43.5% consumed fish at ≥ 3 days per week. Table 1 shows details of these and other characteristics distribution. Participants who were diagnosed to have AD in the follow-up were more likely to be older, female gender, illiterate, rich, and underweight, but less likely to smoke, drink alcohol, have ETS exposure and have hyperlipidemia and stroke at baseline. There were no significant differences in consumptions of fish and vegetables, doing exercise, having hypertension, diabetes, ischemic heart disease, Parkinson's disease, depression and family history of dementia between participants with and without AD (Table 1).

Table 2 shows the numbers, rates and adjusted ORs of AD among participants with three levels of AP exposure. Overall, the rate of AD increased with level of exposure to air pollutants, except for O_3. After adjustment for age, sex, education and financial situation (Model 1), the OR of AD significantly increased with exposure to $PM_{2.5}$ and PM_{10} in a dose-response relationship, and with CO exposure at level 2. It was not related to NO_2 nor SO_2 exposure, while it decreased with O_3 level 2. After further adjustment for BMI, lifestyles, ETS, consumptions of fish and vegetables, co-morbidities and family history of dementia (Model 2), the patterns of the OR of AD in the six air pollutants were not substantially changed. In these models, we performed the interaction effects of each air pollutant exposure with fish consumption on the risk of AD and found none of them were statistically significant (all p values >0.05).

Table 3 shows the numbers and rates of AD among participants with three levels of AP exposure by low and high consumption of fish. The overall patterns of increased risk of AD in relation to AP levels between these two groups were similar, but participants with low consumption of fish had a higher risk of AD in each of the air pollutants at level 3 exposure compared to their counterparts. Table 4 shows the fully-adjusted ORs of AD in participants with

each air pollutant AP exposure by low and high consumption of fish. The differences in the association of AP with AD between two groups were not statistically significant. However, an increased OR of AD in participants with $PM_{2.5}$ exposure level 3 may be higher in participants with low consumption of fish than those with a high consumption of fish; ratio of ORs 1.79 approached conventional statistical significance (p=0.054) (Table 4).

Discussion

Our community-based cohort study in China examined the impact of exposure to six air pollutants on the risk of AD and found that $PM_{2.5}$, PM_{10}, and CO were significantly and independently associated with an increased risk of AD. There were no significant associations of NO_2 and SO_2 exposure with AD in this study, while the data of O_3 exposure may show an inverse association with AD. The patterns of these associations were similar between participants with low and high consumption of fish, but the association of $PM_{2.5}$ with AD might be reduced in older people with high consumption of fish.

In the UK, Carey et al examined the data of a perspective population-based cohort study of 130,978 adults aged 50-79 years with a mean follow-up of seven years and found that the risk of AD significantly increased with exposure to $PM_{2.5}$ (adjusted hazard ratio - HR 1.10, 95%CI 1.02-1.18), and NO_2 (1.23, 1.07-1.43), but decreased with O_3 (0.78, 0.66-0.92) (Carey et al., 2018). In Italy, a hospital-based cohort study of 350,844 elders aged 65-100 years in Rome showed that exposure to O_3 was not significantly associated with AD, while exposure to $PM_{2.5}$, PM_{10}, NO_2, and NO_x were inversely associated with AD risk (adjusted HR were 0.95 (0.91-0.99), 0.91(0.85-0.97), 0.91(0.89-0.94) and 0.96(0.94-0.98) respectively (Cerza et al., 2019). A population-based cohort study of 95,690 individuals age $\geq$ 65 with 10 years follow-up in Taiwan found that per 9.63 ppb increase in O_3 concentration at baseline was associated with an increased risk of AD (adjusted HR 1.06, 1.00-1.12), but not significantly in $PM_{2.5}$ (1.03, 0.95-1.11) (Jung et al., 2015). The data from a 15-year period longitudinal Betula study of 1567

participants in Northern Sweden (Oudin et al. 2019) found that compared to the first quartiles of NO_x exposure, the AD risk in the third quartiles of NO_x exposure was significantly increased (adjusted HR 1.72, 1.12-2.65), but not significant in the second (1.25, 0.79-1.98) and fourth quartiles (1.53, 0.99-2.36) of NOx exposure.

