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Observational studies in Alzheimer disease: bridging preclinical studies and clinical trials

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Abstract

Recent high-profile failures of Alzheimer disease treatments at the clinical trial stage have led to renewed efforts to identify and test novel interventions for Alzheimer disease and related dementias (ADRD). In this Perspective, we highlight the importance of including well-designed observational studies as part of these efforts. Observational research is an important cornerstone for gathering evidence on risk factors and causes of ADRD; this evidence can then be combined with data from preclinical studies and randomized controlled trials to inform the development of effective interventions. Observational study designs can be particularly beneficial for hypothesis generation, posing questions that are unethical or impractical for a trial setting, studying life-course associations, research in populations typically not included in trials, and public health surveillance. Here, we discuss each of these situations in the specific context of ADRD research. We also highlight novel approaches to enhance causal inference and provide a timely discussion on how observational epidemiological studies help provide a bridge between preclinical studies and successful interventions for ADRD.

Introduction

Alzheimer disease and related dementias (ADRD) are an important and growing problem worldwide; a report published in 2020 estimated that >50 million people have ADRD and that this number will increase to 152 million by 2050 (ref.[1]). Most individuals with dementia are found to have Alzheimer disease (AD) or AD plus other pathologies at autopsy[2]. Substantial research efforts have been dedicated to identifying the aetiological causes of ADRD and to developing pharmacological treatments. Evidence indicates that a complex combination of genetic and environmental exposures contributes to cognitive decline and development of dementia[3]. Estimates suggest that life-course risk factors, such as education, cardiovascular health and physical activity, account for up to 40% of dementia worldwide

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W.D.B. researched data for the article. All authors contributed substantially to discussion of the content. All authors wrote the article. All authors reviewed and/or edited the manuscript before submission.

and that these risk factors could be targeted to reduce dementia prevalence[4,5]. Numerous treatments and interventions for ADRD have been evaluated in clinical trials, yet the vast majority have failed to slow cognitive decline or dementia progression[6]. These failures suggest a need to refine our hypotheses around the treatment and prevention of dementia and to address methodological and other challenges to identifying effective treatments. Although in evaluating treatments there is often a focus on preclinical studies and clinical trials[7,8], observational research in human participants (for example, studies without interventions) has an important role in knowledge generation. Such studies will be essential if we are to move the field forward towards identifying effective strategies to prevent and slow dementia onset.

Well-designed observational studies are essential to bridge the gaps between preclinical studies and randomized controlled trials (RCTs) and to provide real-world data. Here, we use the term preclinical studies to refer to studies that investigate disease mechanisms or contribute to drug discovery and drug development prior to testing in human participants. These preclinical studies primarily test cell lines, animal-based models or human biospecimens in a controlled environment. Although preclinical studies are crucial for knowledge and hypothesis generation, their results have limited generalizability to human populations and require confirmation in human participants; indeed, most dementia therapies that have produced promising preclinical results have not been successful in RCTs[6,9].

The efficacy and safety of a novel drug must be demonstrated in RCTs in human participants before it can be approved for use in patients. Well-designed RCTs can provide robust evidence of the effects of treatments or interventions. However, they are often of limited duration (several years) and scope owing to costs and feasibility, which can make it more difficult to detect some treatment effects. Even RCTs of sufficient size and duration often require participants to meet strict eligibility criteria, which can exclude individuals with comorbid disease and under-represented minorities. Furthermore, for many research questions, such as to understand the effects of harmful exposures, conducting an RCT is not ethical or feasible[10]. Therefore, for many research questions, well-designed observational studies can help bridge and complement experimental designs[7,8].

Because observational studies are more prone to biases, such as unmeasured confounding and selection bias, than well-designed RCTs[11,12], the development and use of rigorous approaches that enhance causal inference are essential[13]. Nevertheless, different research questions and settings require different approaches and study designs to yield relevant and valid answers. Therefore, evidence should be evaluated on the basis of quality as opposed to purely on the type of study design[14]. In this Perspective, we present our view on the important role of observational studies in ADRD research. We discuss the challenges of using RCTs to study ADRD and highlight specific ADRD research topics that are suited for observational studies. Finally, we discuss emerging approaches to improve causal inference using observational data and other future research directions.

Observational studies

Observational research is a general term for studies that involve no intervention, manipulation, or experimentation of participants or samples. The term can apply to both basic science and clinical research; here, we focus on observational studies in the context of human clinical and epidemiological research. Observational studies differ from RCTs in two important aspects. First, RCTs involve an intervention, for example, a drug treatment, medical procedure, or psychological or behavioural training. Second, in RCTs, allocation to receive the intervention or not (control) is assigned by random chance; this provides clear temporal order of exposure and outcome and is not as susceptible to confounding by other characteristics. See Table 1 for a more detailed comparison of the advantages and disadvantages of RCTs and observational study designs.

