Associations between long-term exposure to ambient air pollution and Parkinson’s disease: a cross-sectional study

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\section*{Abstract}

\textbf{Background:} Epidemiological studies have reported contradictory results regarding the effects of ambient air pollution on Parkinson’s disease (PD). This study investigated the associations between long-term exposure to particulate matter < 2.5 \(\mu\text{m}\) in diameter (PM\textsubscript{2.5}) and nitrogen dioxide (NO\textsubscript{2}) and PD among participants in the 45 and Up Study, which comprised adults older than 45 years living in New South Wales, Australia.

\textbf{Methods:} We conducted a cross-sectional analysis of long-term exposure to PM\textsubscript{2.5} and NO\textsubscript{2} concentrations and prevalence of PD using data from around 240,000 cohort members from the 45 and Up Study, NSW. Annual average concentrations of NO\textsubscript{2} and PM\textsubscript{2.5} were estimated at the participants’ residential address using satellite-based land use regression models. Logistic regression was used to quantify the associations between these pollutants and ever physician-diagnosed PD, after adjusting for a range of individual- and area-level covariates.

\textbf{Results:} Among the 236,390 participants with complete data, 1,428 (0.6\%) reported physician-diagnosed PD. Annual mean PM\textsubscript{2.5} and NO\textsubscript{2} concentrations for the cohort were 5.8 and 11.9 \(\mu\text{g.m}^{-3}\), respectively, and were positively, but not statistically significantly associated with PD. The odds ratio for a 1 \(\mu\text{g.m}^{-3}\) increase in PM\textsubscript{2.5} was 1.01 (95\% confidence interval (CI): 0.98 – 1.04). The adjusted odds ratio for a 5 \(\mu\text{g.m}^{-3}\) increase in NO\textsubscript{2} was 1.03 (95\% CI: 0.98 – 1.08). In subgroup analyses, larger associations for NO\textsubscript{2} were observed among past smokers (OR 1.11 (95\% CI: 1.02 – 1.20) per 5 \(\mu\text{g.m}^{-3}\) increase).

\textbf{Conclusions:} Overall, we found limited evidence of associations between long-term exposure to NO\textsubscript{2} or PM\textsubscript{2.5} and PD. The associations observed among past smokers require further corroboration.

\textbf{Keywords:} Parkinson’s disease, air pollution, particulate matter, 45 and Up Study

\section*{1. Introduction}

Parkinson’s disease (PD) is a progressive and disabling neurodegenerative disorder, which, after Alzheimer’s disease, is the most common neurodegenerative disorder (De Lau and Breteler 2006; Jankovic 2008). The
incidence of PD is low before 50 years of age, after which it increases sharply prior to peaking above 80 years of age (Kalia and Lang 2015). Meta-analyses of world-wide data showed a prevalence of 1,903 PD cases per 100,000 persons older than 80 years (Pringsheim et al. 2014). Studies have found evidence of a greater incidence and prevalence of PD in men compared with women (De Lau and Breteler 2006).

A meta-analysis of the risk factors for PD found lower risk of PD in smokers, with a 40% lower risk in ever smokers (Noyce et al. 2012). However, it is unclear whether the association is causal and what biological mechanisms may be involved (Ritz and Rhodes 2010). Apart from age and smoking, the aetiology of PD is still largely unknown, however, emerging evidence suggests that the interplay between genetic and environmental factors may contribute to the development of PD (Kalia and Lang 2015).

Air pollution, particularly particulate matter (PM), has been implicated as a chronic source of neuroinflammation and reactive oxygen species that may lead to neurological dysfunction (Block and Calderón-Garcidueñas 2009; Genc et al. 2012). Studies that have assessed the associations between long-term exposure to air pollution and PD have shown inconsistent findings (Cerza et al. 2018; C-Y Chen et al. 2017; H Chen et al. 2017a; Finkelstein and Jerrett 2007; Kioumourtzoglou et al. 2015; Lee et al. 2016; Liu et al. 2016; Palacios et al. 2014a; Palacios et al. 2014b; Palacios et al. 2017; Ritz et al. 2016; Shin et al. 2018). Therefore, this study aimed to examine the association between exposure to ambient PM$_{2.5}$ and NO$_2$ and the risk of PD using the baseline data from an established cohort of more than 265,000 people aged 45 years and older living in New South Wales (NSW), Australia.

