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The PREVENT study: a prospective cohort study to identify mid-life biomarkers of late-onset Alzheimer's disease

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ABSTRACT

Introduction: Epidemiological studies indicate that significant decreases in the incidence of Alzheimer's disease (AD) may be obtained by targeting multiple middle-age risk factors. However, as dementia is unlikely to be diagnosed for decades, short-term outcome measures are required. AD biomarker changes precede clinical symptoms by many years, but their sensitivity to mid-life change remains unknown.

Methods and analysis: PREVENT is a prospective cohort study examining biomarker status at mid-life in at least 150 individuals genetically at high, medium or low risk of late-onset AD. Participants are children of individuals with or without a diagnosed AD allocated to high, medium and low-risk groups according to parental clinical status and ApoE genotype. The biomarkers examined over 2 years are plasma and CSF A β 42 amyloid, Tau and pTau, proinflammatory cytokines, acute-phase proteins, medial temporal-lobe atrophy, white matter lesion volume, cognitive performance related to transentorhinal and hippocampal functioning and hypothalamic–pituitary–adrenal and sympathetic axes regulation.

Ethics and dissemination: Detected pathologies are communicated to the participant's general practitioner with their permission. Risk status by genotype would not be revealed. The results of the study would be published in peer-reviewed journals and validated biomarkers used to construct a randomised controlled intervention study.

INTRODUCTION

In the face of a pandemic of dementia with predicted increases of 100% in developed countries between 2001 and 2020,¹ even small reductions in the incidence, or delaying the age of the onset, are likely to have significant effects with regard to the enormous associated public health burden. The exact cause of the dementia remains

unknown, however, epidemiological studies conducted over the past decade together suggest a complex interaction of exposures which contribute differentially to the probability and timing of the disease onset and could be used as the basis for strategies to reduce risk and delay onset in the absence of specific disease-modifying treatments. While no single risk factor explains a sufficient variance to be used individually as a basis for prevention, simulation studies in analytical epidemiology show that highly significant decreases in population incidence might be obtained by targeting simultaneously multiple high-risk factors.^{2–3} Exposure to many of these risk factors occurs in middle age, for example, hypertension and diabetes, suggesting that maximal impact is likely to be obtained by targeting middle-age populations with a high risk of a later-life dementia. The pivotal question, however, is what to measure as an outcome indicator at this early stage given that clinical dementia is unlikely to be diagnosed for another 20–40 years.

Recent research on cognitive, neuroimaging and biological markers suggest that changes in several parameters may well precede overt clinical symptoms by not just many years, but decades. Only one study to our knowledge has attempted to examine a biomarker at this very early stage; Alexopoulos *et al*⁴ have shown that young (mean age 24), healthy ApoE ϵ 4 carriers have statistically significantly smaller hippocampal volumes than ApoE ϵ 2 carriers. This observation is in support of our assumption, however, it requires confirmation in another data set and hippocampal size alone is an insufficient evidence of early AD vulnerability. The aim of the PREVENT study is to examine the sensitivity of a wide range of candidate markers in mid-life to provide measures for future interventional research.

METHODS

Selection of candidate biomarkers

Amyloid

There is increasing evidence that A β deposition in plaques precedes any sign of dementia by years, if not decades.^{5 6} Though more accessible, plasma A β has given inconclusive results in terms of its predictive value⁷ when compared to PIB PET,⁸ while the predictive value of cerebrospinal fluid (CSF) A β ₄₂ appears to directly reflect early brain deposition.^{9 10} A β ₄₂ paradoxically decreases in CSF with an increasing deposition, hypothesised to be due to plaques acting as an A β ₄₂ 'sink' preventing the transport of soluble A β ₄₂ to the CSF.¹¹ In the progression of pathology, plaque formation and the associated capture of the central A β into the plaque with consequential lowering of CSF A β is considered a primary event that precedes the hyperphosphorylation of tau and neuronal disintegration. A β ₄₂ has thus been recommended for use as an endpoint for future preventive programmes in younger adults⁹ and has also been incorporated into the revised diagnostic criteria for preclinical dementia.¹² Alternatively amyloid may be intracerebrally observed and quantified through functional imaging of a radio-labelled A β ligand, however this method is far more expensive and less widely applicable.^{8 10 13}

Tau

Like A β ₄₂, tau and phosphorylated tau have emerged as important CSF biomarkers for preclinical Alzheimer's disease (AD). Increased concentrations of tau and phosphorylated tau correlate with both neuritic-plaque density and Braak NFT stage. In conjunction with A β ₄₂, tau and phosphorylated tau seem to be useful as prognostic biomarkers for conversion not only from cognitive impairment to dementia, but also from cognitively normal to mild cognitive impairment.^{8 10 13–15} As an indicator of neuronal death CSF tau is elevated in all types of neurodegenerative diseases as well as post stroke. As the hyperphosphorylation of Tau is believed to be relatively specific to AD, the observation of elevated CSF pTau is thought to be a more specific early indicator of neurodegeneration secondary to AD. The combination of high tau and low A β ₄₂ as a ratio is considered to have an even greater accuracy for identifying AD.¹⁶