Epidemiological questions can be assessed with a variety of observational study designs[15]. Many of these study designs draw inference on causes of disease by comparing health factors of interest (often called a risk factor or exposure) between those with and without the disease of interest (often called the outcome). Factors of interest can include social and demographic factors, lifestyle and health behaviours, molecular or biological indicators, and other health conditions. Observational studies can also be used to assess and validate screening and diagnostic tools or to monitor trends in disease prevalence over time. Various epidemiology textbooks describe study designs and their considerations in detail[15,16]; we summarize common designs in Box 1. In each of these designs, data can be collected from a variety of sources, including clinical examinations, biological measurement questionnaires, electronic medical records, insurance claims data, and/or census information.

Taken into the context of translational science, in which discoveries are translated from basic research and discovery to clinical care or public health measures, observational studies can be used to inform various stages, from basic science to clinical practice[17,18]. Box 2 summarizes the types of clinical and epidemiological research questions that are suited for observational studies. Below, we further highlight the challenges of performing RCTs in ADRD research and provide specific examples of ADRD research questions that observational epidemiological studies are well suited to address.

Limitations of RCTs

In addition to the general advantages and disadvantages set out in Table 1, RCTs have specific disadvantages in the context of dementia. First, dementia develops over decades and, by the time cognitive impairment is detected, the underlying pathological changes might be too advanced for therapy to be effective[3]. One reason for the failure of so many clinical trials of disease-modifying interventions in dementia might be that interventions are given too late to significantly slow the disease process and prevent neurodegeneration[19]. Second, dementia is a heterogeneous syndrome that encompasses a variety of underlying brain pathologies[2]. Although AD is the most common subtype — comprising 50–70% of dementias[2] — most individuals have multiple co-occurring pathologies at autopsy (termed mixed neuropathology), including AD, vascular pathology, Lewy body disease and TDP43 proteinopathy[20,21]. These pathologies could act additively or interact to increase the risk

of dementia[22-25] or could contribute to the misdiagnosis of clinical dementia subtypes[26]. This broad range of overlapping dementia aetiologies highlights the complexity of brain ageing and suggests that there will be no 'magic bullet' treatment, as one drug is unlikely to affect more than one mechanism or pathology. This heterogeneity thus poses a problem for conducting RCTs. Indeed, even the most optimistic estimates suggest that antiamyloid treatments have small effects on cognition[27], a high risk of adverse effects[28] and are of uncertain benefit for patients who have comorbid medical conditions such as vascular disease[29]. Because animal models of AD tend to mimic a specific and limited number of pathologies, the high prevalence of mixed pathologies in older adults might be part of the reason for failed efficacy of treatments that are promising in animal models.

Applications in AD research

Hypothesis generation

Pathophysiology.—Historically, observational studies have contributed many insights into AD pathophysiology. In the early 1900s, case reports by Alois Alzheimer and others described plaques, tangles and neurodegeneration in the brains of individuals with early-onset dementia, which helped establish AD as a distinct disease[30]. Observational studies have also identified a correlation of neuropathological, imaging and other biomarkers of AD with dementia symptoms over time[3,31,32], genetic variants associated with AD and cognitive decline[33,34], and lifestyle, social and clinical risk factors for AD[5]. Early observational studies on dementia and AD led to the identification of candidate genes such as *APP*[35] and *APOE*[36], neuropathologies associated with dementia[31,37], and staging and diagnostic criteria for AD and other dementias[38-40]. Together, this observational data informed subsequent laboratory studies and the development of the amyloid cascade hypothesis[41], which has since dominated the field and driven the development of drug targets such as amyloid-β-directed monoclonal antibody treatments, including the controversially approved aducanumab[28]. Observational studies also include large-scale genome-wide association studies[34,42] that have identified many AD-associated genetic variants with roles in the production of tau and the innate immune response, which are now being investigated as novel drug targets.

Alongside laboratory studies, observational epidemiological studies have an important role in refining and validating scientific knowledge. For example, observational post-mortem studies identified amyloid-β plaques and tau neurofibrillary tangles as characteristic neuropathological features of AD[31,38], which were used to develop diagnostic criteria. These observations then motivated the development of in vivo diagnostic testing for AD, including PET imaging[43,44], cerebral spinal fluid biomarkers[45] and, more recently, blood-based biomarkers for amyloid and tau burden[32]. Observational biomarker studies examining longitudinal change in AD biomarkers and cognitive decline[46,47] are helping to refine the hypothesized pathophysiological cascade of AD[3] and contributed to the development of the AT(N) framework for the diagnosis of biological AD[48]; this work is ongoing. Improving our understanding of biomarker changes in AD and the duration of the preclinical phase of ADRD will be essential for designing better studies in the future.

Risk factor identification.—Early case–control studies found limited risk factors for dementia[49-51]; however, starting in the 1990s, a shift to large cohort studies with longer follow-up[52] as well as access to electronic medical record databases has resulted in the identification of numerous potential risk factors. Systematic reviews and meta-analyses of observational studies suggest that education, hypertension, vascular disease, diabetes, physical activity, a history of smoking, diet, cognitive engagement, depression, sleep quality, and traumatic brain injury influence the risk of cognitive decline and dementia[4,5,53,54]. Such observational evidence has informed the design of clinical trials testing interventions that aim to slow cognitive decline, for example, vitamin supplementation[55], exercise[56], cognitive stimulation[57], hypertension and cardiovascular risk control[58].