2. Methods

2.1. Study population

We conducted a cross-sectional analysis using data from the ‘45 and Up Study’, described in detail elsewhere (45 and Up Study Collaborators 2008). Briefly, the 45 and Up Study was established by the Sax Institute and during 2006 to 2009 recruited 266,969 adults aged 45 years and over in NSW, Australia. Participants were sampled from the Australia’s Department of Human Services enrolment database. At recruitment, participants in rural and regional areas were over-sampled to ensure a sufficient sample size for analyses relevant to rural risk factors. Each participant gave signed consent for follow-up and linkage of their information to routine health databases. Participants completed a comprehensive questionnaire at baseline that included information on demographic and social characteristics, personal health behaviours, and health-related data. The study region included all areas of NSW and included a sample size of 266,969 participants.

2.2. Outcome assessment

Persons with PD in the 45 and Up Study were identified from the baseline survey conducted during 2006-2009. Participants reported whether they had ever been diagnosed with PD by a physician and, if so, the age at which the disease was first diagnosed.

2.3. Covariate data

We defined potential covariates a priori based on previous studies and known risk or protective factors for PD. Covariate data on age, sex, smoking status, body mass index (BMI), family history of PD, and education were obtained from the 45 And Up Study dataset. The Index of Relative Socioeconomic Disadvantage (IRSD) from the 2006 Census was used as the measure of area level SES. This index is a composite measure of a range of information on income, education, and unemployment for individuals and households within a Census Collection District, a small geographical spatial unit with an average of 220 dwellings in urban areas (ABS 2006). A lower IRSD score indicates relatively greater disadvantage (ABS 2008). Participants’ IRSD scores were ranked and grouped into quintiles where category 1 represents the most disadvantaged (lowest SES) and category 5 the least disadvantaged (highest SES).

2.4. Exposure assessment

National satellite-based land use regression (Sat-LUR) models, which had undergone external validation (Knibbs et al. 2014; Knibbs et al. 2016; Knibbs et al. 2018), were used to estimate exposure to ambient NO$_2$ and PM$_{2.5}$ concentrations. Briefly, Sat-LUR utilises satellite observations and land-use variables to estimate annual average concentrations of both pollutants. Each participant was assigned the 2007 annual average NO$_2$ and PM$_{2.5}$ concentrations estimated for at the centroid of the mesh block in which they resided. Mesh blocks
are the smallest geographical area defined by the Australian Bureau of Statistics and contain 30-60 dwellings, on average.

2.5. Statistical analyses

The associations between exposure to air pollutants and PD were estimated using multivariable logistic regression models performed separately for each pollutant. Following an approach similar to the European Study of Cohorts for Air Pollution Effects (ESCAPE) study (Beelen et al. 2014), effects of exposure to NO₂ and PM₂.₅ were adjusted for potential confounders, determined a priori, in three steps: Model 1) baseline age (in 5-year age groups), and sex; Model 2) Model 1 plus smoking status (current, previous and never smoker), body mass index (BMI) (underweight, normal, overweight, obese), physical activity (sufficient vs insufficient), education (below high school, high school, or university), marital status (single vs partnered), and family history of PD (yes/no); Model 3) Model 2 plus additional adjustment for area-level socioeconomic status (SES) (using Index of Relative Socio Economic Disadvantage). All models (1-3) were run using the Model 3 dataset with no missing covariates (n = 236,390).

Epidemiological studies have consistently observed a lower risk of PD among smokers (Chen et al. 2010). Furthermore, differences in PD incidence (Haaxma et al. 2007) with different risk factors such as diet (Chen et al. 2002) and sex have been suggested. Therefore, we evaluated potential interactions by including a multiplicative interaction with exposure and sex / smoking status in the regression model. We also conducted stratified analyses by sex and baseline smoking status.