The discrepancies of the findings of the associations of air pollutants with AD among these studies conducted in HIC/regions could be related to various characteristics within the study population, study design, sample size, adjustment and different measurements of AP exposure. It has been noted that the association varied with air pollutants. Although some studies (Oudin et al., 2016) seemingly showed no significant dose-response relationship between air pollution exposure and AD risk, our study demonstrated the dose-response relationship of $PM_{2.5}$ and PM_{10} exposure with AD risk, which did not exist in other air pollutants. These may reflect that not only the mechanisms underlying the impact of different air pollutant on AD were different, but also the mechanisms underlying the impact of different levels of the same air pollutant were different. Whether there is a different mechanism underlying this phenomenon and safe levels of air pollutants exposure warrants further research.

Recently Fu and Yung (Fu et al., 2020) carried out a systematic literature review including nine papers, and their meta-analysis showed that there was no significant association of each individual air pollutant - $PM_{2.5}$, PM_{10}, O_3 and NO_2 with AD, but putting all the air pollutants together as an overall AP exposure for analysis made a marginal significance in the association with AD. An earlier meta-analysis by Tsai TL et al (Tsai TL, 2019) tried to examine the association of AP with AD, however the study had methodological issues, e.g., having missed two eligible studies and including an ineligible study (Kioumourtzoglou MA et al 2016) for analysis. Nevertheless, there have been no published studies from LMICs. Our study in rural and suburban China showed that exposure to particulate matters and CO would increase the

risk of AD.

The impact of air pollution on AD could be explained from a biological perspective. Evidence from experimental and animal studies have shown that inhalation of PM enhanced reactive oxygen species and inflammatory responses in the brain, associated with precipitating amyloid beta protein (Aβ) peptides (Calderón-Garcidueñas et al., 2008a), disruption of the blood-brain barrier (Levesque et al., 2011), and microglial activation (Block et al., 2011), all of which contribute to AD. Some epidemiological studies have also indicated the association between exposure to air pollution and pathological change in the brain, which may be prodrome or change of AD. A study conducted by Calderón-Garcidueñas et al (2008b) found that people living in areas with high air pollution accumulate more Aβ and in neurons and astrocytes than people living in areas with low air pollution. In the Framingham Offspring Study (Wilker et al., 2015) the brain volume was diminished by 0.32% as the concentration of $PM_{2.5}$ increased by 2ug/m^3. In the Women's Health Initiative Memory Study (WHIMS) (Chen et al., 2015), the white matter volume and total brain volume of the exposed persons diminished relative to the high concentration of $PM_{2.5}$. Additionally, the findings from quasi-experiment studies could provide some evidence of mechanism of air pollution caused AD (Chen et al., 2020). Despite these, the exact mechanisms of air pollution interaction with AD need further research.

As for as we know, there has been no study examining the interaction effect of AP exposure with fish intake on AD. Our study showed that the main impact of AP exposure on AD was from $PM_{2.5}$, while there appeared to be a stronger impact of $PM_{2.5}$ on AD in participants with low consumption of fish. The "weakened" association between $PM_{2.5}$ and AD in people with high consumption of fish may suggest that increased consumption of fish could mitigate the impact of $PM_{2.5}$ on AD. The finding was in line with those in previous study (Chen et al., 2020). In a study of 1,315 women aged 65-80 year in the US who lived in high AP areas, Chen et al (2020) found that participants with the lowest blood concentration of omega-3 fatty acids

had more brain shrinkage than those who had the highest level, and considered that taking enough omega-3 fatty acids may counteract the effects of air pollution on the brain.

Implications

Our findings have important public health implications. As a progressive neurological disease, AD is a representative of a large group of at-risk people with forecasted high expenditures and care needs in the future, particularly in LMICs. Whilst some studies showed higher level of overall AP exposure is associated with faster cognitive decline, the impact of AP on AD in old people is not well understood, and there have been no studies in LMICs. Our findings from 6,115 older people in China demonstrated that increased levels of $PM_{2.5}$, PM_{10}, and CO were significantly associated with AD. Although the concentrations of these air pollutants were relatively lower than the national average since the participants lived in the rural or suburban areas in China, the dose-response relationship of particulate matters with AD risk appeared to exist, which suggested that there may be no absolute safe threshold of air pollution on AD. The findings of possible mitigating effect of fish intake on the association of $PM_{2.5}$ with AD would encourage older people to consume more fish to reduce AD risk globally.

Strength and limitation

Our study is the first to assess the impacts of six air pollutants on AD simultaneously in LMICs, presenting the full picture of the association between air pollution and AD in older people. The study has accounted for several important confounders such as depression and fish intake, minimizing the residual effect of the association. It is the first study to examine the mitigating effect of fish intake on the association of AP with AD, which has helped to better understand the impacts of different air pollutants exposure on AD and guide strategies to prevent AD from AP exposure.