Because observational studies suggest that ADRD are likely to be caused by a complex set of lifestyle and health factors[4,5,53,54], several health domains might need to be targeted to achieve meaningful dementia reduction. Indeed, multi-domain interventions seem to be particularly promising options for dementia prevention. These approaches combine several interventions, for example, dietary changes, exercise, cognitive training, monitoring of vascular and other health risks, and psychosocial interventions[59-61]. Examples of clinical trials testing multi-domain interventions include the Prevention of Dementia by Intensive Vascular care (preDIVA) trial, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial, the worldwide FINGER studies, and the Systematic Multi-domain Alzheimer's Risk Reduction Trial (SMARRT). The FINGER study is one of few RCTs to have reported slower cognitive decline with intervention[60]. More results are expected from the recently completed SMARRT and ongoing worldwide FINGER study in the next few years.

Observational studies continue to identify and investigate novel potential risk factors for AD. Study designs well suited to this purpose include established prospective, population-based cohort studies that have been running for years (for example, the Framingham Study[62]) as well as emerging data biobanks (for example, UK Biobank)[63], electronic health record databases and registries[64], or data-pooling projects that combine multiple cohorts[65]. AD risk factors that have emerged over the last decade include napping and sleep disturbances[66], peripheral hearing impairment and sensory loss[67], neighbourhood effects such as exposure to air pollution[68], viral infections such as herpesvirus[64], altered gut microbiota[69], and mitochondrial dysfunction[70].

Taking vision impairments (an emerging risk factor for dementia) as an example, a systematic review published in 2022 identified 110 studies that investigated this risk factor, 48% were cross-sectional, 39% longitudinal and 13% were case–control studies[71]. Approximately 50% of the studies were performed with participants enroled in population-based studies and 10% used insurance claims data. Although relatively few studies (n = 17) were rated as being of high quality and having limited potential for bias, the majority were moderate and well-designed observational studies that can provide compelling evidence. Another study published in 2022 found that, among individuals with cataracts, cataract extraction was associated with a reduced risk of dementia[72]. This study combined cohort study data with medical records from an integrated health-care system and used robust analytical methods to account for biases. Furthermore, the researchers used glaucoma

surgery, which does not restore vision, as a negative control. Overall, evidence from these studies suggests that bidirectional associations exist between vision impairment and dementia, and that cataract surgery is associated with a reduced risk of dementia. Future observational studies in this area are needed to build on this evidence and could inform whether and which vision interventions can protect against dementia.

Not all associations established in observational studies have held up in clinical trial settings (for example, hormone therapy)[73,74] nor have the majority of therapeutics developed in preclinical studies[9]. In our opinion, strong observational data help provides critical justification for testing interventions and new avenues for mechanistic research. Ideally, observational studies will be informed by preclinical studies and will also lead to new preclinical studies to help build translational evidence.

Research not suitable for RCTs

Some interventions and exposures cannot be investigated in RCTs or with experimental designs for reasons of ethics, practicality or feasibility[75]. For example, ethical approval for randomization requires equipoise, that is, there is uncertainty over the relative therapeutic merits of each treatment arm[10]. However, unproven interventions increase the risk for participants compared with standard care and many exposures that would be interesting to study in the context of ADRD risk would cause participants harm. These exposures include harmful environmental factors (air pollution, pesticides, harmful chemicals)[68], lifestyle and health conditions (smoking[76], obesity[77], traumatic brain injury[50]), and social determinants of health (racism[78], discrimination, poverty[79]).

Beyond ethics, many exposures that are of interest in ADRD are not feasible for randomized intervention. These include exposures that are difficult to change (for example, personality traits), difficult to assign randomly (for example, treatments that are already in widespread use), and long-term exposures and effects[75,80]. The effect of cancer and cancer treatment on ADRD risk is one such area of research. Although cognitive complaints are common after cancer treatment[81], many observational studies suggest that cancer history is associated with a reduced risk of ADRD in the long term[82]. Therefore, although RCTs for cancer treatments can provide insights into short-term cognitive side effects, the full picture of long-term effects only becomes clear when you look at the observational data.

Larger-scale exposures, such as those at the community level, are also rarely feasible in RCTs. Social determinants of health, defined by the WHO as conditions in the environments where people are born, live, learn, work, play and age, are especially challenging variables for which to design and implement RCTs[83]. These social determinants of health include education, income or wealth, race and ethnicity, sex, health insurance status, neighbourhood characteristics, and other social influences, all of which might contribute to disparities in ADRD but typically are only altered by policies and legislation[84]. Observational studies addressing social determinants of health have identified clear inequalities in dementia incidence. Older adults of lower socioeconomic status (SES)[85] or those who identify as Black or African American or Hispanic have a higher incidence of ADRD than older adults with higher SES levels and those who identify as white or Asian[86]. However, SES and race might also contribute to the underdiagnosis or misdiagnosis of dementia; for example, an

observational study in Denmark reported that patients with dementia with lower SES were diagnosed at more severe stages and later time points than those with high SES[87]. This study was performed by linking several population-based Danish registries on dementia care referrals, demographics and other health conditions.