To test the robustness of our results, we applied the following sensitivity analyses: 1) Model 3 was further adjusted for alcohol consumption; 2) since previous studies have shown that participants residing in the same area may share similar characteristics and exposure conditions, we applied mixed effect multiple logistic regression models with a random intercept by neighbourhood to account for the potential clustering.

3. Results

Of the 266,969 participants residing in the areas with available PM₂.₅ and NO₂ exposure estimates, 30,579 (11%) were excluded due to missing information on outcome and/or covariates. Of the 236,390 remaining participants, 1,428 (0.6%) reported physician-diagnosed PD. PD cases were more likely to be older, male, to have not completed high school, and were more likely to have a family history of PD (Table 1).

PM₂.₅ and NO₂ concentrations were relatively low (Table 2). Mean PM₂.₅ and NO₂ concentrations estimated at the participants’ residences were 5.8 and 11.9 μg. m⁻³, respectively.

Table 1: Characteristics of the 236,390 45 and up study participants according to PD diagnosis at baseline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No PD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>234,962 (99.4)</td>
<td>1,428 (0.6)</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>62.4 (11.0)</td>
<td>71.4 (10.5)</td>
</tr>
<tr>
<td>Male, %</td>
<td>47.4</td>
<td>56.5</td>
</tr>
<tr>
<td>Education, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>completed some high school</td>
<td>33.7</td>
<td>43.5</td>
</tr>
<tr>
<td>completed high school</td>
<td>42.4</td>
<td>39.8</td>
</tr>
<tr>
<td>Completed University</td>
<td>23.9</td>
<td>16.6</td>
</tr>
<tr>
<td>Smoking status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>7.2</td>
<td>5.3</td>
</tr>
<tr>
<td>Past</td>
<td>35.9</td>
<td>33.9</td>
</tr>
<tr>
<td>Never</td>
<td>56.8</td>
<td>60.7</td>
</tr>
</tbody>
</table>
Family history of PD, % 4.6 12.4

Area level SES, %
1, most disadvantaged 20.0 25.4
2 20.0 19.5
3 20.0 18.6
4 20.0 20.0
5, least disadvantaged 20.0 16.5

Table 2: PM$_{2.5}$ and NO$_2$ summary statistics, 45 and Up Study.

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>N</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Range</th>
<th>10$^{th}$ pct.</th>
<th>25$^{th}$ pct.</th>
<th>75$^{th}$ pct.</th>
<th>90$^{th}$ pct.</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM$_{2.5}$</td>
<td>236,362</td>
<td>5.75</td>
<td>6.00</td>
<td>1.66</td>
<td>0.10 – 10.30</td>
<td>3.40</td>
<td>4.60</td>
<td>7.00</td>
<td>7.70</td>
<td>2.40</td>
</tr>
<tr>
<td>(µg.m$^{-3}$)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO$_2$</td>
<td>236,390</td>
<td>11.92</td>
<td>10.58</td>
<td>5.76</td>
<td>4.21 – 71.20</td>
<td>5.68</td>
<td>7.22</td>
<td>15.66</td>
<td>19.98</td>
<td>8.44</td>
</tr>
<tr>
<td>(µg.m$^{-3}$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

The associations between annual mean exposure to PM$_{2.5}$ and NO$_2$ and PD are shown in Table 3. Further adjustments for covariates had little effects on the crude ORs for the association between exposure to the air pollutants and PD (Table 3). As Model 3 was adjusted for the greatest number of covariates chosen a priori it was chosen as the main model for all further analyses.

Overall, exposures to ambient PM$_{2.5}$ and NO$_2$ were positively, but not statistically significantly associated with ever physician-diagnosed PD (Table 3). PM$_{2.5}$ and NO$_2$ exposures were associated with a higher odds of PD among men compared with women, however, the inclusion of sex as an interaction term was not statistically significant (Table 4).