Inflammation

The occurrence of plaque-dependant inflammation in AD has been consistently observed in both humans and transgenic models^{17 18} with animal studies suggesting that a pro-inflammatory process may even be initiated before plaque deposition^{17 18} making it potentially the earliest preclinical indicator. Imaging studies provide further support for this hypothesis with observations of microglia activation before plaque formation. Further support comes from epidemiological observations of cognitive decline due to systemic infections and peri-operatively where elevation of systemic inflammatory

proteins such as cytokines and interleukins may mediate a reactive activation of glial cells and consequent acceleration of oligomerisation.¹⁹ Taken together, it would appear that inflammatory markers may elevate prior to a lowering of CSF A β (as a marker of A β oligomerisation) which in turn precedes the elevation of tau (as a marker of neurodegeneration). The sequence of events is still, however, poorly understood although vital to the development of prevention programmes as it is likely to be a dynamic indicator differing according to distance from the dementia onset at the time of CSF sampling.

Structural brain imaging

Atrophy is particularly difficult to measure in the preclinical stages of dementia, when it superficially resembles the inconspicuous volume loss commonly observed among ageing individuals without neurodegeneration. Distinguishing such subtle differences is now possible using high-resolution quantitative MRI²⁰ which is able to predict not only a progression from mild cognitive impairment to AD,²¹ but also from normal cognition to mild cognitive changes.²² Numerous cross-sectional and longitudinal MRI studies have now been conducted to identify markers which may indicate presymptomatic dementia. The focus of these studies has been on medial temporal atrophy, with the hippocampus and entorhinal cortex being affected before symptoms emerge.^{23 24} It has been estimated that subjects with cognitive difficulties in the years before dementia diagnosis already show hippocampal loss of 7–15%²⁵ and entorhinal cortical loss of 5–32%.²⁶ Although atrophy is often thought to be a downstream marker from amyloid in the cascade leading to dementia,²⁷ it appears to represent both neuronal loss and the presence of tau pathology, so may be directly related to the AD pathophysiological process.²⁸ Both hippocampal volume loss and white-matter lesions are seen in other disorders which are significant up-stream risk factors for dementia, such as depression.²⁹

Cognition

While cognitive dysfunction is generally considered to occur closer to the time of AD clinical manifestation, this is probably largely due to the nature of the cognitive tests which have been used, which have been principally derived from comparisons of AD and normal subjects. Sing-Manoux *et al*³⁰ have recently observed a cognitive decline in adults aged 45–49 years in a large prospective cohort study; however, while the authors suggest that this group may be at a high risk of later dementia, no association was sought either with other dementia-related risk factors or later-life biomarkers. Dizygotic twin studies in which only one twin developed AD have shown on the other hand that significant differences in cognitive performance may be evidenced up to 20 years before AD diagnosis.³¹ While there is currently very little evidence as to which tests may be sensitive decades before diagnosis, histopathological studies point to the transentorhinal cortex as the first anatomical target

followed by the entorhinal cortex and hippocampus. Evidence from lesion studies in humans and experimental animals^{32 33} and functional neuroimaging in normal adults³⁴ suggest on this basis that a decline in visuospatial associative learning to be a primary candidate for a very early marker. Longitudinal studies of prodromal dementia accompanied by a blind assessment of MRI imaging suggests that diffuse cerebral and mediotemporal-lobe atrophy in preclinical cases may also be evidenced by a lower verbal memory and visuospatial analyses tasks before evidence on brain imaging.³⁵ While verbal learning tasks are often included in a dementia assessment, the more complex processes of visuospatial information processing have till date been inadequately explored in preclinical studies.

