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Review Article

Is late-onset Alzheimer's disease really a disease of midlife?

Karen Ritchie[a,b,*,1], Craig W. Ritchie[c,d,1], Kristine Yaffe[e], Ingmar Skoog[f], Nikolaos Scarmeas[g,h]

[a]Institut National de la Santé et de la Recherche Médicale, U1061 Neuropsychiatry, Montpellier, France
[b]Faculty of Medicine, University of Montpellier, France
[c]Faculty of Medicine, Imperial College London, UK
[d]Department of Psychiatry, University of Edinburgh, UK
[e]University of California at San Francisco, USA
[f]Centre for Health and Ageing (AgeCap), Institute of Neuroscience and Physiology, Sahlgrenska Academy at the University of Gothenburg, Sweden
[g]Department of Social Medicine, Psychiatry and Neurology, National and Kapodistrian University of Athens, Greece
[h]Taub Institute for Research in Alzheimer's Disease and the Aging Brain, the Gertrude H. Sergievsky Center, Department of Neurology, Columbia University, New York, NY, USA

Abstract

Introduction: Increasing evidence suggests that Alzheimer's disease (AD) may begin decades before evidence of dementia, indicating that it may be a disorder of midlife rather than old age.

Methods: In the absence of long-term prospective studies from early adulthood specifically designed to address this question, a group of international experts examined evidence presently available from previous clinical and population studies to provide an evidence-based opinion as to whether such a change in conceptualization may be justified.

Results: Although still lacking confirmation from dedicated prospective biomarker studies, there is already considerable evidence to suggest both risk factor exposure and brain changes may be already present in midlife.

Discussion: Current evidence suggests (1) that a change in clinical approach notably involving promotion of cardiovascular health in persons with a family history of AD may considerably reduce disease risk and (2) that the development of biomarkers at this early stage will lead to the possibility of clinical trials at a much earlier stage.

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Keywords: Dementia; Risk factors; Alzheimer's disease; Intervention

1. Introduction

Both clinical practice and research in sporadic Alzheimer's disease (AD) have long been based on the dual assumptions that it is a disorder of old age and synonymous with dementia. Research has thus targeted elderly cohorts, taking the onset of cognitive decline with accompanying functional loss in everyday activities as the point of disease onset. Clinical practice has followed from these conclusions with AD being excluded as a diagnosis in the absence of signs of dementia. Epidemiologic observations suggest, however, that exposure to the principal risk factors occurs much earlier [1,2] with simulation studies indicating that very significant decreases in population incidence might be obtained by targeting simultaneously multiple high-risk factors occurring in midlife, notably cardiovascular risk factors, depression, poor diet, activity levels, and insulin resistance. Such interventions appear to be potentially more powerful than even modification of the principal genetic risk factor [1]. This together with increasing evidence of brain changes in genetically at-risk younger persons, and theoretical models of biomarker progression indicating most significant changes to occur years if not decades before diagnosis [3,4], has led us to question current assumptions.

An alternative hypothesis is that sporadic AD is not a disease of the elderly but rather a clinically silent pathology of midlife (approximately 40–65 years or even younger), whose terminal phase is characterized by dementia. If this were so,

[1]Joint first authors.

*Corresponding author. Tel.: +33-499-614-560; Fax: +33-499-614-579.
E-mail address: karen.ritchie@inserm.fr

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then on the broadest social level AD would no longer be considered a disease of end-of-life but rather a disease of the young. The clinical consequences of such a change would also be significant, reorientating disease management away from palliative care to active prevention strategies in younger, healthier individuals. Screening of high-risk younger adults using innovative biomarkers and more sensitive cognitive assessments may then be followed by midlife intervention programs in parallel with the development of new potential drug targets. Disease-modifying drugs which have previously failed on clinical testing may further prove more efficacious at earlier ages for secondary prevention.

In this context, there are a number of key questions which may be asked.

Is there biomarker and clinical evidence to suggest AD may be present in nonsymptomatic persons in the decades before diagnosis?

Do longitudinal population studies which have tracked normal persons from midlife up to a diagnosis of AD confirm clinical biomarker studies?

Can epidemiologic studies suggest which risk factors during the preclinical period would be most strongly associated with a later diagnosis of dementia due to AD?