Table 3: Exposure to PM$_{2.5}$ and NO$_2$ and odds of PD.

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>PD cases</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM$<em>{2.5}$ (per 1 µg.m$^{-3}$ change in PM$</em>{2.5}$)</td>
<td>1,428</td>
<td>1.02 (0.99 – 1.05)</td>
<td>1.01 (0.98 – 1.05)</td>
<td>1.01 (0.98 – 1.04)</td>
</tr>
<tr>
<td>NO$_2$ (per 5 µg.m$^{-3}$ change in NO$_2$)</td>
<td>1,428</td>
<td>1.01 (0.97 – 1.06)</td>
<td>1.02 (0.97 – 1.07)</td>
<td>1.03 (0.98 – 1.08)</td>
</tr>
</tbody>
</table>

Model 1: adjusted for age and sex  
Model 2: model 1 plus education, smoking status, physical activity, marital status, BMI and family history of PD  
Model 3: model2 plus area level socio-economic status

Table 4: Exposure to PM$_{2.5}$ and NO$_2$ and risk of PD, stratified by sex. Odds ratios are for 1 and 5 µg.m$^{-3}$ changes in PM$_{2.5}$ and NO$_2$ concentrations, respectively.

<table>
<thead>
<tr>
<th>By sex</th>
<th>Male (n = 110,542)</th>
<th>Female (n = 125,848)</th>
<th>p-Int</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD cases</td>
<td>OR and 95% CI</td>
<td>PD cases</td>
<td>OR and 95% CI</td>
</tr>
<tr>
<td>PM$_{2.5}$</td>
<td>807</td>
<td>1.02 (0.97 – 1.06)</td>
<td>621</td>
</tr>
</tbody>
</table>
The inclusion of smoking status as an interaction term was statistically significant for NO$_2$ ($p = 0.02$ but not PM$_{2.5}$ ($p = 0.51$). In the sub-analysis stratified by smoking (Table 5), exposure to NO$_2$ was associated with an increased risk of PD among past smokers, OR = 1.11 (1.02 – 1.20) per unit increase in PM$_{2.5}$, while no such associations were found in current or never smokers. Application of the mixed effect model did not materially alter the effect estimates.

Table 5: Exposure to PM$_{2.5}$ and NO$_2$ and risk of PD, by smoking status. Odds ratios are for 1 and 5 µg.m$^{-3}$ changes in PM$_{2.5}$ and NO$_2$ levels, respectively.

<table>
<thead>
<tr>
<th>By smoking status</th>
<th>Current smokers</th>
<th>Past smokers</th>
<th>Never smokers</th>
<th>p-Int</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PD cases</td>
<td>OR and 95% CI</td>
<td>PD cases</td>
<td>OR and 95% CI</td>
</tr>
<tr>
<td>PM$_{2.5}$</td>
<td>76</td>
<td>1.00 (0.87 – 1.14)</td>
<td>485</td>
<td>1.03 (0.98 – 1.09)</td>
</tr>
<tr>
<td>NO$_2$</td>
<td>76</td>
<td>0.91 (0.73 – 1.13)</td>
<td>485</td>
<td>1.11 (1.02 – 1.20)</td>
</tr>
</tbody>
</table>

4. Discussion

In this study, we found positive, but not statistically significant associations between exposure to low level PM$_{2.5}$ and NO$_2$ and self-reported physician-diagnosed PD. The associations with NO$_2$ was statistically significant in past smokers while no such associations were found in current and non-smokers.

Studies that have examined the associations between long-term exposure to PM$_{10}$, PM$_{2.5}$ and NO$_2$ and PD are summarised in Table 6. Nine of 11 studies found positive associations with five results being statistically significant. Two reported negative associations. Studies have also found positive statistically significant associations with NO$_2$ more often than PM$_{2.5}$. The different findings across the literature may be ascribed to varying population characteristics, study designs and different PM chemical compositions at different locations.

