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Dementia risk prediction models

what do policymakers need to know?

UNIVERSITY OF CAMBRIDGE

Author

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Executive summary

Background

With population growth and ageing, the number of people living with dementia worldwide is projected to rise rapidly over the coming decades, despite a decline in age-specific incidence rates of dementia in high-income countries. This projected increase in global dementia burden, combined with the repeated failure of treatment trials, has led to urgent calls for action on dementia prevention.

Prevention of dementia can occur at three levels: primary (preventing or delaying the onset of disease), secondary (screening and early detection of disease) or tertiary (reducing the progression of disease and managing disability and complications among people living with dementia).

This report focuses on dementia risk prediction as a tool to enable primary prevention, although some of the issues associated with future risk prediction also apply to early detection.

- It provides an overview of current dementia risk prediction tools along with their uses and validity in different settings and populations
- Using a combination of literature review and informant interviews, the report describes the key issues and challenges around dementia risk prediction for policymakers, including identifying potential benefits, harms and uncertainties
- Finally, it outlines the research needed to enhance the utility of approaches to dementia risk prediction at population level

Summary of findings

Current UK policies promote early diagnosis of dementia among people with symptoms of the condition, but do not support either screening or prediction of future dementia risk among apparently healthy individuals.

A range of evidence gaps associated with dementia risk prediction in the general population of apparently healthy individuals have been identified. More than 70 models aiming to predict future dementia risk have been developed in research settings, but most have uncertain validity for predicting dementia across different populations, age groups and timescales.

A major gap was a lack of effective interventions to offer people identified by these models as being at high dementia risk. There were also uncertainties about how best to communicate risk to the public; the value of communicating a high risk status to individuals when there is little evidence that it would alter clinical outcomes; and a variety of ethical, legal and social issues (a detailed analysis of which is outside the scope of this report). There is concern about the opportunity costs of implementing dementia risk prediction and the potential effect on overstretched health systems.

In summary, at present there is insufficient evidence that dementia risk prediction using existing models in the general population would provide an acceptable balance of benefits to harms, given the uncertainties in areas ranging from model validity to lack of clinical interventions and agreed care pathways, as well as a range of ethical and implementation issues.

Conclusions

While risk prediction models are valuable tools for dementia research, they are not yet suitable for clinical use in the general population.

- Future research should focus on generating better evidence for dementia prevention initiatives including the optimum target group (whole populations versus high-risk groups).
- New and existing risk prediction models should be validated across populations for specific age groups and contexts.
- Further research is needed into the implications for individuals, health systems and wider society of labelling people as being at high risk of dementia.

1. Introduction

Context

The aim of this report and the research and analysis it presents is to inform health policymakers responsible for dementia prevention initiatives about recent developments in dementia risk prediction models. In particular, it provides an overview of current methods for predicting future dementia risk, and considers the validity and limitations of these approaches, as well as areas for future research.

The report also discusses the utility of dementia risk prediction models, attitudes of patients, health and research professionals towards predicting dementia risk, and identifies broader ethical, legal and social issues surrounding dementia risk prediction.

Contents include:

- Description of the medical and societal context around dementia risk prediction
- Identification of potential benefits and harms or uncertainties of using dementia risk prediction models
- An overview of current dementia risk prediction tools, their uses and validity in different settings and populations
- An outline of future developments needed to enhance the utility of approaches to dementia risk prediction

Overview of methods

A review of the academic literature relating to dementia risk prediction was undertaken through a tailored search of peer reviewed papers, informed by consultations with subject experts. This was supplemented by searches for policy documents on dementia prevention, early identification and risk prediction in the UK from the websites of government and national health organisations.

Information about topical cross-cutting issues in prediction modelling for clinical medicine was also gathered at a symposium held in Edinburgh on 24 April 2018, organised by the Asthma UK Centre for Applied Research.

Interviews with nine key experts were also carried out to explore the views of dementia researchers from a range of backgrounds (primary care, neurology, public health, sociology, statistics) about dementia risk prediction and current models. Thematic analysis of interview data supplemented literature findings.

