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Association between air pollutants and dementia risk in the elderly

Yun-Chun Wu[a,1], Yuan-Chien Lin[b,1], Hwa-Lung Yu[b], Jen-Hau Chen[c], Ta-Fu Chen[d], Yu Sun[e], Li-Li Wen[f], Ping-Keung Yip[g], Yi-Min Chu[h], Yen-Ching Chen[a,i,j,*]

[a]*Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan*
[b]*Department of Bioenvironmental Systems Engineering, National Taiwan University, Taipei, Taiwan*
[c]*Department of Geriatrics and Gerontology, National Taiwan University Hospital, Taipei, Taiwan*
[d]*Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan*
[e]*Department of Neurology, En Chu Kong Hospital, Taipei, Taiwan*
[f]*Department of Laboratory Medicine, En Chu Kong Hospital, Taipei, Taiwan*
[g]*College of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan*
[h]*Department of Laboratory Medicine, Cardinal Tien Hospital, Taipei, Taiwan*
[i]*Department of Public Health, College of Public Health, National Taiwan University, Taipei, Taiwan*
[j]*Research Center for Genes, Environment and Human Health, College of Public Health, National Taiwan University, Taipei, Taiwan*

Abstract

Background: The aging rate in Taiwan is the second highest in the world. As the population ages quickly, the prevalence of dementia increases rapidly. There are some studies that have explored the association between air pollution and cognitive decline, but the association between air pollution and dementia has not been directly evaluated.

Methods: This was a case-control study comprising 249 Alzheimer's disease (AD) patients, 125 vascular dementia (VaD) patients, and 497 controls from three teaching hospitals in northern Taiwan from 2007 to 2010. Data of particulate matter <10 μm in diameter (PM_{10}) and ozone were obtained from the Taiwan Environmental Protection Administration for 12 and 14 years, respectively. Blood samples were collected to determine the apolipoprotein E (*APOE*) ε4 haplotype. Bayesian maximum entropy was used to estimate the individual exposure level of air pollutants, which was then tertiled for analysis. Conditional logistic regression models were used to estimate adjusted odds ratios (AORs) and 95% confidence intervals between the association of PM_{10} and ozone exposure with AD and VaD risk.

Results: The highest tertile of PM_{10} ($\geq$49.23 μg/m^3) or ozone ($\geq$21.56 ppb) exposure was associated with increased AD risk (highest vs. lowest tertile of PM_{10}: AOR = 4.17; highest vs. lowest tertile of ozone: AOR = 2.00). Similar finding was observed for VaD. The association with AD and VaD risk remained for the highest tertile PM_{10} exposure after stratification by *APOE* ε4 status and gender.

Conclusions: Long-term exposure to the highest tertile of PM_{10} or ozone was significantly associated with an increased risk of AD and VaD.

Keywords: Air pollutant; Particulate matter; Ozone; Alzheimer's disease; Vascular dementia; The elderly

1. Introduction

Every 4 seconds a new dementia case occurs around the world, and the number of dementia cases doubles every 20 years [1]. In the United States, Alzheimer's disease (AD) is the leading type of dementia, and it was ranked the fifth leading cause of death in the elderly in 2010 [2].

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[1]Yun-Chun Wu and Yuan-Chien Lin contributed equally to this work.

*Corresponding author. Tel.: +886-2-3366-8019; Fax: +886-2-2351-1955.

E-mail address: karenchen@ntu.edu.tw

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From 1999 to 2004, the mortality rate of AD increased by 31% [3], which might also be a result of improved reporting. In Taiwan, the prevalence of dementia was 8.04% in the elderly (age ≥65 years) based on a recent National Survey in 2011 to 2012 [4]. As the aging rate increases rapidly worldwide, dementia has become an important health issue in the elderly.