Our study has limitations. First, we do not have the data of participants with AD cases at baseline and do not know whether all these AD diagnosed in the health survey in 2019 were

incident AD. Previous studies showed around half of people with AD or dementia died within five years after diagnosis (Joling et al., 2020) and thus the half of those AD patients in the ZJMPHS study could be newly diagnosed in 2019 since the cohort had a five years follow-up. Furthermore, the current data analysis of the 6115 participants did not have those 1406 participants who had CI at baseline (He et al., 2020), meaning that all 6115 participants in the follow-up had normal cognitive function at baseline. These may suggest that the participants who were diagnosed with AD in 2019 would be more likely to have not had dementia in 2014. Nevertheless, we could not entirely ensure that all AD cases diagnosed in the follow-up were new cases, which might partly contribute to a high number of AD cases in the current cohort for analysis (the high AD number could be from the high levels of the low education and living in rural and suburban areas in China, increasing the risk of AD), and a further wave health survey is required to confirm the impact of different air pollutants exposure on incident AD. Second, after excluding those 832 deaths, we interviewed 6,115 participants, while 2,406 cohort members were not caught up for the interview in the cohort follow-up of 2019. It is not known whether they had a higher or lower level of risk in developing AD than those 6,115. This needs further research on its effect on the findings. However, the follow-up interview rate of our study (71.8%) was similar to those in some studies undertaken in HICs (Peters et al., 2019), and the findings of our study could be comparable to those in HICs. Third, the participants were residents from the six counties in Zhejiang province. Caution should be exercised in generalizing our findings to China's 250 million older inhabitants. More studies are required from other places in China, including urban areas to assess and confirm the impact of air pollution on AD in older people.

Conclusions

Our community-based cohort study in China demonstrated that the risk of AD increased among people having been exposed to $PM_{2.5}$, PM_{10}, or CO. Exposure to NO_2 and SO_2 were not

significantly associated with the risk of AD, while O_3 was inversely associated with AD. Increased consumption of fish may mitigate the impact of $PM_{2.5}$ on AD. Making the air clean and lowering the levels of $PM_{2.5}$, PM_{10} and CO would reduce the risk of AD in the whole population. Strategies that target most important air pollutants and involve increasing the consumption of fish should be an integral component of AD risk reduction in older people.

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Table 1. Basic characteristics of participants in the ZJMPHS cohort study, China

Variable	Total Participants N=6115 (%)	Alzheimer's Disease: No N=5129, (%)	Alzheimer's Disease: Yes N=986, (%)	*P*
Age (sd)	68.0 (6.6)	67.6 (6.5)	70.5 (7.0)	<0.001
Gender (female)	3050 (49.9)	2426 (41.3)	624 (63.3)	<0.001
Educational level				
Illiterate	2937 (48.0)	2339 (45.6)	598 (60.7)	<0.001
Perception financial situation				
≥Relatively rich	611 (10.0)	467 (9.1)	144 (14.6)	<0.001
Average	4834 (79.1)	4051 (79.0)	783 (79.4)	
≤Relatively difficult	670 (11.0)	611 (11.9)	59 (6.0)	
Smoking status				
Never-	4123 (67.4)	3383 (66.0)	740 (75.1)	<0.001
Ex-	588 (9.6)	515 (10.0)	73 (7.4)	
Current-	1404 (23.0)	1231 (24.0)	173 (17.6)	
Exposure to ETS				
No	4366 (71.4)	3620 (70.6)	746 (75.7)	0.001
Yes	1749 (28.6)	1509 (29.4)	240 (24.3)	
Alcohol Drinking				
Non-drinkers	3946 (64.5)	3278 (63.9)	668 (67.8)	0.016
Ex-drinkers	509 (8.3)	422 (8.2)	87 (8.8)	
Current drinkers	1660 (27.2)	1429 (27.9)	231 (23.4)	
Consumption of Fish				
≥ 3 days per week	2662 (43.5)	2249 (43.9)	413 (41.9)	0.255
Consumption of Vegetable				
≥ 3 days per week	5970 (97.6)	5005 (97.6)	965 (97.9)	0.587
Do exercise (%)	1167 (19.1)	987 (19.2)	180 (18.3)	0.470
Body mass index (kg/m^2) [@1]				
<20	831 (13.6)	662 (12.9)	169 (17.1)	0.001
20-<23	2328 (38.1)	1950 (38.0)	378 (38.3)	
23-<26	1788 (29.2)	1533 (29.9)	255 (25.9)	
≥ 26	1168 (19.1)	984 (19.2)	184 (18.7)	
Co-morbidities				
Hyperlipidemia	320 (5.2)	292 (5.7)	28 (2.8)	<0.001
Hypertension	2733 (44.7)	2272 (44.3)	461 (46.8)	0.155
Diabetes	524 (8.6)	445 (8.7)	79 (8.0)	0.495
Ischemic Heart Dis	184 (3.0)	153 (3.0)	31 (3.1)	0.786
Stroke	114 (1.9)	104 (2.0)	10 (1.0)	0.031
Parkinson's disease [#]	5 (0.1)	4 (0.1)	1 (0.1)	0.585