2. Dementia

Overview of dementia

The term 'dementia' describes a syndrome of brain failure in which there is persistent decline in cognitive ability sufficient to interfere with activities of daily life, not explained by delirium or major psychiatric disorders . Cognitive or behavioural changes seen in dementia may include an impaired ability to acquire and remember new information, problems with reasoning and planning, difficulties with recognition of objects or faces and impaired language skills. There may also be changes in personality, mood or behaviour as well as disturbances to sleep and appetite.

Dementia is very strongly associated with age, and is commonest among people aged 80 years and over. Alzheimer's disease is reported by expert consensus to account for around 60% of dementia cases in this age group[2]. It is characterised by an insidious onset, clear worsening of cognition and the prominence of short-term memory loss, although in some cases difficulties with word-finding, visuospatial problems or impaired problem-solving may predominate.

Smaller proportions of dementia cases result from cerebrovascular disease, mixed causes (such as Alzheimer's disease and vascular dementia combined), dementia with Lewy bodies and other rarer causes e.g. frontotemporal dementia[2].

In patients aged under 65 years, vascular dementia is less common and a greater proportion of cases are due to frontotemporal dementia, which is more likely to run in families than other forms of dementia[3]. Dementia may also occur in other conditions including Huntington's disease, HIV/AIDS, alcohol abuse, brain injury and Creutzfeld-Jacob disease.

Whether dementia is formally diagnosed at all, and whether specialist input is sought to identify a subtype, is highly subjective and depends on clinician, patient and family wishes

There is no single diagnostic test for dementia. Diagnosis requires a history of ongoing difficulties with executive function, and may involve formal tests of cognitive function and other investigations such as blood tests and brain imaging. Identifying neuropathological features such as beta amyloid plaques and neurofibrillary tangles through brain imaging is insufficient for a dementia diagnosis, as these features may also be present in people with normal cognitive function, especially at older ages[4].

Whether dementia is formally diagnosed at all, and whether specialist input is sought to identify a subtype, is highly subjective and depends on clinician, patient and family wishes. Dementia frequently coexists with other health problems in older people[5], and it may or may not be a prominent concern.

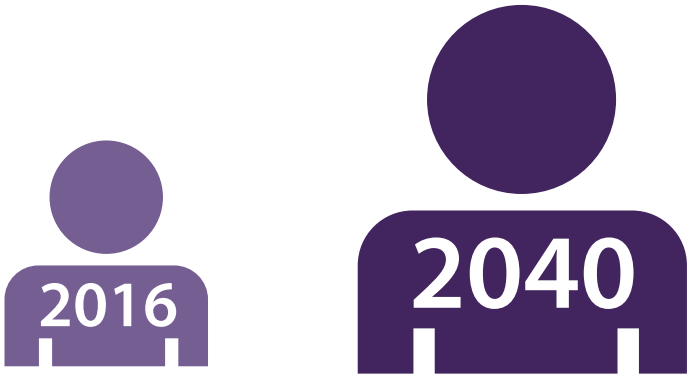
Treatments for dementia are supportive rather than curative. Some pharmacological therapies including acetylcholinesterase inhibitors are recommended as options for managing mild to moderate Alzheimer's disease[6]. Recent guidelines also emphasise the importance of co-ordinating care, making services accessible, and offering interventions to promote cognition, independence and wellbeing, as well as managing other co-morbid conditions and non-cognitive symptoms[6].

Incidence, burden and mortality

Dementia was reported as the leading cause of death in England and Wales in 2015, with 12% of death certificates including dementia as one of the underlying causes of death[7]. However, obtaining accurate figures for the number of people living with dementia is challenging due to geographic and temporal variations in care-seeking behaviour and disease definitions, as well as the effect of incentive schemes aimed at increasing dementia recording by reducing the 'gap' of undiagnosed dementia[8, 9].

It was estimated in 2017 that around 68% of those with dementia in England had a formal diagnosis[10]. Cohort studies such as the Cognitive Function and Ageing Studies (CFAS) I and II of community-dwelling older individuals indicate that in the UK there has been a reduction in the age-specific incidence of dementia over time[11]. Despite this, the disease burden due to dementia is projected to increase substantially both in the UK and globally with population growth and ageing.