Using observational studies to implement interventions and policy changes can be justified in the following situations: first, when performing RCTs for the exposure of interest is unethical, impossible or infeasible; second, when waiting to intervene would be a detriment to population health; finally, when the observational evidence is consistent and strong across multiple settings and designs[80]. For example, decades of observational data on social determinants of health have been key for building consensus on possible policy changes and community-wide initiatives to address health disparities[84,88]. Recommendations from the 2008 WHO Commission on Social Determinants of Health final report and current governmental health initiatives include improving access to education, housing, jobs, transportation, green spaces and health care[84,89]. Likewise, consensus groups have relied on observational data to identify improved education, reduction in vascular risk factors and comorbidities, and promoting healthy lifestyles through late life as targets for dementia prevention[5,90].

Life-course associations and timing of exposures

Many exposures are thought to contribute to the risk of ADRD over decades and midlife might be a critical time period for accumulating risk of AD[91]. This slow accumulation of risk is an added challenge for RCTs as these trials last a few years at most, which might be too short for interventions to have a significant effect on cognitive outcomes. Disease modification therapies might need to be given during the preclinical phases of AD whereas primary prevention efforts might need to occur even earlier such as during midlife[92,93] (Fig. 1).

Data from observational studies suggest that cumulative, long-term exposure (as opposed to short-term exposures) to factors such as high blood pressure[65], smoking[76] and depression[94,95] is associated with the highest risk of poor cognition and dementia. Such cumulative effects might also help explain some inequalities in the risk of ADRD. For example, evidence indicates that differences in dementia incidence between Black Americans and white Americans are partly explained by higher blood pressure over the long term in Black Americans[65]. In contrast, obesity in midlife has been associated with an increased risk of AD but the association is null or inverse for obesity in late life, indicating that midlife could be a critical period during which a high body mass index increases the risk of dementia[62]. Early-life experiences and health status might also influence other health and lifestyle factors in a dynamic fashion over an individual's life course[96] (Fig. 2). These aspects of life-course epidemiology are difficult to study in the context of clinical trials but are important for understanding AD aetiology and for identifying interventions to reduce disparities. Identifying the timing of exposures and biomarkers of underlying pathology will also help identify windows during which intervention might be most effective, which is essential for designing better RCTs and moving on from recent trial failures.

Under-represented populations

RCTs generally have strict eligibility criteria that select the samples most likely to demonstrate treatment effects. Invasive study procedures, such as PET scans or lumbar punctures, and requirements for a study partner (proxy respondent) are additional factors that can limit recruitment specifically in AD trials[97]. In addition to eligibility criteria, some individuals might face further barriers to inclusion such as lack of transportation or nearby study sites, language difficulties, and distrust of the medical establishment. Together, these factors might limit the inclusion of important subpopulations in RCTs for ADRD, for example, under-represented and minoritized groups, the oldest-old (age ≥90 years), individuals with lower SES, individuals from rural areas, individuals living alone, or those with medical comorbidities, disability or psychiatric conditions[29].

Evidence indicates that, compared with white Americans, Black or African American individuals have a higher incidence of AD[86] and are more likely to have mixed pathologies and other comorbidities[98] but are less likely to be enroled in RCTs[99]. Furthermore, adults aged ≥90 years also tend to be excluded from RCTs and have more comorbidities, and those with dementia are more likely to have mixed and non-AD pathologies compared with adults <90 years[100]. Clarifying whether new treatments are effective and safe in these and other subgroups is essential for clinical practice. The exclusion of specific groups from participating in RCTs limits the generalizability of study findings and could cast doubt upon the efficacy and safety of treatments for real-world use. For example, evidence indicates that individuals with physical frailty and additional comorbidities have higher rates of discontinuation of anticholinergic medication for dementia than the general dementia population; this discontinuation is hypothesized to be the result of increased side effects[101]. Evidence published in 2021 suggests that 90% of Medicare beneficiaries with AD would have been excluded from the clinical trials for the newly approved aducanumab[29]. Together, this lack of representation in clinical trials means that drugs effective in RCT samples are likely to have reduced real-world effectiveness. Furthermore, the RCT setting often has more structured intervention strategies and methods to ensure adherence that might not be replicable in real-world settings.

Ideally, RCTs that include samples representative of all patients and conducted in real-world settings (for example, pragmatic trials) would be implemented for all newly approved treatments; however, observational studies evaluating treatment use, effects and adverse events are also useful in informing real-world implementation of drugs or other interventions and identifying disparities. As an example, acetylcholinesterase inhibitors are one of the few approved treatments for AD, with RCTs showing modest benefits over a few months of follow-up[102]. Long-term effects on cognition and mortality were then examined in a cohort study, which compared individuals with dementia treated with acetylcholinesterase inhibitors to untreated individuals with dementia over an average of 5 years of follow-up[103]. The findings suggested that there were small but long-term benefits associated with the use of acetylcholinesterase inhibitors, including slower rates of cognitive decline and reduced mortality. Observational studies are also useful for studying the effects of commonly used drugs (approved for the treatment of other conditions; for example, anticholinergics[104] and benzodiazepines[105]) on the risk of ADRD.