If AD is reconceptualized as a disorder of midlife, what are the consequences for clinical practice?

2. Methods

International experts in the areas of epidemiology, brain imaging, and clinical research were asked to consider currently available evidence that might support the conceptualization of AD as a disease of the young on the basis of current research and clinical experience. The literature relating to preclinical, biological, and clinical markers is vast, methodologically heterogeneous, and difficult for a nonspecialist to interpret. This overview does not attempt a comprehensive review of all the literature but rather provides critical summary statements derived from expert reading of current evidence illustrated by the most significant and robust findings which would be more accessible to the nonspecialist. The aim has thus not been to provide an exhaustive systematic review but rather to open a debate using the currently available empirical evidence to determine whether it is time to reframe our current conceptualization of this disorder.

3. Results

3.1. Evidence for preclinical brain changes

A potentially useful way to approach the complex problem of midlife brain changes is to subdivide the question into two separate parts: (1) when can subtle cognitive changes relating to AD first be observed and (2) when do subtle biological changes relating to AD start? We outline certain recent but also older studies that have attempted to address these issues.

We briefly note that although the main focus of this article is midlife changes, the exact earliest timing of either cognitive or biological changes in relation to AD is not known; there is research suggesting alterations even at young age or even at childhood. To the degree that such early changes are directly linked with AD and related dementia manifestations, they add considerable additional support to the argument of reorienting our scientific and research decades before late-life. "When do subtle cognitive changes start?" Findings from the Nun study have suggested that linguistic ability obtained from autobiographies at the age of 22 (as quantified in the form of idea density and grammatical complexity) relate not only to cognitive function 58 years later but also to AD–related neuropathologic measures (neurofibrillary tangles) in late-life [5]. Moving the clock even earlier, data from the 1946 Medical Research Council birth cohort in England, Scotland and Wales suggest that an overall mental ability test (including assessment of analogies, comprehension, numerical reasoning, matching, spatial analysis, and nonverbal reasoning) as well a test of verbal comprehension at age 15, were related to decline in memory (word-list learning) and speed-concentration (timed visual search) decline between the ages 43 and 53 [6]. An even earlier birth cohort from Britain suggested similar associations. Subjects born in 1921 in the Lothian birth cohort who were evaluated cognitively with the Moray House test in 1932 (age 11) were followed for dementia diagnosis up to 1997: late-onset dementia was associated with lower mental ability scores in childhood [7]. Subsequent analyses from the same cohort suggested that lower childhood cognitive scores were noted for vascular dementia cases (rather than AD) [8].

"When do subtle biological changes relating to AD start?" There have been a series of publications examining *APOE*-related structural and functional brain changes before late-life [9]. Middle-aged cognitively normal ε4 carriers have been shown to have cerebral metabolic reductions (as assessed by fludeoxyglucose positron emission tomography) in areas where metabolic deficits are usually noted in patients with Alzheimer's dementia (i.e. parietal, parietotemporal, posterior cingulate, frontal, and so forth) [10]. A similar cerebral metabolic pattern has been demonstrated also for young ε4 carriers [11]. *APOE*-related cerebral blood flow changes have been demonstrated even for college age subjects [12]. Moving the clock even earlier, structural brain imaging in 162 healthy typically developing 2–25 month-old infants suggested differences in white matter myelin water fraction and gray matter volume between ε4 carriers and noncarriers [13].

Moving from *APOE* (as a surrogate of AD–related changes) to amyloid per se, probably the most central neuropathologic change underlying AD, at least two studies have examined rates of amyloid accumulation with repeated PET brain imaging over time. According to data from 200 participants received repeated ^{11}C-PIB imaging every 1.5 years over the course of 3.8 years as part of the Australian Imaging

Biomarker and Lifestyle study, it was estimated that it takes 12 years to move from amyloid values noted in healthy controls to an amyloid positivity threshold and an additional 19 years to reach amyloid levels noted in established Alzheimer's dementia [14]. According to data from 246 participants from the Mayo Clinic group who underwent repeated amyloid imaging, it was estimated that the time required to move from a low threshold of amyloid positivity (standard uptake value ratio of 1.5) to that often noted in Alzheimer's Dementia (standard uptake value ratio levels of 2.5) is approximately 15 years [15].

