## Editorial

# Using Cross-Cultural Studies to Improve Evidence on Dementia Prevention: Lessons from the Special Issue Sponsored by the International Research Network on Dementia Prevention (IRNDP)

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The manuscripts presented in this issue of the journal highlight the value of including diverse populations and settings in research on Alzheimer's disease and related disorders (ADRD). Evidence from populations typically underrepresented in ADRD research —including low- and middle-income countries (LMICs) as well as underrepresented groups in high-income countries—can offer greater scientific insight than evidence from populations already well studied. By integrating evidence from diverse settings, we can better address questions of causality and identify effective intervention strategies to reduce the burden of Alzheimer's disease.

This issue of the *Journal of Alzheimer's Disease* includes 8 articles drawing on cross-national or cross-cultural studies of Alzheimer's disease and related disorders (ADRD). Collectively, these studies highlight several scientific advantages and challenges of broadening research on ADRD to include more diverse populations, settings, and study designs. Evidence from populations typically underrepresented in ADRD research—including low- and middle-income countries (LMICs) as well as underrepresented groups in high-income countries—holds promise for revealing successful intervention and prevention strategies. To capitalize on such opportunities, however, we need thoughtful design and data harmonization and analysis approaches.

The era of evaluating ADRD "risk factors" without rigorous consideration of causality is over. Causal understanding provides the path to effective prevention and treatment. In many cases we have several studies showing that a risk factor is associated with or predictive of ADRD, yet substantial debate about causality remains. This fundamental challenge is implicit in recent high profile estimates of the fraction of ADRD that could be prevented, because all such estimates rely on the assumption that we have accurate assessments of causal effects [1]. To identify the

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causal determinants of ADRD, we will need novel research approaches. Although individual studies are unlikely to provide conclusive evidence about causal effects, we can carefully knit together evidence from different study designs and research settings to evaluate alternative causal structures. This process has been referred to as "triangulation" and offers the best promise for learning about causal structures from observational data [2–4]. Triangulation recognizes that no study is perfect, but aims to identify alternative study designs with different, unrelated weaknesses. By combining results from different approaches, the overall strength of evidence gains strength. For example, a very strong association between education and cognitive test scores has been documented in numerous high-income countries. The major limitations in these studies is the difficulty of ruling out the confounding influence of individual characteristics such as intelligence or childhood socioeconomic status that may influence both schooling and late-life cognition. Evidence from studies in settings with very different confounders [5], or based on natural experiments that could not plausibly be influenced by individual characteristics [6], strengthens the overall evidence base, even if the new studies have different limitations.

Cross-national studies, especially research drawing on LMICs, are particularly valuable in efforts to evaluate causality. Cross-national comparisons offer a potential solution to the problem of disentangling confounders from causal factors: confounding bias that is intractable in one country may be completely different in other settings, offering opportunities to triangulate on the true effects. This phenomenon means that evidence from *new* populations often has greater potential scientific impact than evidence from well-studied communities. Although in some cases homogeneity has been argued to be an advantage for individual studies, when considering ADRD research as a whole, diversity and heterogeneity of populations and designs will be more powerful and enlightening. Additional costs are entailed in fielding studies in low-resource settings or recruiting individuals from underrepresented communities into ADRD studies, so recognizing that such participants also provide additional benefit is important. Ignoring LMICs is a missed opportunity for revealing the underlying etiology of ADRD and determinants of outcomes experienced by people living with ADRD.

If we are to take best advantage of newly emerging evidence from LMICs, cross-national studies, or numerous small studies in diverse populations, we must harmonize our research studies and adopt more formal approaches to integrating evidence. Harmonization is the process of making data from different studies comparable so the evidence from multiple sources can be combined. This means harmonizing outcome assessments, exposure assessments, and analytic approaches in future research and finding ways to cross-walk between results from existing studies that were not harmonized in advance. Both non-statistical methods such as identifying shared items and statistical methods such as latent variable modeling are relevant for harmonization [7, 8]. Differences in cultural context create additional challenges in harmonizing surveys, but these challenges are unavoidable: we must grapple with the role of cultural context eventually if we are to field interventions in diverse settings. The Health and Retirement Study international sister studies have been extremely successful at identifying shared data elements that could appropriately be fielded in numerous international settings [9]. The international replications of the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGERS) trial are also inevitably grappling with how to operationalize this multi-component intervention in diverse settings and achieve harmonized outcome assessments to facilitate integration of results [10].