Public health surveillance

Last is the role of observational data for public health surveillance of ADRD and the relevant risk factors. Understanding and monitoring the prevalence and incidence of dementia is crucial for understanding the burden of disease and prioritizing policies and interventions. Estimates of the burden of ADRD are high and large increases are expected over the coming decades, which has helped to highlight ADRD as an issue of national[106] and global importance[107]. Data published in 2020 indicate a decline in dementia incidence over the preceding 25 years[108], which gives hope that improvements in education, health behaviours and health care can reduce dementia risk. Beyond highlighting cohort and time trends; observational studies have also identified disparities in dementia incidence such as by race, gender, geography, medical comorbidity status or primary language[47,86,107]. Another observational study highlighted distributions of risk factors across subpopulations, which might be useful for prioritizing the application of prevention methods to reduce dementia disparities[109]. Together, such studies inform progress towards ADRD risk reduction and help identify interventions to reduce inequalities.

Causal inference

Observational studies are generally associated with a greater potential for systematic bias, such as confounding and reverse causation, than RCTs[110] (Table 1 and Box 3). In some cases, treatments that were associated with beneficial health effects in observational studies have subsequently been found to have harmful effects in RCTs. For example, oestrogen therapy for postmenopausal symptoms was associated with a reduced risk of dementia in many observational studies[111]; however, in the Women's Health Initiative clinical trials (1993–2002), combined oestrogen and progestin therapy was associated with an increased risk for dementia[112]. The trials were stopped early owing to health risks associated with the treatment. Causal inference approaches generally seek to emulate a hypothetical RCT and to use statistical and methodological techniques to ensure that exposure groups are otherwise similar to each other (as randomization does in an RCT; Fig. 3a). One set of causal inference methods — for example, marginal structural models[113] and propensity score methods[114] — use statistical sample-weighting techniques to account for potential confounding. These approaches attempt to balance comparison groups in terms of confounders and are usually based on a two-step process: first, the probability or 'propensity' for the exposure is estimated; second, the weights of that propensity are incorporated into the analysis through matching or covariate adjustment. These models can also be used to estimate factors associated with sample selection or missing data[115]. Statistical sample-weighting techniques can be useful for identifying and reducing biased findings; for example, one study found that cognitive activities, such as newspaper reading, were associated with a reduced risk of dementia in a traditional model but, when using weights to account for prior levels of cognitive functioning, this association disappeared[116].

Natural experiments or quasi-experiments are another type of study design that can help infer causality from observational data. A quasi-experiment involves an intervention; however, the circumstances that led to the intervention were not controlled by the researchers. These experiments require some aspect of intervention assignment to be

independent of the characteristics of the participant and the outcome[117] (Fig. 3b). For example, many countries implemented mandatory schooling laws in the twentieth century that resulted in the vast majority of students attending school for longer. Comparing dementia risk between individuals who finished school just before the law change and individuals who finished school just after the law change can provide evidence regarding the effect of duration of education on dementia risk. This approach helps to control for confounders such as family SES or childhood health status that would otherwise influence the duration of education. To date, studies using this approach to study the relationship between education and dementia risk have produced mixed findings: no, or small, effects of education on dementia risk were reported in some countries, for example, Sweden[118] but larger estimated benefits of education were observed in the USA[119] and China[120].

Studies examining policies as natural experiments often employ a method called instrumental variable analysis, in which a third variable is used as an instrument or proxy variable for the main exposure of interest[121]. Under certain assumptions, instrumental variable models can provide valid estimates of causal effects, for example, that the instrument is not associated with unmeasured confounders, that the instrument predicts the exposure of interest, and that the instrument does not directly affect the outcome of interest. An increasingly popular type of instrumental variable analysis is Mendelian randomization, which leverages genes as the instrumental variable (Fig. 3c). Mendelian randomization is based on the premise that an individual's genes are randomly allocated from parents at birth and this genetic variation is not susceptible to typical confounders[122]. Genetic variants have been linked to many diseases, biological pathways, health behaviours and even lifestyle factors, facilitating a range of Mendelian randomization studies. For example, a Mendelian randomization study used 77 genetic variants previously associated with sleep duration and found evidence that short and long sleep duration might worsen cognition in older adults[123]. In another study, higher genetic risk scores for AD (based on 23 genetic variants previously associated with late-onset AD, including APOE) were associated with reduced sleep duration in older adults without dementia[124], suggesting a bidirectional relationship between sleep and ADRD. However, other Mendelian randomization studies reported limited effects of education[119], obesity[125] and anti-hypertensive drugs[126] on the risk of AD. Over the last decade, methods have been developed to enable the relaxation of some of the usual assumptions in the setting of Mendelian randomization studies, particularly to allow for pleiotropic effects of genes[127]. Although the results of such studies should be interpreted with caution, they can still provide novel insights into ADRD aetiology[128]. Detailed reviews of contemporary and novel Mendelian randomization methods are outside the scope of this Perspective but other sources provide extensive information (see ref.[127]) and this is an active area for future innovations.