Hypothalamic–pituitary–adrenal axis functioning

Physiological mediators such as glucocorticoids (hypothalamic–pituitary–adrenal, HPA, axis) from the adrenal cortex and adrenalin (sympathetic axis) from the adrenal medulla act upon receptors in various tissues and organs to produce effects that are damaging if continuously activated.³⁶ In response to stressful conditions, chronic overactivity and dysregulation of these stress systems can thus play a pivotal role in critical biological processes, such as growth, intermediary metabolism and diabetes, immune and inflammatory reactions as well as (cardio)vascular and central nervous system functions. Glucocorticoids generally work in opposition to insulin, except under a state of chronic glucocorticoid elevation, in which case they act to promote hepatic glycogen deposition and lipogenesis that leads to fat deposition, while raising insulin levels and impairing insulin actions on their receptors. It has been demonstrated³⁷ that whereas cardiovascular risk factors, type 2 diabetes and stroke form anthropometric, metabolic and haemodynamic clusters in correlation analyses in the general population, most of these risk factors also seem to form one tightly assembled cluster in individuals with HPA axis dysregulation suggesting this could be an overriding factor for the established risk factors targeted in this study and may thus constitute a very early biomarker of an increased risk for cognitive decline. Disturbance on cortisol secretion has been reported in cognitive impairment and AD.^{38–41} In a mouse model of AD, glucocorticoid increased A β and tau pathology, but an inverse weak association was found in a small clinical study of AD patients.^{42 43} Increase in cortisol levels and in mineralocorticoid receptor expression in the frontal cortex has been reported in AD and this correlated negatively to global cognitive function and positively to frontal cortex amyloid- β levels in Apo E4 carriers.⁴⁴ Higher cortisol levels have been associated with hippocampal atrophy. In healthy men, significant negative phenotypic associations were found between cortisol levels and the thickness of left dorsolateral and ventrolateral prefrontal regions, and right dorsolateral and medial orbital frontex.⁴⁵ Recent fMRI studies suggest a

dynamically changing corticosteroid effects with reduced prefrontal and hippocampal responses as well as an altered coupling of the amygdala with the medial prefrontal cortex.^{46 47} Thus, while there is some evidence to suggest a major role of the stress system in the early onset of dementia, this hypothesis has yet to be tested. A number of previous studies being cross-sectional, focusing on elderly and cortisol secretion with a limited number of measurements and limited neuropsychological evaluation were indeed inconclusive regarding the early temporal relation between the whole functioning of stress axes and dementia.

The specific hypotheses being examined within the PREVENT Project are:

1. That at mid-life (40–59 years), individuals at a high risk of dementia show significant decreases in A β 42 amyloid in plasma and CSF and increases in Tau and pTau (and their ratios) as compared to that in low-risk individuals.
2. High-risk individuals show increased mid-life activity on pro-inflammatory cytokines IL-1 α , IL1 β , IL-18, IL-6, IL-8, TNF- α , IFN- γ , acute phase proteins (CRP, haptoglobin, sialic acid pr) and a long-term inflammatory marker (orosomuroid).
3. High-risk individuals at mid-life have increased medial temporal lobe atrophy and white matter lesion volume. The MRI protocol includes entire brain volumetric T1 weighted images (1 \times 1 \times 1 mm) for segmentation and volumetric analyses, dual echo and FLAIR sequences to allow identification and quantification of deep white matter hyperintensities and diffusion-weighted imaging (minimum 16 directions) for identification of changes in normal appearing white matter and major tracts.
4. High-risk individuals have poorer performance (both accuracy and information processing time) in cognitive tasks reflecting transentorhinal and entorhinal cortical changes and hippocampal reduction as evidenced notably by visuospatial associative learning, spatial analysis and working and primary memory tasks.
5. High-risk individuals show evidence at mid-life of HPA and sympathetic axes dysregulation as evidenced by secretion of cortisol and catecholamines, for example, epinephrine, norepinephrine, dopamine and metabolites of degradation (metanephrine, nor-metanephrine).
6. Differences in biomarker levels and cognitive performance will be evidenced on both cross-sectional and longitudinal (over 2 years) measures.

Participants

Participants are the children of individuals diagnosed with AD at the West London Mental Health Trust (WLMHT) Cognitive Disorders and Dementia clinics who have given consent to the study and for whom we have obtained information on genetic risk (ApoE status). Participants are drawn from the locally hosted Dementia Register (DemReg),⁴⁸ which holds details on both patients with dementia and their cares (40% of whom are children).

Mid-life biomarkers of late-onset Alzheimer's disease

Fifty children of the patients diagnosed with AD and an ApoE $\epsilon 4$ allele (high risk), 50 children of demented patients without an ApoE $\epsilon 4$ allele (medium risk) and 50 participants without a parent with dementia (eg, spouses of extant cases on the register) and with an ApoE $\epsilon 2$ and no ApoE $\epsilon 4$ allele (low risk) will be followed up for over 2 years. A medium-risk group is included to detect a possible 'dose' effect and to maintain study blinding, this group will probably number in excess of 50 participants. Power calculations are difficult to make in this context given that SDs on the biomarkers in this younger age group are as yet unknown, apart from the hippocampal volume study of Alexopoulos *et al*⁴ cited hereinbefore. Data from this study were normally distributed, the APOE $\epsilon 2$ group having a hippocampal volume mean (SD) of 4.59 cc (0.50 cc). On this basis, 50 subjects per group would allow us to show a mean difference of 0.327 between the groups; that is, a mean of 4.263 in the APOE $\epsilon 4$ group with an α risk=0.05 and a power of 0.90. Examining data from a very large longitudinal population study of over 10 000 people aged 65 and over (the 3 City Study, Montpellier), we observed the plasma biomarker A β 42 to have the largest SD likely to diminish power. Based on the data from this study we therefore made a supplementary 'worst-case scenario' calculation. The mean (SD) level of plasmatic A β 42 in this study is 38.90 (12.326), and on this basis 50 subjects in each of our groups would permit us to show a mean difference of 8.07 with an α risk=0.05 and 0.90 power. This is clearly poorer, but we are unlikely to see levels this low in the PROGENY cohort with CSF rather than plasmatic A β .