Other studies provide more direct AD–related neuropathologic information in younger subjects. In a cohort of 2332 brains, neuropathologic information was available in slightly more than 700 who were aged $\leq$60 years [16]. Pretangle formations were noted at brainstem nuclei in the ages 10–30 years and in the cortical transentorhinal regions at ages 30–50 years. Neurofibrillary tangles stages I–II were detected in more than 25% in the 30s, close to 40% in the 40s, and close to 50% in the 50s. Neurofibrillary tangles stages III–IV started mostly in the 60s and 70s, while stages V–VI even later. Amyloid pathology was seen mostly in older adults, but some degree of amyloid deposition was seen in $\sim$30% in the 60s. Another study investigated patterns and types of amyloid-β accumulation, particularly of the fibrillogenic 42-amino acid isoform, in brains of 13 normal younger (20–66 years) subjects in comparison with normal aged, AD patients and elderly with very high memory performance [17]. Amyloid-β_{1-42} immunoreactivity was observed intraneuronally in the entire cholinergic population in basal forebrain quite selectively, early in adult life and regardless of age. Increases in the prevalence of intermediate and large molecular weight soluble oligomer species were observed in aged and Alzheimer brains when compared with the young.

Familial AD offers another excellent paradigm that can provide insights into this question. According to brain amyloid imaging results from the Columbian presenilin 1 E280A mutation cohort, fibrillar amyloid seems to begin to accumulate about 16 and 21 years before the predicted ages of mild cognitive impairment (MCI) and dementia onset (i.e. 40–60 years old) [18]. Analyses from the same cohort suggested that MRI atrophy changes, hippocampal and parahippocampal functional MRI activation changes, cerebro-spinal fluid Aβ42, and plasma Aβ42 changes in mutation carriers can be detected between the ages of 18 and 26 [19]. Along similar lines, data from 128 subjects with familial AD mutations participating in the Dominantly Inherited Alzheimer's Network (DIAN) study suggested changes in many biological markers many years before estimated dementia onset: CSF Aβ42 25 years; brain PET ^{11}C-PIB Aβ deposition 15 years; CSF τ, and MRI atrophy 15 years [20].

Before subscribing to the possibility of very early AD–related neurobiological changes, there are many other potential explanations for some of the early cognitive changes findings. A suboptimal cognitive performance, even at a very young age, could provide a lower threshold for dementia diagnosis in later life, even with relatively lower accumulation of AD–related neuropathologic changes. This suboptimal performance may also lead to less healthy or more "neurotoxic" lifestyle choices, which may in turn lead to higher dementia risk (as suggested for example by the association of childhood abilities with higher vascular dementia incidence in late-life [5]). Both early subtle cognitive underperformance and late-life dementia could be also related via another underlying factor (i.e. a common genetic susceptibility).

Regarding early biological changes, very early *APOE*-related brain imaging alterations (even in infancy) may very well represent an *APOE*-related neurophysiological heterogeneity rather than early AD–related biological processes. This heterogeneity may in turn predispose to later AD–related processes. Overall, beyond these caveats, it emerges quite clearly from most studies that AD–related pathologic changes (brain, CSF and plasma Aβ, brain atrophy and CSF) start quite a few years before overt clinical symptoms and deficits—most likely at middle age.

Summarizing, current state of knowledge does not permit a solid and undisputable direct conclusion that such early changes equal early Alzheimer's neuropathologic changes. Additionally, the magnitude of detectable changes (either clinical or biological) in young age is often small. Therefore, although it may carry predictive value, it may not be of clinical significance at much younger ages.

We should also keep in mind that there are many limitations in our current ability to estimate exactly when, what, and how. There are well-known differences between familial and sporadic AD. Imaging and CSF biomarker data for healthy middle-aged persons are largely cross-sectional or with very short follow-up. Similarly, imaging and CSF biomarker data regarding mutation carriers are largely cross-sectional with use of estimated rather than actual age of onset, which may prove to be inaccurate with actual longitudinal data [21]. Finally, we are lacking important information (either imaging or CSF, either cross-sectional or longitudinal) on many other important underlying dementia-related neurobiological processes (i.e. α-synuclein, TDP-43, and so forth). Some of these shortcomings are being addressed by new cohort studies designed specifically to look closely at brain changes, biomarkers, cognition, and risk factors in midlife.