Without this harmonization, we will learn much less from each individual study and we will never be able to draw generalized conclusions about the drivers of disease. Careful harmonization is essential to allow meaningful comparison across studies and therefore to identify factors that attenuate or exacerbate effects of a risk factor. Without rigorous harmonization, when we find different effect estimates in different studies, we will not know if these differences are substantively important or merely artefacts of measurement or design differences.

The relevance of the lifecourse is another theme from these papers, and recognition that lifecourse milestones and stages may differ across settings. To identify causal determinants of ADRD, our research must incorporate more explicit models of the years- or perhaps decades-long development of AD. We have long understood that dementia typically emerges after years of accumulating disease, and it therefore stands to reason that the effects of exposure will depend on when an individual is exposed. This is a fundamental challenge when evaluating time-varying exposures, such as body mass index (BMI), social connections, behavioral patterns, or even modifiable "omic" measures, such as proteomics, but developmentally

specific effects of exposures must be evaluated if we are to design successful interventions.

These points are well illustrated in the interesting array of studies in this issue of the journal. Danat et al. [11] present a meta-analysis of studies evaluating the association between BMI and BMI categories with dementia risk, focusing on community-based studies that assessed BMI among people ages 65+. In this fascinating report, they find that among studies with less than 9 years of follow-up, the overall meta-analyzed relative risk per BMI point is 0.95 (95% CI: 0.93, 0.96), with a non-significant $I^2$ statistic of 21% ($p = 0.25$), indicating most of the heterogeneity between studies could be attributed to sampling variability. In contrast, in studies with 9 or more years of follow-up, they found a meta-analyzed RR of 1.03 (0.96, 1.11), with an $I^2$ of 75% ($p < 0.001$), indicating that most of the variability was likely due to real differences in effects from different studies. This intriguing result illustrates the importance of studies across diverse contexts: there are major modifiers of the effects of even extremely well-studied risk factors such as BMI. These modifiers may relate to age of the sample, duration of the follow-up or contextual factors such that BMI represents distinct physiologic or social risk. Danat et al. [11] highlight the potential for reverse causation: it is very likely that changes in BMI in late life are primarily consequences of disease, rather than determinants, and therefore not useful targets for preventive intervention. A key role for meta-research such as the Danat paper is to identify research gaps. All 16 previously published studies identified in their review were from high-income countries, and they added valuable new results from China. These data from Chinese adults showed a qualitative difference in the association between BMI and dementia risk for men (among whom overweight/obesity predicted higher risk of dementia) compared to women (among whom overweight/obesity predicted lower risk of dementia). New studies in LMICs or other settings with different social patterning of BMI or distinct timing of the obesity epidemic may offer additional leverage for causal identification.

Peters et al. [12] identified 13 cohort studies on air pollution and ADRD, all from high income settings. They considered studies of either incident dementia or rate of cognitive change and found consistent evidence that exposure to particulate matter ≤2.5 m, nitrogen dioxide, nitrous oxides, and carbon monoxide predicted increased risk of dementia or accelerated cognitive decline. Their review illustrates

the challenge of integrating findings from studies with different but clearly related outcome measures, such as cognitive decline and dementia incidence. Environmental determinants of dementia risk, including air pollution, may have tremendous public health consequences because, as Peters et al. note, air pollution is "pervasive, global, life-long" and modifiable. Regulation of air pollutants is already common, and rigorous evidence on effects on dementia risk can help guide the development of those regulations. Peters et al. [12] lay out priority areas for future research, including improved exposure measures, evaluating exposure duration, and understanding how effects differ across settings. Individuals in LMICs face a major burden of premature mortality from air pollution [13], and yet, LMICs were notably missing from the extant literature. Environmental health issues are likely to be extremely relevant to ADRD risk in LMICs. For example, as Peters notes, prior autopsy studies in Mexico City found that exposure to urban air pollution predicted a greater neuropathologic burden even among children and young adults [14]. Developing a foundation of evidence on environmental determinants of ADRD risk is a high priority topic for global dementia research.