Recent modelling work suggests that there will be a 57% increase in numbers living with dementia between 2016 and 2040 in England and Wales, equating to more than 1.2 million people with dementia by 2040[12].



Projected 57% increase in numbers living with dementia between 2016 and 2040 in England and Wales

The family, health and societal costs of dementia are high: in 2015, dementia cost the UK economy £23 billion per year, with costs predicted to treble by 2040[13].

Risk factors over the life course

Age is the strongest risk factor for dementia, which is rare among people aged under 65. One in fourteen people aged over 65 will develop dementia, which rises to one in six people aged over 80 years[2].

Dementia risk factors are complex, and have variable relationships with the syndrome depending on the age at which they are measured. Dementia risk is subject to a range of influences across the life course. These include genetic and in utero factors, effects of early childhood deprivation and lack of education, midlife risk factors including hypertension and obesity, as well as factors occurring in later life such as smoking, depression, lack of physical activity and diabetes[14–16]. In addition, many people experience the combined effects of several risk factors. While midlife hearing loss and social isolation in later life have also been proposed as risk factors for dementia[14], the evidence for these factors is weaker.

It has been estimated that eliminating all known risk factors would reduce dementia cases by only around one third[1]

Notably, it has been estimated that eliminating all known risk factors would reduce dementia cases by only around one third[15], so much remains to be discovered about why some people develop dementia and others do not.