3.2. Evidence from long-term population studies

Long-term population studies have also provided considerable evidence to suggest that late-life Alzheimer's dementia may be linked to exposures occurring in early and midlife. From the prospective population study of women in Gothenburg, which started in 1968 with last follow-up in 2010, it has been reported that higher blood pressure [22], the personality factor neuroticism [23], psychosocial stress [24], number of stressful events [25], poorer lung function [26], oral health [27], diabetes [28], obesity [28], low physical activity [28], larger waist-hip ratio [29], and consumption of spirits [30]

in midlife are related to late-life Alzheimer's dementia occurring more than three decades later. In contrast, wine drinking reduced the risk [30]. In addition, high levels of homocysteine increased the risk for late-life mixed dementia [31]. Furthermore, trajectories of blood pressure [22], cholesterol [32], and body mass index [33] differed over more than three decades between those who developed dementia and those who did not. In these studies, risk factor decline in late-life was associated with increased dementia risk which may indicate a difference in the role of risk factors between mid- and late-life but could also be due to reverse causality [34]. In the population study H70, it was found that the number of stressful events during life was proportionally related to increased risk for dementia between ages 70 and 79 years [35], with the most significant events occurring before age 16 years. Depressive symptomatology associated with Alzheimer's dementia has commonly been considered a reaction to loss of competency; however, there is now evidence to suggest that it is a highly significant midlife risk factor [1,2] whose treatment may significantly reduce later Alzheimer's dementia risk [36].

Support for the notion that very early factors in life may constitute important risk factors for late-life pathology is also confirmed by the finding that smaller total intracranial volume on computed tomography (CT) at age 85 years was related to increased odds of dementia [37]; intracranial volume being an indicator of brain size at age 5 years. Further support for the idea that risk factors appear decades before onset of Alzheimer's dementia is the observation that higher blood pressure [38] and being overweight [39] at age 70 years were related to increased risk of dementia after age 80 years. In addition, several Alzheimer's dementia risk factors have also been identified as risk factors for preclinical AD [40,41]. In considering risk and protective factors for Alzheimer's dementia, it is necessary to take into account the observations described in the preceding section indicating that early changes in CSF β-amyloid may occur 2–3 decades before clinical onset of Alzheimer's dementia [4]. This means that the earliest pathologic events may already have occurred when the risk factors are measured. It may therefore be more pertinent to talk about promoters or delayers of the disease process. This may have important implications for prevention in the future, as those with low levels of CSF β-amyloid in midlife may derive more benefit from preventive activities, such as diet, exercise, brain stimulating activities, and treatment of vascular risk factors, than those with higher levels. However, it may also be so that some of the designated "risk factors" for Alzheimer's dementia are actually early symptoms of the disease, even if observed decades before clinical onset.

These observations should be seen in the light of findings from the Honolulu Aging Study, where it was found that higher midlife blood pressure was related to Alzheimer brain pathology at autopsy in late-life [42], and the findings from a neuropathologic study of brains from persons from middle to old age which reported an association between hypertension and Alzheimer pathology [43]. Ischemic white matter lesions (WMLs) on MRI [44] and CT [45] have also been related to increased risk for dementia during follow-up. These late-life changes have been associated with midlife diastolic hypertension [46], giving a possible explanation for the association between hypertension and Alzheimer's dementia. Recently, it was reported that there was an association between WMLs on MRI and lower levels of CSF β-amyloid already before symptoms of dementia [47]. Similar associations have also been observed for WMLs on CT (Skoog personal communication from analyses prepared for this discussion). This might indicate an early association between β-amyloid and vessel wall changes in the pathogenesis of AD, with previous experimental evidence from Iadecola et al. [48] also suggesting that vascular pathology may also in turn influence β-amyloid deposition. Similarly, several population-based studies, including the Atherosclerosis Risk in Communities study, the Framingham Offspring Cohort Study, and the Lothian Birth Cohort, have found that physical activity and other vascular risk factors such as cholesterol and diabetes are associated with measures of atrophy and ischemia in older adults [49–51]. Increasing evidence also suggests that an increased burden of vascular risk factors contributes to the accumulation of amyloid pathology [52].