Evans et al. [15] identified sixty-five articles on aspects of social isolation and cognitive function or dementia risk in older adults, restricting to studies with at least one year of follow-up after the measurement of social isolation. Social relationships and the downstream consequences are complex to measure. Comprehensive assessments are typically based on long questionnaires and rarely fielded in large population based studies (with some notable exceptions [16]), thus most research on social ties and cognitive function draws on brief summary reports of engagement in social activities, number of close ties, or self-assessed adequacy of social support. In the Evans review [15], they found fairly consistent associations of social activity or networks with cognitive outcomes, regardless of the duration of follow-up time, gender of respondent, or outcome domain. As the authors note, there are several caveats, in that incipient ADRD almost certainly leads to social withdrawal years prior to diagnosis. They also found evidence of publication bias, indicating that results consistent with expectation are more likely to be published. Given the large number of studies to date using similar research designs to evaluate the links between social activity and ADRD risk, the most valuable future directions in this area will adopt novel designs to circumvent major challenges

to establishing causality. This might include quasi-experimental approaches or, as Evans et al. [15] notes, randomized interventions. Because there have been numerous randomized studies intervening on social experiences for individuals in diverse settings, such as caregivers or patients with various diagnoses [17, 18], such efforts might leverage existing studies by incorporating new cognitive measures.

Radford et al.'s study [19] of factors associated with dementia in a sample of 336 Aboriginal Australians aged 60+ years illustrates both the promise and challenges of focusing research attention in communities rarely represented in dementia studies. Previous work indicates Aboriginal Australians have substantially higher dementia risk than other Australians [20], and although the existing evidence base is limited, this demonstrates the relevance of ADRD for Aboriginal health. Radford et al. [19] identified social (childhood trauma and low-skill occupation), behavioral (past high-risk alcohol use) and medical conditions (stroke, head injury) as significant predictors of prevalent dementia. These results are not surprising and indicate general consistency with dementia predictors in other studies, although Radford et al. [19] note that education in this sample was not independently associated with dementia. More specifically, the association between education and dementia was not statistically significant, although the effect estimate (OR = 0.82) reported by Radford was protective similar to estimates reported elsewhere, but not precisely estimated. In other words, the association in their data was not statistically significant, but an effect size indicating an 18% reduction in odds of dementia would be substantively important if it were precisely estimated. This is an intrinsic challenge in studying hard-to-reach populations: the studies are often expensive and typically face major resource constraints. This calls not only for more resources for this research, but also for a consideration of best statistical methods for evaluating familiar risk factors in novel populations. In such studies, we must carefully consider our null hypothesis: instead of testing the null that a risk factor has no effect for each population, should we begin with the assumption that effects are the same in all populations and test whether effects differ? If we pursue the standard approach of testing all effects against the null hypothesis of no effect, we risk systematically missing important risk factors in hard-to-reach populations. Another key point brought to light by Radford et al is that it may be impossible to identify the major determinants of dementia in a population by fielding a study within only that population. As Rose's classic work beautifully illustrated, if everyone within a population is exposed to a particular risk factor, it is impossible to show the role of that risk factor unless it can be compared to a population with less exposure [21]. This is particularly important in extremely disadvantaged communities, in which poor quality education, exposure to discrimination, experiences of trauma or other social risks may be nearly universal. By combining studies across diverse settings, we have the potential to learn much more.