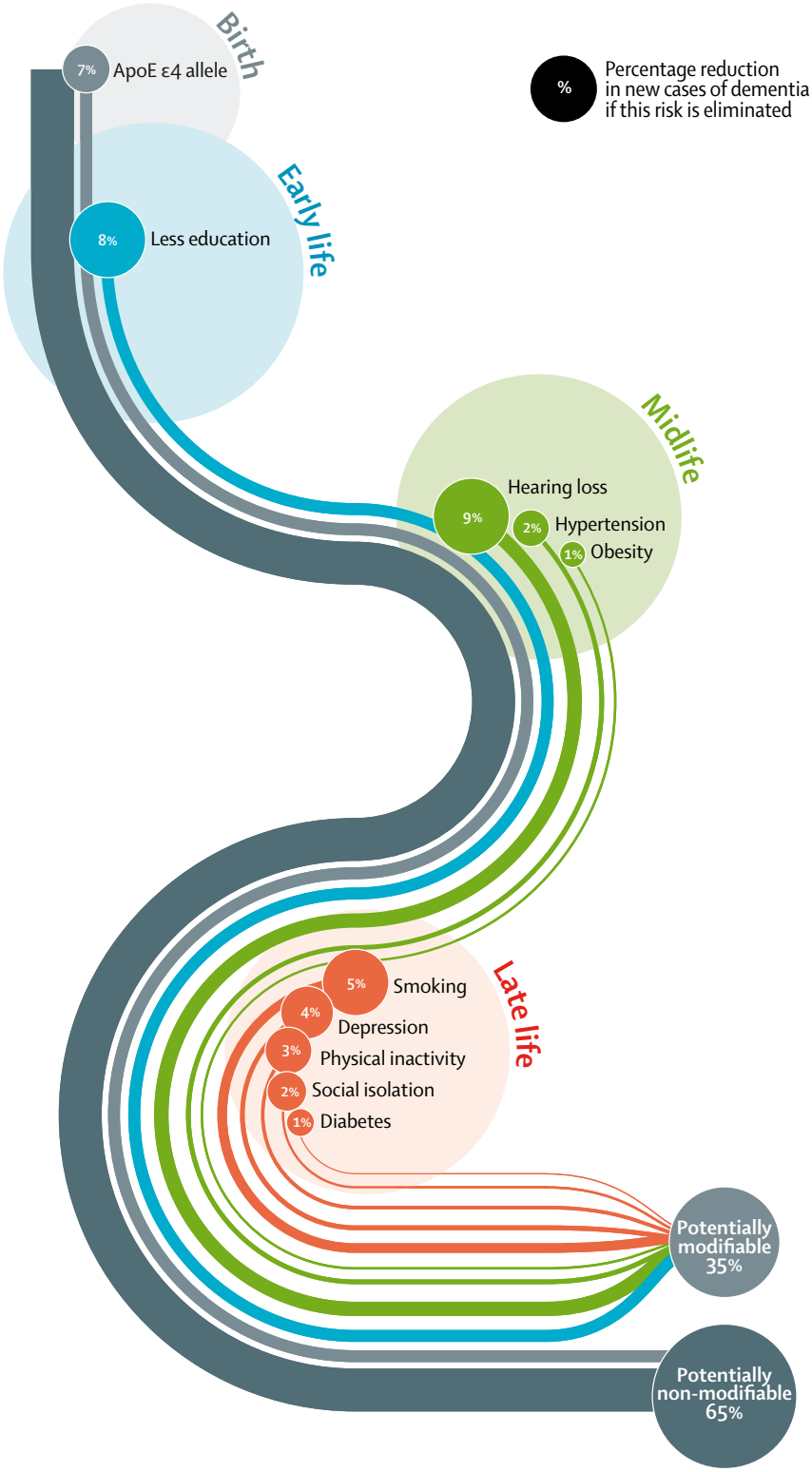
Genetic risk factors

While late-onset Alzheimer's disease (LOAD) can appear to run in families, the underlying genetics are complex and incompletely understood. Results from a large body of genetic research into Alzheimer's disease suggest that many gene variants play a small part in increasing the overall risk of dementia[17–19]. Work is ongoing to identify clusters of gene variants[20]. However, identification of the presence of even the best characterised risk variant – the apolipoprotein E4 allele, *APOE4* – is not helpful for clinical practice: carrying this allele is neither necessary nor sufficient to predict eventual dementia risk.

At least 20 other common susceptibility loci have been identified to be associated with LOAD, in addition to rare variants in genes such as TREM2[17]. Polygenic risk scores for LOAD have been developed that take account of the small increases in risk associated with a range of genetic variants. While studies confirm that LOAD has significant evidence of a polygenic component[17,21], the use of such risk scores is currently confined to research, as they have not been validated for use in general populations.

For rare, early-onset Alzheimer's disease (EOAD), three highly penetrant autosomal dominant mutations in the genes amyloid precursor protein (*APP*), presenilin 1 and presenilin 2 (*PSEN1/2*) are recognised to cause dementia among people aged in their 40s and 50s[22]. Studies are ongoing into other genetic predictors of EOAD[23]. For some other rare conditions leading to dementia, such as Huntington's disease, genetic risk is well described. Here, an autosomal dominant mutation in the huntingtin (*HTT*) gene leading to an expanded CAG trinucleotide repeat is associated with disease[24].

In summary, while genetic information may be informative for people with a personal or family history of early-onset dementia, genetic information is not currently used in clinical settings either to diagnose dementia or to predict future dementia risk for most people.



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3. Dementia risk prediction

Overview of dementia risk prediction

Dementia risk prediction differs from diagnosis or case finding, as it aims to identify individuals who are at high risk of developing dementia in the future, rather than those who already have the condition. Dementia risk prediction models are not currently used in clinical practice (outside of highly specialised settings, such as the care of families affected by early-onset Alzheimer's disease), but they abound in research settings. These statistical models predict future dementia risk based upon a variety of information about an individual, such as their age, health status and lifestyle behaviours.

Models used to assess the probability that an individual will develop a condition in the future are known as 'prognostic models', which contrast with 'diagnostic models' used to assess the probability that an individual already has a condition. However, because dementia has an insidious onset and a slow trajectory of decline, it is likely that people identified with a raised risk of developing dementia within a short timescale (e.g. under 3 years using a prognostic model) may in fact be exhibiting early signs of the condition.

In research settings, dementia risk prediction models have several uses, including examining factors that potentially confer risk or resilience to dementia. Such research may inform the design of trials of preventive interventions and help to identify target populations for those trials.