There are other common methodological approaches for quasi-experiments that have been so far underutilized in ADRD research but are promising options for future studies; these include regression discontinuity — an approach that uses treatment qualification thresholds in continuous values (for example, blood pressure) to assign participants to groups. The logic is that individuals just above and below the threshold will receive different treatments but are likely to be otherwise similar, allowing the effect of treatment to be studied[129]. Interrupted time series uses the regression discontinuity approach but applies it to changes

across time such as the implementation of specific laws or events. This approach has also been used to estimate the effects of education on dementia risk by examining completion of primary school surrounding the Great Famine in China[120]. China's Great Famine of 1959–1961 resulted in malnutrition, higher mortality rates and social disorder, including school closures. The authors of the study leveraged this event as a natural experiment based on the premise that those born just before 1948 are more likely to complete primary school than those born just after; they found that the group with a higher likelihood of primary school completion (for example, those born within 1944–1948) had better cognition in late life than the group born within 1949–1953. As an interrupted times series model, this study focused on the narrow bands around the 1948 threshold, which reduces the likelihood that results are driven by other cohort differences such as malnutrition[120]. Difference-in-difference studies examine differences in effects before and after treatment (or intervention) periods in treated versus untreated participants and can evaluate the implementation of health programmes and policies[117].

In ideal scenarios, the approaches described in this section can provide strong evidence for causality; however, they also rest on assumptions and can be prone to biases depending on study design[11,130]. For example, Mendelian randomization studies can be biased if genes have pleiotropic effects on the outcome[122,131] and studies that examine trends over time can be biased if there are other concurrent changes with time[130]. As for any analytical model, the limitations of these approaches should be explored and discussed when interpreting findings.

Conclusions and future directions

Dementia is a devastating condition with few treatment options, many questions remain around ADRD aetiology and risk factors, and novel potential risk factors and mechanisms are continually identified. The examples discussed here demonstrated the continued importance of well-designed observational studies in the ADRD field. We highlight the particular utility of such studies for hypothesis generation, for research infeasible or unethical for RCTs, to estimate life-course associations and timing of exposures, to collect real-world evidence on populations not typically included in RCTs, and for public health surveillance. Therefore, promoting high-quality, valid observational research should be a priority. High-quality research requires clear research questions, well-defined study designs, robust outcome measures, an a priori analytical plan, and transparent identification of potential sources of bias in reporting[132].

Given the limited treatment options for dementia and the failure of many clinical trials, we suggest that observational studies investigating a range of potential risk factors are needed to generate novel hypotheses. These future studies should leverage machine learning and big data, including medico-administrative data (for example, insurance claims, electronic health records) and/or high-dimensional biological data (for example, genome-sequencing or high-resolution imaging data)[133], to identify novel predictors of ADRD. Indeed, machine learning algorithms have proven useful for evaluating high-dimensional data and have already been used to predict the risk of ADRD based on metabolomic biomarkers[134], neuroimaging data[135], and social and health risk-factor data[136]. In the future, we expect that

such machine-learning approaches will provide novel insights into ADRD pathophysiology and inform the development of effective risk-stratification and diagnostic strategies.

Although a range of life-course risk factors for ADRD has been identified, many remain poorly understood. This gap in our knowledge applies to more recently identified factors, such as sleep disturbances, sensory loss, air pollution, microbiome and mitochondrial function, as well as the more established but still debated risk factors such as depression, body mass index, and social and cognitive engagement. Therefore, further well-designed and innovative observational research is required to establish whether these and other potential risk factors cause ADRD. Evidence triangulation is the idea that consistent findings across several study approaches can enhance causal inference, particularly when studies are based on several different sets of underlying assumptions[13]. This concept highlights the importance and value of replicating research findings across different observational study designs, including both traditional observational studies and innovative quasi-experimental designs that leverage observational data. The proliferation of blood-based and PET imaging biomarkers for ADRD provides new opportunities to understand how risk factors relate to biological processes in ADRD and to tease apart causative factors from early markers of disease.

Another urgent area for future observational research involves the health inequalities that affect ADRD risk. For example, understanding how and which aspects of structural racism, discrimination, social factors and built environments affect the development of ADRD is essential. Such information is needed to identify feasible approaches to reduce inequalities in ADRD incidence and dementia care.

In conclusion, the strongest evidence for causes of ADRD comes from using a variety of study designs and complementing RCTs and laboratory science with observational epidemiological and clinical research. Observational epidemiological research is a key building block to obtain evidence for potential causes of ADRD that might lead to new drug targets and preventive strategies to reduce the burden of dementia in diverse ageing populations.

Competing interests

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Glossary

Amyloid cascade hypothesis
The hypothesis that amyloid-β is the main pathological agent that causes Alzheimer disease.

Big data
Large-scale data comprising many observations and/or many traits.

Causal inference

Inferring the independent effect of one factor on an outcome, typically from data of observations.

Pleiotropic effects
When one gene influences two or more phenotypic traits.

Pragmatic trials
Clinical trials developed after drug approval to test the effectiveness of a drug in a real-world setting.

Real-world data
Observational data that represent real-world settings, for example, health-care records in a large health system.

