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Review Articles

Guidelines for reporting methodological challenges and evaluating potential bias in dementia research

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Abstract Clinical and population research on dementia and related neurologic conditions, including Alzheimer's disease, faces several unique methodological challenges. Progress to identify preventive and therapeutic strategies rests on valid and rigorous analytic approaches, but the research literature reflects little consensus on "best practices." We present findings from a large scientific working group on research methods for clinical and population studies of dementia, which identified five categories of methodological challenges as follows: (1) attrition/sample selection, including selective survival; (2) measurement, including uncertainty in diagnostic criteria, measurement error in neuropsychological assessments, and practice or retest effects; (3) specification of longitudinal models when participants are followed for months, years, or even decades; (4) time-varying measurements; and (5) high-dimensional data. We explain why each challenge is important in dementia research and how it could compromise the translation of research findings into effective prevention or care strategies. We advance a checklist of potential sources of bias that should be routinely addressed when reporting dementia research.

Keywords: Alzheimer disease; Dementia; Neuropsychological tests; Longitudinal studies; Epidemiologic factors; Statistical models; Selection bias; Survival bias; Big data; Genomics; Brain imaging

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1. Introduction

Despite more than two decades of research on prevention and treatment of dementia and aging-related cognitive decline, highly effective preventive and therapeutic strategies remain elusive. Many features of dementia render it especially challenging: supposedly distinct underlying pathologies lead to similar clinical manifestations, development of disease occurs insidiously over the course of years or decades, and the causes of disease and determinants of its severity are likely multifactorial. However, progress in preventing and treating dementia also rests on how dementia research is conducted: informative research requires valid and rigorous analytic approaches, and yet the research literature reflects little consensus on "best practices."

Several methodological challenges arise in studies of the determinants of dementia risk and cognitive decline. Some challenges, such as unmeasured confounding or missing data, are common in many research areas; others, such as outcome measurement error and lack of a "gold standard" outcome assessment, are more pervasive or more severe in dementia research [1–3]. Currently, researchers handle these challenges differently, making it difficult to directly compare studies and combine evidence. Although some methodological differences across studies arise because analytic methods are explicitly tailored to the study design and realities of the data at hand, other differences arise for less substantive reasons. Modifiable sources of inconsistency include the absence of consensus and definitive standards for best analytic approaches; different disciplinary traditions in epidemiology, clinical research, biostatistics, neuropsychology, psychiatry, geriatrics, and neurology; and software and technical barriers.

The various analytic methods used in dementia research often address subtly distinct scientific questions, depend on different assumptions, and provide differing levels of statistical precision. Unfortunately, there is often insufficient attention to whether a chosen method addresses the most relevant scientific question and relies on plausible assumptions. Some common methods likely provide biased answers—i.e., answers that diverge systematically from the truth—to the most relevant scientific questions. Even if several alternative approaches might be appropriate and innovative or novel analyses used in individual studies may be valuable, it can be advantageous to report results using a shared approach [4,5]. The "inconsistent application of optimal methods" within and across studies makes it difficult to qualitatively or quantitatively summarize results across studies (meta-analyses). By contrast, a core set of shared analytic approaches would enhance opportunities to synthesize results and more conclusively address our research questions. Applying a set of standardized sensitivity analyses would help evaluate the plausible magnitude of various sources of bias or violations of assumptions. In randomized clinical trials (RCTs), for example, there are strict rules regarding intention-to-treat analyses, which are often complemented with additional approaches, such as per protocol analysis or modeling the complier average causal effect to account for noncompliance.

The CONsolidated Standards of Reporting Trials (CONSORT) [6] and Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines [7] provide helpful indications of broad relevance in human subjects research but are too broad to address several specific methodological difficulties in dementia research. Topic-specific guidelines building on STROBE have proven useful in several domains, such as genetic association studies [8]. The MEthods in LOngitudinal research on DEMentia (MELODEM) initiative was formed in 2012 to address these difficulties and achieve greater consistency in the process of selecting and applying preferred analytic methods across research on dementia risk and cognitive aging. The initial MELODEM findings outline a set of methodological problems that should routinely be addressed in dementia research, summarized in the guidelines in Fig. 1. We advance this list as a working set of guidelines for transparent reporting of methods and results and therefore the best chance of accelerating scientific progress in identifying determinants as well as validating biomarkers for earlier diagnosis of Alzheimer's disease (AD). The goals of MELODEM include fostering methodological innovation to address these challenges and improving understanding of tools to address each challenge. In this initial report from MELODEM, we focus on outlining major categories of bias and why they are especially relevant in dementia research. We briefly discuss in the following, with more details in the online supplement, five major challenges: (1) selection, i.e., handling selection stemming from study participation, attrition, and mortality; (2) measurement, i.e., dealing with the quality of measurements of exposure and outcomes and how imperfect measurement quality affects analysis and interpretation of results; (3) alternative timescale, i.e., specifying the timescale and the shape of trajectories in longitudinal models; (4) time-varying exposures and confounding, i.e., accounting for changes in explanatory variables; and (5) high-dimensional data, i.e., analyzing complex and multidimensional data such as neuroimaging, genomic information, or database linkages.

For some topics in the checklist (Fig. 1), substantial controversy remains regarding optimal analytic approaches, especially when considering both bias and variance of the methods. In many cases, although the potential for bias is clear, it has not been established that this bias is substantial in real data. The guidelines in Fig. 1 are intended as a first step toward improved evaluation and reporting of methodological challenges in dementia research, to support a move toward field-wide consensus on best practices, and identifying the highest priority areas for methodological innovations.