While the concept of transferring dementia risk prediction models from research into clinical settings for either early detection of disease or determination of 'at-risk' states is appealing, it is essential that the clinical validity, utility and ethics of such approaches is carefully scrutinised

In recent years, the recognition that neuropathological changes may predate any measurable clinical signs or impaired cognition associated with Alzheimer's disease by many years, has also led to the definition of a 'preclinical' phase of Alzheimer's disease characterised by biomarkers, which is intended for research use[25]. However, concerns have been raised that the conceptual evolution of dementia from a clinical syndrome to a biological continuum raises ethical and social challenges[26].

While the concept of transferring dementia risk prediction models from research into clinical settings for either early detection of disease (with diagnostic models) or determination of 'at-risk' states (with prognostic models) is appealing, it is essential that the clinical validity, utility and ethics of such approaches is carefully scrutinised[4].

Policy around dementia prevention, risk prediction and case finding

The lack of effective treatments for Alzheimer's disease and repeated failure of clinical trials of potential new drugs has prompted a shift towards dementia prevention in both global and UK policy. Prevention and risk reduction formed one of the pillars of the WISH Dementia Forum report 2015[27], while the World Alzheimer Report 2014 took dementia risk reduction as its theme[28]. The Lancet Commission also urged ambitious action on the known modifiable risk factors for dementia[14].

In England, the National Institute of Health and Care Excellence (NICE) published guidance on promoting healthy lifestyles in midlife to delay or prevent the onset of dementia, disability and frailty in later life[29]. This aligned with the Blackfriars Consensus statement on promoting brain health, which called for action on and further research into dementia risk reduction strategies[30].

In dementia, the term 'prevention' is challenging: primary prevention (i.e. removing risk factors among those without evidence of disease) may not be adequately distinguished from secondary prevention, whereby attempts are made to modify early biological changes that may signify future dementia.

While few policies focus specifically on prediction of future dementia risk, the importance of early diagnosis is emphasised in a number of government initiatives including the National Dementia Strategy 2009, the Prime Minister's Challenge 2012, and Prime Minister's Challenge on Dementia 2020[13,31]. The governmental NHS Mandate in 2016-7 and 2018-9 included an objective to maintain a minimum diagnosis rate of two thirds for people with dementia[31].

Specific policies to enhance dementia case finding in England include: the development of a toolkit by the Royal College of General Practitioners (RCGP); a Dementia Identification Scheme to reward GP practices for improving dementia detection rates in 2014-5; and national Commissioning for Quality and Innovation (CQUIN) targets to incentivise dementia case finding, prompt referral to specialist services and improved dementia care.

These initiatives have tended to focus on 'at-risk' populations such as people aged 60 years and over with cardiovascular disease, people aged 40 years and over with Down's syndrome and people with neurodegenerative conditions such as Parkinson's disease.

NHS Health Checks, offered free to individuals aged 40-74 years, also aim to identify people at higher risk of developing a range of health conditions that predispose to dementia, although this programme has been criticised for the lack of trial-based evidence to support its effectiveness and cost-effectiveness[32].

However, existing policies do not support screening unselected populations for dementia. The 2015 position of the UK National Screening Committee (NSC) was not to recommend universal screening for dementia[33]. This was based on uncertainty about the natural history of the condition, lack of validity of current tests and a lack of confidence that early treatment would slow or prevent the disease. The NSC's position is widely endorsed by charities such as Alzheimer's Research UK[34] and professional organisations including the Royal College of General Practitioners[35].

No policies about future dementia risk prediction using prognostic models in clinical settings had been identified at the time of writing.

Expert opinions on potential benefits and harms of dementia risk prediction

Expert informants were asked for opinions on potential benefits and harms of implementing risk prediction for dementia among apparently healthy individuals in the general population.

The only suggested benefits for patients were:

- Motivation to initiate or sustain lifestyle changes or increase compliance with secondary stroke prevention advice - although a systematic review of the effect of communicating genetic risk information for future conditions suggested that it did not motivate risk-reducing behaviour[36]
- Enabling people to plan for the future - although there is little evidence that this happens in practice[37]
- Identifying high-risk people early for clinical trials aimed at changing the underlying biological profiles associated with higher dementia risk at particular ages in the future

Suggested harms and uncertainties of predicting future dementia risk were grouped into different themes.

