Health and Place 54 (2018) 132–137

Contents lists available at ScienceDirect

Health & Place

journal homepage: www.elsevier.com/locate/healthplace

Is the risk of developing Alzheimer's disease really higher in rural areas? A multilevel longitudinal study of 261,669 Australians aged 45 years and older tracked over 11 years

Thomas Astell-Burt[a,b,c,*], Xiaoqi Feng[a,b]

[a] Population Wellbeing and Environment Research Lab (PowerLab), School of Health and Society, Faculty of Social Sciences, University of Wollongong, Wollongong, New South Wales, Australia
[b] Menzies Centre for Health Policy, University of Sydney, Sydney, New South Wales, Australia
[c] School of Public Health, Peking Union Medical College and the Chinese Academy of Medical Sciences, Beijing, China

ARTICLE INFO

Keywords:
Alzheimer's disease
Disadvantage
Environmental epidemiology: longitudinal studies
Remoteness

ABSTRACT

Cross-sectional studies of Alzheimer's disease tend to report higher risk in 'rural' areas. Multilevel longitudinal analysis of 261,669 participants in the Sax Institute's 45 and Up Study was conducted, tracking incidence of Alzheimer's disease defined by the first cholinesterase inhibitor prescription via linked records from the Department of Human Services in Australia. Alzheimer's disease was diagnosed in 3046 participants over 11 years. Adjusting for age, gender, education, income and area disadvantage, Alzheimer's disease risk was lower in 'outer regional and remote areas' (incident rate ratio 0.81, 95%CI 0.67–0.97) compared with 'major cities'. Further research on environmental factors is warranted.

1. Introduction

With high (or rising) life expectancy in many countries, one of the most significant public health ambitions is to advance wellbeing in the senior years (Beard et al., 2016). Dementia, of which the most common form is Alzheimer's disease, represents a major stumbling block to realising this ambition, affecting an estimated 47 million people worldwide (Orgeta et al., 2018). For an individual, Alzheimer's disease involves the loss of memory, cognition, reasoning, the ability to participate in lifestyles that they value and an increased dependency on caregivers (Winblad et al., 2016). The total cost of dementia in 2015 was an estimated US$ 818 billion and is expected to rise to US$ 2 trillion by 2030 (Alzheimer's Disease International, 2015). Approximately 85% of the financial costs are borne by the individuals directly affected, their families and local authorities (Jönsson et al., 2017; Orgeta et al., 2018).

Alzheimer's disease has been reported to have decreased in recent years (Prince et al., 2013; Satizabal et al., 2016; Wu et al., 2016). This is not thought to be attributable to pharmaceutical intervention, since cholinesterase inhibitors decelerate disease progression and provide symptomatic relief, but are no cure (Kumar and Singh, 2015). Concrete knowledge of risk factors for Alzheimer's disease remains thin, but some of the best evidence available recommends educational attainment, physical activity and prevention of cardiovascular diseases (Orgeta et al., 2018; Sharp and Gatz, 2011; Yaffe, 2018). This suggests a role for environmental risk factors and public policies that might shape them (Reitz et al., 2011), such as the integration of healthy design principles within city planning (Giles-Corti et al., 2016; Sallis et al., 2016).

Yet surprisingly few studies have been conducted to examine environmental contributions to the incidence of Alzheimer's disease and multilevel longitudinal studies are especially scarce, as reported by a systematic review (Killin et al., 2016). Some work has reported within-country geographic variation in the prevalence of Alzheimer's disease in western European nations (Russ et al., 2015), while a another systematic review and meta-analysis concluded that a number of studies have reported higher prevalence of dementia in rural communities (Russ et al., 2012). This meta-analysis estimated an odds ratios of 1.20 (95% CI 0.84–1.71) and 1.11 (95%CI 0.79–1.57) for rural to urban differences in Alzheimer's disease incidence (n studies = 5) and prevalence (n studies = 13), respectively. These studies were set in the US, Canada, UK, Italy, Turkey, Nigeria, China, Peru, Mexico, and India.

Given the previous reliance upon cross-sectional data and small sample sizes, the prevalence studies in particular were unable to discount the potential for selective migration of people who are diagnosed

* Corresponding author at: Population Wellbeing and Environment Research Lab (PowerLab), School of Health and Society, Faculty of Social Sciences, University of Wollongong, Wollongong, New South Wales, Australia.
E-mail address: thomasab@uow.edu.au (T. Astell-Burt).

https://doi.org/10.1016/j.healthplace.2018.09.003
Received 2 June 2018; Received in revised form 28 August 2018; Accepted 4 September 2018

with Alzheimer's disease moving into care homes and retirement villages to benefit from better access to centralised caregiving resources and medical care, of which may typically be located the leafy fringes of cities and in rural areas more generally. This is also likely to be a problem in studies of incidence that do not utilise a measure of environmental circumstances taken prior to diagnosis being made. This is important as the results may then underplay the importance of potential risk factors that are known to cluster spatially within cities. Air pollution, for example, may reduce cognitive functioning and increase the risk of Alzheimer's disease and is typically clustered in cities (Chin-Chan et al., 2015; Costa et al., 2017). Recent work has suggested a potentially protective role for cognitive functioning via contact with green space (Cherrie et al., 2018; Zijlema et al., 2017), which is generally more plentiful outside of cities. Furthermore, an elevated risk of dementia incidence has been reported among people who live near major roads even after adjusting for air pollution (Chen et al., 2017), suggesting a potential role for chronic exposure to noise and related psychosocial stressors that are also more common in cities (Münzel et al., 2014; Tzivian et al., 2017).