Procedures

Potentially eligible individuals will be sent a Participant Information Sheet by post. All participants in the study are seen at the West London Cognitive Disorders Treatment and Research Unit in West London Mental Health Trust, West London. The other principal interest of this clinical service is that its catchment area is principally of Asian Indian origin, with very high rates of AD risk factors (diabetes, hypertension and stroke). On attendance, one of the study clinicians would present the project and take informed consent. Separate consents would be taken for CSF sampling so that participants may still be part of the PREVENT cohort for subsequent studies if they refused the CSF extraction, however, only subjects accepting this procedure would be included in this first biomarker validation study. Consented participants would then be interviewed by the study team who complete a standardised neuropsychiatric interview and a life-style questionnaire covering diet, occupation, work, education, life-time activity, adverse environmental exposures, alcohol and drug use. A battery of neuropsychometric tests focusing particularly on entorhinal and hippocampal functioning (the COGNITO battery) is administered using a tactile screen to permit recording of response latencies and qualitative aspects of performance (the manual for this test may be viewed on the following site: <http://www.montp.inserm.fr/u1061/SiteU1061/PDF/COGNITO%20MANUAL%20ENGLISH.pdf>).

Our group has also developed a visual short-term memory binding paradigm that has been shown to predict familial AD 10–15 years before appearance of clinical symptoms in the absence of detectable changes in other neuropsychological tests⁴⁹ which would be applied as a supplementary cognitive test.

Upon completion, a blood sample would be taken and a physical examination conducted including anthropometry and pulse/BP. Saliva samples would be collected 4 times on the day of the clinical visit and participants would be asked to be prepared for a further four on a quiet day at home. Arrangements would also be made for CSF sampling and MRI. All procedures would be repeated at 24 months.

ApoE genotyping would be performed immediately after consent has been given permitting the research study manager to allocate subjects to high-risk, medium-risk and low-risk groups. Group allocation is known only to the manager, all other members of the research and clinical teams including the principal investigators being blind to group membership until all examinations have been conducted both at recruitment and follow-up.

ETHICS AND DISSEMINATION OF THE RESULTS

The principal ethical considerations relate to revelation of high AD risk status to participants and procedures to follow where pathology is detected. Following a discussion with the London Ethics Committee, it has been decided that as the risk status of potential participants is already known to them in that they have a parent with AD, it is not possible for them to be ignorant of their risk group, however, they would also be informed that this only places them at a higher risk and does not necessarily mean they will develop the disorder in their life-time. Results from genetic testing would not, however, be transmitted as this is neither an inevitable nor a treatable risk factor. Where pathologies are detected, the participant would be informed and permission requested to forward the relevant information to the individual's general practitioner.

Results from the PREVENT study would be published in peer-reviewed journals. Should valid biomarkers be found, after the 150 participants are entered, recruitment would continue for participation in future intervention studies as well as to provide greater analytical power for both baseline and longitudinal analyses.

Analyses

The preclinical biomarkers of AD would be compared between the three groups of subjects using analysis of variance for continuous variables with an approximately normal distribution or using the Kruskal-Wallis non parametric test for non normal continuous variables. The other characteristics of the subjects would also be compared between the three groups using the ANOVA or the Kruskal-Wallis tests for continuous variables and the χ^2 test

for categorical variables. In case of differences on socio-economic variables or other confounding variables between the three groups adjusted group comparisons would be undertaken using polytomous logistic regression.

CONCLUSIONS

The PREVENT Project would provide information on mid-life biomarker change in individuals at a high risk of late-onset AD. Should significant differences be found on any of the candidate measures, these biomarkers would then constitute endpoints for the construction of a large population randomised controlled trial based on intervention strategies already identified by our research teams. The results of the present study are also crucial to the development of other pharmaceutical and non-pharmaceutical interventions targeting early interventions in individuals at a risk of AD, and as such this study constitutes an important step forward for future prevention.

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Competing interests None.

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