	Total	Alzheimer's Disease		
Depression	463 (7.6)	390 (7.6)	73 (7.4)	0.828
Family history of dementia [#]	45 (0.7)	37 (0.7)	8 (0.8)	0.687

[@1] cut-off BMI points were more suitable for Chinese older people.

[#] Fisher exact test.

Table 2. Numbers, rates and adjusted odds ratios of Alzheimer's disease among participants with six air pollutants exposure: the ZJMPHS cohort study, China

Air pollutant	Participants			Model 1			Model 2		
	All	AD (%)*		*OR*	95% *CI*	*P*	*OR*	95% *CI*	*P*
$PM_{2.5}$									
Level 1 (<=50)	2899	344	11.9	1.00			1.00		
Level 2 (>50-60)	2288	345	15.1	1.60	1.03-2.48	0.038	1.50	0.90-2.50	0.119
Level 3 (>60)	928	297	32.0	4.06	2.35-7.01	<0.001	3.92	2.09-7.36	<0.001
PM_{10}									
Level 1 (<=70)	794	69	8.7	1.00			1.00		
Level 2 (>70-80)	2105	275	13.1	1.52	0.60-3.82	0.378	1.74	0.65-4.56	0.263
Level 3 (>80)	3216	642	20.0	2.94	1.23-7.02	0.015	3.00	1.22-7.41	0.017
CO									
Level 1 (<=0.8)	794	69	8.7	1.00			1.00		
Level 2 (>0.8-0.9)	4343	832	19.2	2.70	1.24-5.91	0.013	2.86	1.32-6.20	0.008
Level 3 (>0.9)	978	85	8.7	1.08	0.40-2.90	0.884	1.19	0.45-3.18	0.725
NO_2									
Level 1 (<=30)	1127	190	16.9	1.00			1.00		
Level 2 (>30-40)	1703	214	12.6	0.75	0.21-2.75	0.667	0.63	0.17-2.27	0.475
Level 3 (>40)	3285	582	17.7	1.07	0.32-3.62	0.915	0.95	0.28-3.19	0.937
SO_2									
Level 1 (<=15)	1127	190	16.9	1.00			1.00		
Level 2 (>15-25)	1772	154	8.7	0.49	0.22-1.09	0.081	0.44	0.19-1.01	0.053
Level 3 (>25)	3216	642	20.0	1.40	0.67-2.92	0.370	1.21	0.56-2.62	0.627
O_3									
Level 1 (<=90)	1837	442	24.1	1.00			1.00		
Level 2 (>90-100)	2899	344	11.9	0.36	0.20-0.65	0.001	0.38	0.20-0.74	0.004
Level 3 (>100)	1379	200	14.5	0.51	0.23-1.12	0.094	0.50	0.21-1.21	0.124

*Chi-sq test in each pollutant $p<0.001$. Model 1: adjusted for age, sex, education and financial situation,
Model 2: adjusted for age, sex, education, financial situation, BMI (category), smoking, ETS, drinking, exercise, vegetable consumption, fish/shrimp consumption, hypertension, hyperlipidemia, diabetes, stroke, ischemic heart disease, Parkinson's disease, depression and family history of dementia.