3.3. The central role of cardiovascular risk factors

Epidemiologic studies have established a critical role for cardiovascular risk factors in the development of late-life cognitive impairment and dementia; however, few studies have considered the nature of this association in midlife or before [34,49,53,54]. Emerging data from the Coronary Artery Risk Development in Young Adults (CARDIA) Study, a prospective cohort of young adults between the ages of 18 and 30, indicate that cardiovascular risk factors could affect cognitive health in earlier stages of the life-course. Over a 25-year period, CARDIA repeatedly measured cardiovascular risk factors and outcomes in over 3000 black and white participants, and at midlife (year 25 of the study, participant mean age ≈ 50) a cognitive evaluation included three tests, the Rey auditory verbal learning test, digit symbol substitution rest, and Stroop test. Preliminary results provide evidence for the contribution of cardiovascular risk factors across the life span.

In CARDIA, early adult cumulative exposure to cardiovascular risk factors demonstrated significant associations with midlife cognitive function [55]. Cumulative cardiovascular risk factor exposure over 25 years was estimated by the area under the curve for systolic blood pressure, diastolic blood pressure, cholesterol, and fasting blood glucose. Cumulative exposure to systolic and diastolic blood pressure as well as fasting blood glucose was consistently associated with worse performance on executive function, processing speed, and verbal memory at midlife, and when recommended guidelines were used as cutoffs (defined as systolic blood pressure >120 mm Hg, diastolic blood pressure >80 mm Hg, fasting blood glucose >100 mg/dL, and total cholesterol >200 mg/

dL) [56]; associations between elevated levels of cumulative cardiovascular risk factors and cognitive performance were even stronger. For each standard deviation increase in cumulative exposure to subclinical but elevated levels of cardiovascular risk factors, standardized test scores were between 0.06 and 0.30 points less ($P < .05$, for all) adjusting for age, race, sex, and education. Although effect sizes were small, these results highlight the critical role of cardiovascular risk factors even beginning in young adulthood.

CARDIA findings also indicate that maintaining optimal cardiovascular health contributes to better cognitive function in midlife [57]. The American Heart Association has designated seven ideal cardiovascular health components which include body mass index <25 kg/m^2, nonsmoking or quitting >1-year ago, physical activity >150 minutes of moderate activity or >75 minutes of vigorous activity/week, 4–5 components of a healthy diet, total cholesterol <200 mg/dL, blood pressure <120/80 mm Hg, and fasting blood glucose <100 mg/dL [47]. Adults with a greater number of ideal cardiovascular health components at both early adulthood and midlife had better midlife cognitive performance on all three cognitive tests. Furthermore, adults who maintained ideal cardiovascular health over 25 years had better executive function, processing speed, and verbal memory at midlife (P for trend <.01, for all).

Although poor cognitive performance is not AD, it remains one of the most significant risk factors, being also likely to reflect a diminution of cognitive reserve and capacity to compensate for accumulating pathology. The evidence presented here, along with complementary findings for additional components of cardiovascular risk, including subclinical atherosclerosis and cardiorespiratory fitness [58] and hypercholesterolemia [59,60] suggest that the pathologic changes underlying poor cognitive performance are similar to those associated with dementia as early as midlife. In addition, although future studies will need to model trajectories of cognitive function; these results warrant consideration of prevention strategies that encompass earlier stages of the life span.

4. Discussion

4.1. What do we need to know?

Overall, this is an exciting but at the same time evolving story and the overall picture is still quite incomplete. The validation of the midlife hypothesis will require very long-term follow-up of biomarker and subtle preclinical changes in young adults and ideally birth cohorts. In the meantime, further information is being obtained from epidemiologic studies with longitudinal biological samples and validated information on midlife risk exposures and clinical studies of persons at high risk, such as the children of persons with AD. Recently initiated prospective cohort studies in mid-life such as the PREVENT Project [61] will yield important information on the interplay between risk factors and both biological and clinical features but also the sequencing of disease processes. These data will then provide improved stratification of risk, better upstream targets for secondary prevention, and clarity on optimal outcomes to be used to measure an intervention's effect in midlife.