Table 6: Summary table on the literature on associations between air pollution and PD

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design</th>
<th>Location</th>
<th>Population, n (age year)</th>
<th>Pollutant</th>
<th>Association</th>
<th>Statistically significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>This study</td>
<td>Cross-sectional</td>
<td>Australia</td>
<td>232,053 (&gt;= 45 years at baseline)</td>
<td>PM$<em>{2.5}$ PM$</em>{2.5}$ NO$_2$</td>
<td>Positive</td>
<td>No</td>
</tr>
<tr>
<td>Palacios et al. (2014b)</td>
<td>Prospective cohort</td>
<td>USA</td>
<td>111,769 (30-55 at baseline, women)</td>
<td>PM$<em>{10}$ PM$</em>{2.5}$ PM$_{2.5-10}$</td>
<td>Positive</td>
<td>No</td>
</tr>
<tr>
<td>Kirrane et al. (2015)</td>
<td>Cross-sectional</td>
<td>USA</td>
<td>83,343 (12 – 92 at enrolment)</td>
<td>Ozone PM$_{2.5}$</td>
<td>Positive</td>
<td>No</td>
</tr>
<tr>
<td>Lee et al. (2016)</td>
<td>Case-control</td>
<td>Taiwan</td>
<td>11,117 cases, 44,468 controls</td>
<td>NOx SO2</td>
<td>Positive</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Air pollution, particularly PM, has been implicated in the aetiology of neurological dysfunction (Block and Calderón-Garcidueñas 2009; Genc et al. 2012). Evidence suggests that air pollution can induce neuroinflammation, oxidative stress, microglial activation which can contribute to central nervous system pathology (Gene et al. 2012).

Animal studies have found that exposure to different ambient air pollutants such as urban fine particles, diesel exhaust, and ultrafine particles causes elevated proinflammatory cytokines and oxidative stress in the brain (Cheng et al. 2016; Levesque et al. 2011; Mumaw et al. 2016). PM uptake is thought to take place through olfactory neurons (Calderón-Garcidueñas et al. 2008) and ultrafine PM (< 100 nm) can translocate to the central nervous system where they can activate innate immune response.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Country</th>
<th>Cases/Controls</th>
<th>Pollutants</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al. (2016)</td>
<td>Case-control</td>
<td>USA</td>
<td>1,556/3,313</td>
<td>CO, Ozone, PM$_{10}$, NO$_2$</td>
<td>Positive/Yes, No/NA</td>
</tr>
<tr>
<td>Ritz et al. (2016)</td>
<td>Case-control</td>
<td>Denmark</td>
<td>1,696/1,800</td>
<td>CO, Ozone, PM$_{2.5}$</td>
<td>Positive/Yes, No/No</td>
</tr>
<tr>
<td>C-Y Chen et al. (2017)</td>
<td>Case-control</td>
<td>Taiwan</td>
<td>1,060/4,240</td>
<td>CO, Ozone, PM$_{10}$, SO$_2$</td>
<td>Positive/No, No/No</td>
</tr>
<tr>
<td>H Chen et al. (2017b)</td>
<td>Population-based cohort</td>
<td>Canada</td>
<td>2,165,282(55–85 years)</td>
<td>Traffic proximity</td>
<td>Positive/Yes</td>
</tr>
<tr>
<td>Palacios et al. (2017)</td>
<td>Prospective cohort</td>
<td>USA</td>
<td>50,352(40–75 years at enrolment, men)</td>
<td>PM$<em>{10}$, PM$</em>{2.5}$, PM$_{2.5-10}$</td>
<td>Negative/No</td>
</tr>
<tr>
<td>Cerza et al. (2018)</td>
<td>Population-based cohort</td>
<td>Italy</td>
<td>1,008,253 (&gt;50)</td>
<td>NO$<em>2$, Ozone, PM$</em>{10}$, PM$<em>{2.5}$, PM$</em>{2.5-10}$, PM$_{2.5}$ absorbance</td>
<td>Negative/No</td>
</tr>
<tr>
<td>Shin et al. (2018)</td>
<td>Population-based cohort</td>
<td>Canada</td>
<td>2,194,519(55–85 years)</td>
<td>NO$<em>2$, Ozone, PM$</em>{2.5}$</td>
<td>Positive/Yes</td>
</tr>
</tbody>
</table>
Ultrafine particle concentration correlates better with NO$_2$ than PM$_{2.5}$ in ambient air (Eeftens et al. 2015) since NO$_2$ and ultrafine particles are both more affected by traffic related air pollution compared with PM$_{2.5}$. Therefore, NO$_2$ may better represents exposure to ultrafine particles. This may explain the higher associations we observed with NO$_2$ and the fact that studies in the literature have found stronger associations between PD and NO$_2$ than PM$_{2.5}$. This suggests the need to conduct epidemiological studies to assess the associations between long-term exposure to the ultrafine particles and PD.