Table 3. Numbers and rates of Alzheimer's disease among participants with six air pollutants exposure by levels of fish intake: the ZJMPHS cohort study, China

Air pollution	Participants eat fish < 3 days/wk				Participants eat fish ≥ 3 days/wk			
	All	AD (%)			All	AD (%)		
	N=3453	573	(16.6%)	*P**	N=2662	413	(15.5%)	*P**
$PM_{2.5}$								
Level 1 (<=50)	1305	129	9.9	<0.001	1594	215	13.5	<0.001
Level 2 (>50-60)	1634	248	15.2		654	97	14.8	
Level 3 (>60)	514	196	38.1		414	101	24.4	
PM_{10}								
Level 1 (<=70)	750	67	8.9	<0.001	44	2	4.5	0.001
Level 2 (>70-80)	555	62	11.2		1550	213	13.7	
Level 3 (>80)	2148	444	20.7		1068	198	18.5	
CO								
Level 1 (<=0.8)	750	67	8.9	<0.001	44	2	4.5	<0.001
Level 2 (>0.8-0.9)	2221	458	20.6		2122	374	17.6	
Level 3 (>0.9)	482	48	10.0		496	37	7.5	
NO_2								
Level 1 (<=30)	73	14	19.2	<0.001	1054	176	16.7	0.382
Level 2 (>30-40)	1333	158	11.9		370	56	15.1	
Level 3 (>40)	2047	401	19.6		1238	181	14.6	
SO_2								
Level 1 (<=15)	73	14	19.2	<0.001	1054	176	16.7	<0.001
Level 2 (>15-25)	1232	115	9.3		540	39	7.2	
Level 3 (>25)	2148	444	20.7		1068	198	18.5	
O_3								
Level 1 (<=90)	1097	287	26.2	<0.001	740	155	20.9	<0.001
Level 2 (>90-100)	1305	129	9.9		1594	215	13.5	
Level 3 (>100)	1051	157	14.9		328	43	13.1	

*Chi-sq test

Table 4. Adjusted odds ratios of Alzheimer's disease among participants with six air pollutants exposure by levels of fish intake: the ZJMPHS cohort study, China

	Participants eat fish < 3 days/wk			Participants eat fish ≥ 3 days/wk				
Air pollutant	OR†	95% CI	*P*	OR†	95% CI	*P*	ROR	*P*‡
$PM_{2.5}$								
Level 1 (<=50)	1.00			1.00				
Level 2 (>50-60)	1.80	1.39-2.33	<0.001	1.38	0.78-2.47	0.272	1.30	*0.205*
Level 3 (>60)	5.18	3.93-6.82	<0.001	2.89	1.50-5.59	0.002	1.79	*0.054*
PM_{10} €								
Level 1 (<=70)	0.66	0.23-1.86	0.433	0.28	0.05-1.50	0.136	2.36	*0.200*
Level 2 (>70-80)	1.00			1.00				
Level 3 (>80)	1.91	0.86-4.24	0.111	1.67	0.84-3.31	0.145	1.14	*0.401*
CO €								
Level 1 (<=0.8)	0.35	0.15-0.81	0.014	0.18	0.04-0.87	0.034	1.94	*0.229*
Level 2 (>0.8-0.9)	1.00			1.00				
Level 3 (>0.9)	0.39	0.16-0.91	0.030	0.44	0.20-0.94	0.033	0.89	*0.419*
NO_2								
Level 1 (<=30)	1.00			1.00				
Level 2 (>30-40)	0.60	0.14-2.50	0.480	0.70	0.18-2.78	0.615	0.86	*0.440*
Level 3 (>40)	0.93	0.24-3.63	0.920	0.93	0.28-3.12	0.912	1.00	*0.500*
SO_2								
Level 1 (<=15)	1.00			1.00				
Level 2 (>15-25)	0.43	0.15-1.25	0.120	0.44	0.19-1.03	0.058	0.98	*0.487*
Level 3 (>25)	1.17	0.42-3.24	0.767	1.28	0.63-2.60	0.499	0.91	*0.444*
O_3								
Level 1 (<=90)	1.00			1.00				
Level 2 (>90-100)	0.34	0.18-0.66	0.001	0.42	0.24-0.75	0.003	0.81	*0.316*
Level 3 (>100)	0.50	0.22-1.13 4	0.098	0.45	0.22-0.93	0.031	1.11	*0.425*

†adjusted for age, sex, education, financial situation, BMI (category), smoking habits, ETS, alcohol drinking, exercise, vegetable consumption, hypertension, hyperlipidemia, diabetes, stroke, ischemic heart disease, Parkinson's disease, and depression and family history of dementia. ‡ one-side p value. €due to a small number of participants in level 1 exposure, the level 2 exposure was taken as a reference group.