Literature on very early biological and clinical changes suggests that much more needs to be learned on biomarker and clinical-cognitive alterations in younger ages. At present, not much relevant scientific research has been conducted, but it would be very important to accumulate much more information regarding proportions of amyloid and other related biomarker positivity (either with PET or CSF studies) in young subjects, alterations of more sensitive MRI structural changes, rates and directionality of biomarker and structural changes at young age, the role and interaction of *APOE*, and subtle cognitive performance indices with respect to such biomarker changes and so forth.

4.2. What will this mean for future treatment?

Although at present there is no empirical data which would allow us to determine which markers in midlife are most closely associated with an early disease process, and even less the values which would permit individual diagnosis, there is sufficient evidence to suggest preventive measures in midlife are worthwhile. This underpins the global effort to establish a platform (or series of platforms) on which trials can take place which aim to prevent dementia in people at very high risk of disease progression who already have existing evidence of disease (as accurately indexed by biomarkers) without a diagnosis of dementia. One such initiative is the EPAD (European prevention of Alzheimer's dementia) project to be initiated in early 2015. This project will see the establishment of a large cohort across Europe (n = 6000) drawn from existing cohorts. This cohort will provide data for better disease models as well as feeding people into an adaptive, standing proof of concept trial (n = 1500) with multiple arms that will accelerate drug development (and potentially nonpharmacologic interventions) toward secondary prevention. Provided efforts such as EPAD (or other similar ones) are successful, and similar research endeavors (possibly more biomarker focused) could be extended to even younger ages.

4.3. What does this mean for the clinician?

Until further information is available from biomarker studies recently initiated in this area, what evidence does exist suggests compellingly that from the point of view of the clinician no more than good practice in relation to cardiovascular risk, in particular for persons with a family history of AD, is highly likely to be of benefit, if not in disease modification, at least in pushing back the time to functional loss. Following the example of the FINGER trial which has shown beneficial effects on cognition in older high-risk persons [62], a similar study is needed in younger at-risk persons

with biomarkers rather than dementia as the outcome measures. In this context, the use of dementia risk scores such as cardiovascular risk factors aging and dementia as used in the FINGER study may be of use in better designating high-risk persons than simply family history. Alerting persons in midlife with a family history to the importance of positive action and monitoring not only cardiovascular health but also rapid treatment of depression and insulin resistance is likely to be effective in reducing dementia risk. More specific modifications to lifestyle will be developed in the next few years as dementia prevention becomes more feasible, reasonable, and backed within governmental and public heath circles. Epidemiologic research currently suggests that such interventions will principally target cognitive and physical activity, diet, and stress management. Hormonal replacement therapy is also being re-evaluated in the light of a consistently demonstrated protective effect, but perhaps suitable only for a subgroup of women who may in the future be genetically determined [63]. Future nonpharmacologic intervention guidelines for persons at high risk will thus cover the entire life-course as presented in Fig. 1.

The next 10 years will witness an interesting shift in the focus for both research and clinical care. Currently, on the disease course, focus has been on the population with MCI—research money has flowed into understanding more about the proximal markers of risk to developing dementia over approximately a 5-year course. This has led to diagnostic proposals from both the United States and Europe for "prodromal AD" and "MCI due to AD" which—by adding biomarkers to criteria—have implied a diagnostic entity for people who have AD (as evidenced by an abnormal biomarker) but do not satisfy criteria for a dementia using International Classification of Diseases, Tenth Revision or *Diagnostic and Statistical Manual of Mental Disorders* criteria. These diagnostic proposals require further validation of the proposed biomarkers with evidence to date suggesting much greater sensitivity than specificity implying correct terminology would be MCI "not" due to AD [64,65]. Clinical pathways have adjusted accordingly with little net benefit to incidence or clinical outcomes. This approach though has to be broadly welcomed. Empirical data from large, prospective, deeply phenotyped cohort studies will add much to the validation or indeed the adaptation of these criteria as more accurate disease models are developed. Such criteria then form the basis of patient stratification for specific secondary prevention approaches. In effect, advances in understanding of the disease processes leading to dementia and the associated massive burdens being placed on individuals and society will mediate this focus dissipating in two directions—earlier and later—so that research will take place at a point earlier in the disease course and target primary and secondary prevention in midlife and later in the disease course to improve palliative care we can provide through both psychosocial and pharmacologic interventions for people with a dementia syndrome now recognized as due to the brain failure associated with multiple pathologic processes and not specific to for instance just AD. Ultimately success in prevention will reduce the need for services and research in dementia. This will obviously not be easy but recent initiatives such as EPAD highlight an incredible willingness by governments, academics, the public, and commercial sectors to change the way we conceptualize AD and the care paradigm. This conceptualization must allow us to draw a distinction between AD (a specific pathologic process), which may originate and develop from midlife with Alzheimer's dementia, which is the clinical consequence of AD once dementia is established which also involves other neurodegenerative disease processes that may be dependent on or independent of AD, such as cerebrovascular disease, oxidative stress, mitochondrial dysfunction, or neuroinflammation. Such a distinction will