Using data from 160 Malay individuals, grouped into four age brackets (30–39, 40–49, 50–59, and 0–69), Abu Bakar et al. [22] apply proteomic approaches to evaluate which protein profiles may differ by age in hopes to gain insight into proteomic patterns linked to cognitive decline. One notable aspect of this paper is the use of pooled samples for proteomic analyses. This approach merits special note because it makes a potentially very expensive analysis more feasible while, if correctly implemented, sacrificing little in terms of evidence quality [23]. Importantly, pooling samples heterogeneous on a risk factor makes it nearly impossible to evaluate the effects of that particular risk factor (e.g., pooling samples for men and women precludes evaluation of the effects of sex on the biomarker of interest in the sample), so detailed advance planning about the analyses of interest is important.

In a large ($n = 4,128$) sample of Australians, Sacre et al. [24] found that the 3.4% of the population with albuminuria had accelerated declines in both memory and processing speed. Less than 1% of the sample ($n = 39$) had frank kidney dysfunction (eGFR < 60 ml/min/1.73 m$^2$), so it is not surprising that they detected no significant association between kidney dysfunction and cognitive decline. Their paper takes advantage of the repeated measures of kidney function to assess the duration of albuminuria required to see an effect on cognition. They find that although albuminuria measured 12 years prior to memory was significantly associated, albuminuria measured only 7 years earlier had almost no association with memory. These results should be replicated in an independent sample but highlight that many risk factors likely to causally impact disease may take over a decade to do so, requiring substantial follow-up to make headway on causal determinants.

Cherbuin et al. [25] used data from the influential 10/66 study to evaluate the relationship between chronic obstructive pulmonary disease (COPD) and risk of incident dementia over 3-years of follow-up.

They found that although COPD was a strong predictor of mortality, it was significantly associated with dementia only in Cuba (out of 7 countries evaluated). Cherbuin et al. [25] undertook formal efforts to address the clear potential bias introduced because COPD increases mortality. Survival bias is a pervasive problem in dementia research, and it is receiving increasing formal attention [26, 27]. The Fine and Gray method adopted by Cherbuin et al. [25] is useful in particular for public health planning about potential future burden of disease [28], though less informative about disease etiology.

Deckers et al. [29] used data from the Dutch Doetinchem Cohort Study to evaluate the relationship between the 'LIfestyle for BRAin Health' (LIBRA) score and cognitive change and indirectly address the controversial topic of gender differences in dementia risk. The LIBRA score, which combines five behavioral measures (diet, alcohol use, cognitive activity, physical activity, and smoking) with seven disease indicators (coronary heart disease, diabetes, hypercholesterolemia, hypertension, depression, obesity, and renal disease). Although describing renal disease, depression, and other complex, life-threatening diseases as "lifestyle" factors is a misnomer, the LIBRA index provides a powerful summary of several risk factors that might be prevented by structural, behavioral, or medical intervention. Deckers et al. [29] found that worse LIBRA scores predicted slightly faster decline in cognitive flexibility and mental speed, with no apparent differences by education level. LIBRA predicted verbal memory decline among women but not men, although given that small differences were observed in only one cognitive outcome, Deckers et al. [29] summarized the evidence as roughly similar associations by education and gender. The possibility of gender differences in ADRD incidence has received substantial research attention, but recent work also highlights the many reasons that small differences may reflect methodological artefacts [30]. The careful sensitivity analyses evaluating the role of cardiovascular disease and baseline differences in cognitive test scores help allay concerns that their these factors may have contributed to their findings [29].

In combination, these studies illustrate the promise of international or cross-national ADRD research and efforts to include often underrepresented populations in ADRD research. Alongside the moral imperative of increasing diversity in ADRD research, we should add the scientific imperative. Understanding the biology of ADRDs and the causal pathways which could be targeted to prevent the devastating cognitive consequences has proven devilishly difficult. Evidence from novel research settings can broaden our vision of prevention strategies and circumvent persistent research challenges.

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