The risk of developing Alzheimer's disease would appear to be higher in cities than rural areas based upon this emerging evidence, yet most prior studies suggest the opposite. As those studies are largely dependent upon cross-sectional data to contrast the prevalence of Alzheimer's disease in cities and rural areas, those studies cannot disentangle potential causation from correlation that is exaggerated or fully induced by health-selective migration. Longitudinal studies that track Alzheimer's incidence among people living in cities compared to communities located outside of cities are needed. This is the purpose of our study, which is the first longitudinal investigation of geographic variation in the risk of developing Alzheimer's disease to be set in Australia. A country in which 85% of the population lives in cities, where there is a demonstrable 'suburbanisation of disadvantage' (Randolph and Tice, 2017) and with rural populations long-known to experience the so-called 'tyranny of distance' (Blainey, 1982).

2. Data and methods

Data for this study comprised The Sax Institute's 45 and Up Study linked with selected records from the Pharmaceutical Benefits Scheme for purposes of case ascertainment over an 11 year time-period. Participants were aged 45 years and older at baseline, residing in the state of New South Wales, Australia. Data collection began in 2006 and was completed in 2009. Recruitment of participants was via the enrolment database of the Department of Human Services (formerly Medicare Australia), which is responsible for administering Australia's publicly funded health insurance scheme. Participants responded to a questionnaire and provided signed consent to long-term follow-up through repeated data collection. Approximately 18% of the questionnaires were returned, resulting in a sample of 266,889 participants. The baseline is broadly representative of people aged $\geq$45 years in Australia (Johar et al., 2012). More detailed information is available (45 and Up Study Collaborators, 2008). Data collection was approved by the University of New South Wales Human Research Ethics Committee (HREC). This study was approved by the University of Wollongong HREC.

3. Alzheimer's disease

Incidence of Alzheimer's disease was identified via the first recorded prescription of any of the four cholinesterase inhibitors listed on the Pharmaceutical Benefits Scheme: Donepezil (item number 8495); Galantamine (2537, 2463, 2531); Memantine (1956, 2492, 2513, 9306); and Rivastigmine (2475, 2477, 2493, 2494, 2526, 2551, 8497, 8498, 8499, 8500, 9161, 9162, 10538, 10541). To receive a prescription, a person would need to present with a Mini-Mental State Examination score of 10–24 inclusive, which is consistent with mild to moderate Alzheimer's disease (Folstein et al., 1975). This score would need to be confirmed by a psychiatrist or a specialist physician from a branch of internal medicine. People with scores outside of the aforementioned range are subjected to further conditions. The prescribing doctor is required to submit written evidence of the person's diagnosis, clinical severity and the Mini-Mental State Examination score to the Department of Human Services (Hollingworth and Byrne, 2011). Data linkage of all records for all cholinesterase inhibitor prescriptions to participants in the 45 and Up Study from January 1st, 2004 to December 31st, 2016 was performed via direct (i.e. 'deterministic') methods using an encrypted unique identification number for each person provided by the Department of Human Services. Participants who had received one or more prescriptions for cholinesterase inhibitors before completion of the baseline questionnaire were omitted (n = 271).

4. Remoteness indicator and area-level socioeconomic circumstances

A total of 261,937 from 266,889 participants at baseline were geocoded by their place of residence. This geocode was used to assign each person to the geographic context in which they resided. One of these variables was a remoteness classification derived from the Accessibility Remoteness Index of Australia (or 'ARIA') (Australian Population and Migration Research Centre, 2012), which was re-categorised by the Australian Bureau of Statistics as follows: (i) 'major city' (ARIA scores between 0 and 0.2); (ii) 'inner regional area' (0.2–2.4); (iii) 'outer regional' (2.4–5.92); (iv) 'remote' (5.92–10.53); and (v) 'very remote' (> 10.53). A map of these ARIA categories is available online (Australian Bureau of Statistics, 2018).

The ARIA index was constructed using Geographic Information Systems to measure road distance between small areas to service centres across Australia. The category of 'major cities' can be used to describe areas as mostly containing communities that have relatively unrestricted geographic accessibility to a wide range of goods and services and opportunities for social interaction. The higher the ARIA score, the more restricted geographic access to those goods, services and opportunities for social interaction people are suggested to have. In this analysis, participants in 'outer regional' 'remote' and 'very remote' areas were aggregated due to small numbers in each separate category. As there is no widely recognised cut-point in ARIA for differentiating between 'urban' and 'rural' areas, no such attempt to dichotomise is made in this study.

As there is variation in area-level socioeconomic circumstances that could potentially modify the risk of developing Alzheimer's disease, as may be the case with other NCDs, this was measured using the Socio Economic Index For Areas Relative Index of Social Disadvantage. This index was derived by the Australian Bureau of Statistics (ABS) via principal components analysis with census data on income, education, employment, occupation, housing and other indicators of relative disadvantage (e.g. no car ownership).

5. Confounding

A conservative approach to confounder selection was taken, given the extent of knowledge about risk factors for Alzheimer's disease that may also shape where people live. Age group (45–54 y, 55–64 y, 65–74 y, 75–84 y, $\geq$85 y) and gender were both included as confounders, as was the level of educational qualifications attained up to the point of completing the questionnaire. Educational qualifications were measured via self-report, with responses classified as: (i) none; (ii) school-level qualifications; (iii) university and higher education-level qualifications; (iv) undeclared. Low educational attainment is sometimes identified as a risk factor for Alzheimer's disease (Sharp and Gatz, 2011) and helps to shape where a person chooses to live, as well as being a proximate cause of many other contributing factors, such as