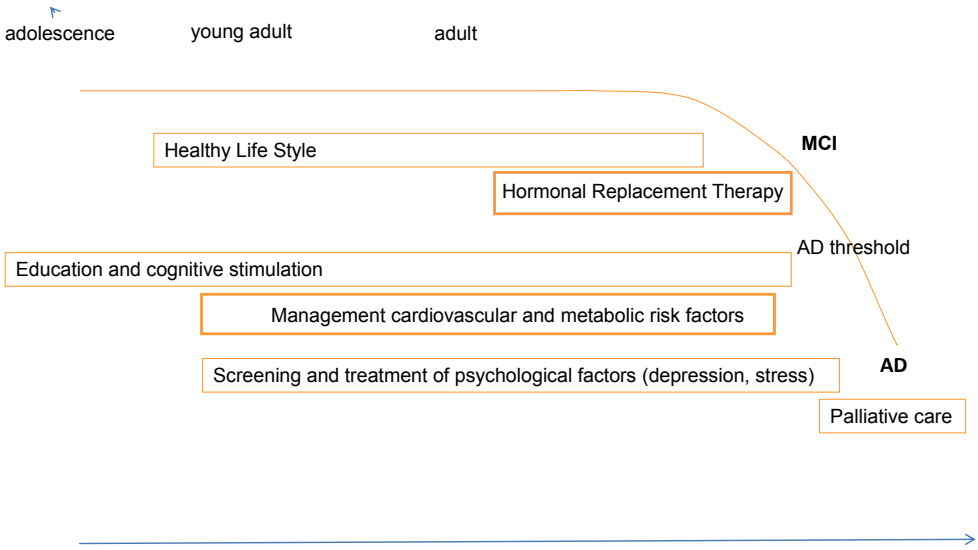

Fig. 1. Theoretical timing of potential intervention windows for prevention/delaying of AD. Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment.

drive a methodological rethink regarding what we choose as outcomes from both epidemiologic and interventional research.

The views expressed in this article are those of the authors. This invited debate was not sponsored, and the authors have no conflicts of interest to declare.

CONCLUSION

- There is evidence from clinical studies of biomarker changes at midlife in persons at risk of future Alzheimer's disease dementia; however, these studies are cross-sectional.
- Prospective epidemiologic studies provide evidence of a causal relationship between biomarker change in midlife and later Alzheimer's disease dementia.
- Epidemiologic studies indicate that the principal exposures in midlife increasing risk for subsequent Alzheimer's disease dementia are cardiovascular, metabolic, stress, and lifestyle factors.
- There is evidence to suggest that Alzheimer's disease may be present at midlife and that clinical intervention at this stage based on known risk factors may reduce the risk or slow progression to dementia.
- Secondary prevention trials that target individuals with evidence of Alzheimer's disease but without dementia require both clinical and biological outcomes reflective of progression of this disease rather than reduction of incident Alzheimer's disease dementia which is a too distant outcome.

RESEARCH IN CONTEXT

1. Systematic Review: Recent research suggests that AD may begin decades before dementia is observed. This research is reviewed by experts in biomarker and epidemiological research.
2. Interpretation: While awaiting the results of on-going research into biomarkers which may indicate new treatments, clinical practitioners may be able to push back the age of onset of dementia in persons at risk (those with a family history) by monitoring and early treatment of risk factors such as depression, diabetes in its earliest possible stages for example by monitoring insulin resistance, low physical and cognitive activity levels, and cardiovascular risk factors.
3. Future directions: Further evidence from birth cohorts and midlife clinical intervention trials are required to validate the hypothesis that Alzheimer's disease is present at midlife.

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