Several factors have been related to dementia risk, for example, age, sex, education, apolipoprotein E (*APOE*) ε4 status, lifestyle, and environment factors [5]. Environmental factors may play an important role in dementia; however, studies are sparse because of its wide spectrum and difficulty in objectively assessing the cumulative exposure of environmental exposure. The exhaust from motor vehicles is the major source of air pollution in Taiwan [6] and has been associated with respiratory and cardiovascular diseases [7]. Particulate matter <10 μm in diameter (PM_{10}) and ozone are especially important as they are the major pollutants for estimating the index of polluted alert region, that is, Pollutants Standard Index, in Taiwan [8,9]. PM_{10} refers to solid and liquid particles composed by mixed compound of chemicals and suspends in the air [10]. Animal studies indicated that PM can be transferred from the upper respiratory tract to the brain, leading to brain inflammation—an important pathological evidence of dementia [11,12]. Ozone is a strong oxidizing agent formed in the troposphere from a series of complex reactions via sunlight on nitrogen dioxide from the exhaust. In rat's hippocampus, exposure to ozone causes oxidative stress and the subsequent progressive neurodegeneration [13]; this seems analogous to that observed in AD patients.

Some studies have explored the relationship between the long-term exposure to traffic-related air pollutants and impaired cognitive function in the elderly [14–18]. These studies found that PM or black carbon (BC) was related to cognitive impairment/decline (PM_{10}: [15], $PM_{2.5\text{-}10}$: [17], $PM_{2.5}$: [17,18], BC: [16]). Similarly, ozone exposure was also related to lower cognitive function [14,18]. However, without considering the effects of air pollutants, only 1.6% to 6.8% people in the community and 1.9% to 9.6% people in the clinic with cognitive impairment progress to dementia annually [19]. Therefore, it is important to clarify the role of air pollutants on dementia occurrence, and studies evaluating this association are lacking.

Long-term exposure to PM_{10} or to ozone on dementia risk remains unclear. Therefore, this study aimed to explore this association over an average duration of 13 years. Because *APOE* ε4 status and gender are important confounding factors for dementia risk, this study further evaluated how they modified this association. A powerful and new statistical approach, Bayesian maximum entropy (BME), which simultaneously considers spatial and temporal estimation with soft data, was used to estimate the long-term exposure to air pollutants.

2. Method

2.1. Study population

This case-control study recruited 483 dementia cases from the neurology clinics of three teaching hospitals in northern Taiwan between 2007 and 2010. Healthy controls (n = 565) were recruited from the elderly health check-up program and volunteers of the hospital during the same time period. All participants were aged ≥60 years. Participants with any of the following conditions were excluded: depression, Parkinson's disease, hemorrhagic stroke, cerebral infarction, brain tumor, or dementia subtypes other than AD or vascular dementia (VaD). Participants without blood sample and those who resided outside the Taipei-Keelung metropolitan area were also excluded. After exclusion, 249 AD patients, 125 VaD patients, and 497 controls were included for data analysis. This study was approved by the Institutional Review Boards of National Taiwan University Hospital, En Chu Kong Hospital, and Cardinal Tien's Hospital. Written informed consent was obtained from all participants. For patients with serious cognitive impairment, their consent was obtained from the legal guardian/next of kin/caregiver, who also helped with the verification of information collected from the questionnaire.

A self-reported questionnaire was administered to collect information on demography, vascular risk factors (hypertension, type 2 diabetes mellitus [DM], and hyperlipidemia, and body mass index [BMI] at age 40s), lifestyle, and family history of diseases. A blood sample was collected in tubes containing sodium ethylenediamine tetraacetic acid from each participant. After centrifugation, genomic DNA was extracted from buffy coat by using QuickGene-Mini80 system (Fujifilm, Tokyo, Japan) and stored at −80°C.

2.2. Evaluation of AD and VaD

At each hospital, one neurologist performed the clinical examination to screen potential dementia cases. Mini-Mental State Examination was used to assess their cognitive function. The diagnosis of dementia was evaluated by *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria [20]. Head magnetic resonance imaging (about 90% of dementia cases) and computed tomography (about 10% of dementia cases) were performed to exclude participants with organic lesions. Diagnosis of probable (typical AD presentation) AD was based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association Alzheimer's Criteria [21]. Diagnosis of VaD was made according to the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria [22]. Because of different etiology between large and small vessel dementia, only VaD patients with small vessel-