We did not find any evidence showing a modifying effect of sex on the associations between exposure to air pollution and PD. Cerza et al. (2018) found negative associations between exposure to PM absorbance and Nitrogen oxides with incidence of PD in women while no such association were observed in men. Generally, lower rates of PD have been reported for women in the literature (Van Den Eeden et al. 2003) which may be due to the protective effect of the activity of oestrogen (Haaxma et al. 2007).

Smoking has been consistently reported as a protective factor for PD. A systematic and meta-analysis of PD and cigarette smoking found consistent statistically significant negative (protective) associations, RR = 0.46 (0.42 – 0.51), between smoking and risk of PD (Breckenridge et al. 2016). We also saw a non-significant protective effect of smoking.

We found positive associations between exposure to NO$_2$ and PD in past smokers (OR = 1.11 (1.02 – 1.20)) while there was no such association in current and never smokers. To our knowledge, this is the first study showing significant modifying effect of smoking status on the associations of air pollution with PD. However, we do not know why past smokers would have a greater risk than current or never smokers. The protective effect of smoking overall was noted, as consistent with the literature.

Ritz et al. (2016) found higher associations between long-term exposure to air pollution and PD in current smokers while the opposite effect of smoking was found in another study (Liu et al. 2016). These findings as well as what we found in this study suggest the possibility of smoking acting as an effect modifier on the casual pathway of exposure to air pollution and PD.

A major strength of our study is its large size and the detailed individual-level information collected on potential confounders. PD cases were identified based on the questionnaire filled in by participants at baseline. Therefore, we may have biased outcome measures.

Moreover, we only had limited cases of PD despite having a large cohort. The small number of cases together with exposure misclassification may result in reduced ability to detect modest associations. In addition, we used the cross-sectional study design, therefore, our findings should be interpreted as associations rather than causality or effects. We plan to conduct future analyses on this study cohort using follow-up data of the cohort.

We also assumed that the 2007 annual average pollutant concentrations were good approximations of their long-term exposure. Knibbs et al. (2014) found a small temporal change in the spatial pattern of NO$_2$ concentrations between 2006-2011. Therefore, we assumed that the exposures participants in 2007 was representative of the long-term exposures. We assessed the historical PM$_{2.5}$ measurements and found that year-to-year differences in spatial pattern of PM$_{2.5}$ concentrations were small and therefore we assumed this year to be representative of annual averages of previous years.

5. Conclusions

In summary, we found limited evidence for associations between exposures to NO$_2$ or PM$_{2.5}$ and PD. The associations with NO$_2$ was stronger and statistically significant in past smokers which warrants further investigation on the modifying effects of smoking.

6. Acknowledgements

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Urban Landscapes (CAUL) hub of the Australian Government's National and Environmental Science Programme (NESP). This study is part of the “Understanding the impact of the social, economic and environmental factors on the health of Australians in mid-later life; where are the opportunities for prevention?” study (National Health & Medical Research Council (NHMRC) Grant 402810) and we wish to acknowledge Phlayrath Phongsavan for her tireless and effective coordination of the project. Yuming Guo was supported by a Career Development Fellowship of the Australian National Health and Medical Research Council (#APP1107107 & #APP1163693).

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