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Box 1

Summary of common epidemiological study designs

Observational studies

Studies based on data that involve no intervention, manipulation, or experimentation of participants or samples

- Case reports and case series: description of observations on one patient or multiple patients (often with unusual or rare findings)
- Cross-sectional studies: comparison between an exposure and disease at one time-point
- Case–control: selection of cases based on disease and a sample of those without the disease (controls) followed by a comparison of exposures
- Cohort studies: selection of sample based on exposure or a population of interest, which is then followed for disease outcomes
- Ecological studies: comparison of aggregate information on exposure and disease in a population (or across populations)

Interventional studies

Studies based on data that involves an intervention, manipulation, or experimentation of participants or samples

- Randomized controlled trials: assignment of participants to the intervention group (or treatment) is random
- Non-randomized interventions: allocation of intervention is not randomly assigned

Box 2

Questions suited for observational studies

Developing interventions

- Hypothesis generation for novel risk factors or treatments
- Validation of in vitro and animal research
- Evaluating and improving diagnosis and biomarkers
- Replication of findings across study designs and populations
- Identification of exposure windows and intervention targets
- Studying exposures that are not ethical or feasible for intervention

Studying real-world effects

- Effectiveness of an intervention or treatment in typical use setting
- Effectiveness of interventions in the general population and in subgroups that are not well represented in clinical trials

Public health surveillance

- Evaluating trends in risk factors, treatments and dementia incidence by person, place and time

Box 3

Types of systematic bias common in clinical research

Confounding

A confounder is a factor that affects both the risk factor (that is, exposure) and the disease (that is, outcome). Confounders distort the observed association of a risk factor and outcome unless properly accounted for in the study design (such as through matching) or analysis stage (such as through inclusion as a covariate in regression models). Common confounders for questions relevant to Alzheimer disease and related dementias (ADRD) include age, education, income, health behaviours and other health conditions.

Reverse causation and confounding by prior outcomes

When an outcome affects the exposure, instead of the exposure affecting the outcome. Establishing the temporal order of late-life risk factors and ADRD is a challenge. This might explain associations in cross-sectional studies and in case–control studies that measure exposures after cases developed dementia. In cohort studies, incipient or preclinical ADRD might act as a confounder by affecting an individual's behaviour and cognition years before a diagnosis of dementia.

Selection bias

A bias that generally arises in selecting a study or analytical sample, such that participants in the analytical sample are not representative of the underlying population. This can happen due to study sampling at recruitment or through attrition in follow-up. In order for bias to occur, selection must be influenced by the exposure and outcome or by a third factor that is also associated with the outcome (this is more generally called collider-stratification bias). An example is that studies based on recruitment in memory centres might lead to an overrepresentation of individuals with a family history of Alzheimer disease and memory loss compared with the general population — this would lead to an overestimation of the association of family history for Alzheimer disease and memory loss.

Information bias or measurement error

Bias that generally arises through inaccurate measurement of exposures, outcomes or confounders. Relevant to both observational and randomized controlled trials; however, many exposures not conducive to intervention are also ones that are difficult to measure (for example, life-course factors, social determinants and underlying biological conditions). Blinding can be an effective solution to reduce differential information bias.

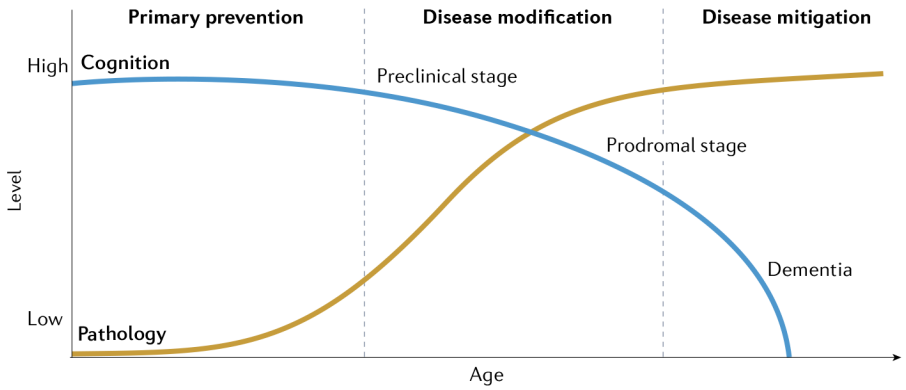

Fig. 1 |. Natural history of Alzheimer disease and related dementias and timing of interventions. Alzheimer disease and related dementias develop over decades and are characterized by long preclinical and prodromal stages of high neuropathological burden but limited or subtle cognitive decline. Interventions could be useful for disease prevention, modification, and mitigation or symptom reduction; however, randomized controlled trials are typically short and might not occur at the optimal points in the disease process. For example, many trials of disease modification strategies could have produced negative results because participants already had a high level of pathology and brain atrophy.

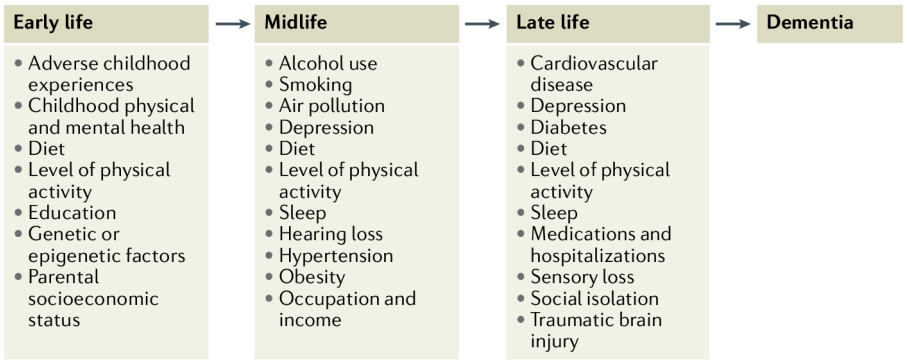

Fig. 2 |. Life-course risk factors for ADRD.

A life-course framework conceptualizes exposures for health as occurring across the lifespan in a dynamic and interconnected fashion. Experiences and conditions in early life might influence health and lifestyle factors in later life stages. Several key risk factors for Alzheimer disease and related dementias (ADRD) relevant to early life, midlife and late life are depicted; this is not a complete list of potential life-course risk factors and, for some risk factors, it is unknown at what life stages they have the biggest effect. The same risk factors might also accumulate or interact across time to influence the development of dementia. Research into the effects of life-course exposures on ADRD risk is best performed via observational studies; such work can also help to prioritize specific windows in which intervention might be effective.

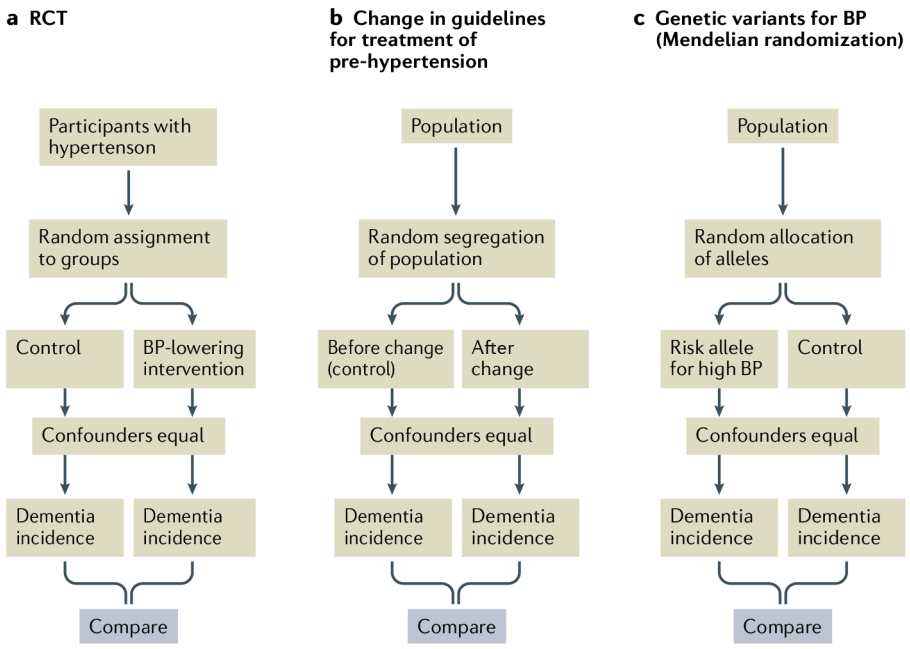

Fig. 3 |. Causal models for randomized and quasi-experimental studies.

Observational evidence suggests high blood pressure (BP) is a risk factor for dementia and that BP treatment might reduce the risk of dementia (part **a**). A key strength of a randomized clinical trial (RCT) is that allocation to treatment is random and is thus independent of potential confounders (common causes) of high blood pressure and dementia. As such, if lowering BP is found to reduce dementia risk in an RCT, there are few plausible alternative explanations for the finding. In theory, quasi-experimental designs can approximate similar inferences as RCTs if there is a third factor that influences BP but is not affected by patient-level confounders. For example, a change in treatment guidelines or policies for BP management (part **b**) or genetic risk for high or low BP (part **c**).

Table 1 |

Strengths and limitations of observational studies and randomized controlled trials

	Observational studies	Randomized controlled trials
Strengths	More feasible for evaluating multiple exposures and/or outcomes; more feasible for evaluating the effects of long-term exposures; can often be conducted using previously collected data (electronic health records); less restrictive eligibility criteria might enhance representativeness	Suited for evaluating treatment effects; random assignment to treatment protects against selection bias at recruitment and unmeasured confounding, and establishes temporal order
Limitations	Susceptible to confounding by other characteristics (factors that affect both exposure and outcome) and selection bias; establishing a clear temporal ordering of exposure and outcome is not always possible	Can be high-cost and logistically intensive; limited duration of intervention and follow-up; experimentation might not be suitable for research questions due to ethics or feasibility; design assumptions that allow a causal interpretation of the results of a randomized controlled trial do hold for post hoc subgroup analyses