Issues with risk prediction tools for dementia

Dementia is a complex condition to predict: it is highly correlated with age and above a certain age (e.g. 80 years), nothing reliably predicts dementia risk[38]. Moreover, the nature of dementia changes with age, as described earlier, but existing tools aimed at predicting dementia are often applied to broad age-bands, making their evaluation difficult. Other issues identified include that:

- When dementia risk prediction models are being developed, there is a lack of technical standards for model specification
- There is also a lack of reporting standards for model performance characteristics
- A lack of longitudinal data in models hampers their accuracy
- Existing models rarely take behaviour change into account
- Few models have been externally validated across different populations; there is therefore uncertainty about the validity of existing risk prediction models for correctly identifying people at high risk of future dementia

All of these factors mean that no single model is currently suitable for use for dementia risk prediction among general populations. Further information about existing models is provided later in this report (see Overview of current risk prediction models).

Problems with the utility of dementia risk prediction

The major issue with dementia risk prediction that echoed throughout both the academic literature and interviews with experts was the lack of effective interventions to offer people identified as high risk. Moreover, the natural history of people at 'high risk' of dementia is not well understood. Even among people with mild cognitive impairment, only a proportion (estimated as 5-15% per year) will progress to dementia[39], whilst others will stay the same and some will show improvement in cognitive function.

Other issues identified included:

- The concept of being 'high risk' is not well understood by patients
- There is a lack of evidence that predicting a future risk will effectively change behaviour, even were there behavioural interventions proven to improve cognition[36,40]
- Interventions such as exercise, addressing vascular risk factors and cognitive training are not proven to lower individual risk in people with high risk scores
- There is uncertainty about whether some existing factors believed to cause dementia are actually linked by reverse causality (i.e. factors such as late-life depression may be signs of early dementia rather than risk factors for dementia)
- Using models to identify people at high risk of future dementia for trials is problematic: drug companies may want further evidence of neuropathological changes, so would still require invasive tests, whilst repeated monitoring and drug testing among people who may never progress to dementia raises ethical concerns

It was suggested that broader public health campaigns (e.g. about healthy lifestyles) may be better for promoting brain health in people without memory symptoms than using risk prediction tools. This has been echoed in literature highlighting the importance of public health approaches and, in particular, primary prevention to reduce later dementia occurrence and disability[14,41,42].

Ethical, legal and social issues arising from dementia risk prediction

Dementia risk prediction was generally considered to pose a range of concerns and questions:

- It is unclear how acceptable dementia risk prediction is, when dementia has been identified as the greatest fear of people aged over 55 years; respect for individual patient choice is paramount
- There is a risk of inducing anxiety and distress, particularly among people in their 50s and 60s and their families
- The potential for stigma associated with dementia may impact upon a person's perception of how they are ageing, as well as their identity and relationships
- Being 'high risk' for dementia is likely to be linked to challenging health and social circumstances; there is a risk of stigmatising people with chronic health problems and on low incomes
- Currently, there is uncertainty about the effect (of a high risk dementia status) on employment, driving and activities such as childcare

- It is possible that insurance premiums could be adversely affected, especially if predictive tests identified early disease
- There are ethical concerns about the lack of effective interventions to offer people identified as being high risk
- There is also thought to be a risk of exacerbating inequalities and screening the worried well

Implementation issues

Overall, it was felt that implementing dementia risk prediction on the basis of current evidence would result in a large increase in clinical workload, mostly in primary care, but would not change outcomes for patients or the population at large. Other implementation issues raised included that:

- The best way to communicate risk to patients is not well understood, nor are the harms of risk communication known, as there have been no trials for such approaches
- There is an opportunity cost associated with identifying and following up people at risk of a condition: resources may be diverted from other purposes such as healthcare for people with dementia
- Health systems do not have the capacity to respond to increasing demand and there would be major staff training needs
- Any programme using risk prediction models would require co-ordination and clarity of roles

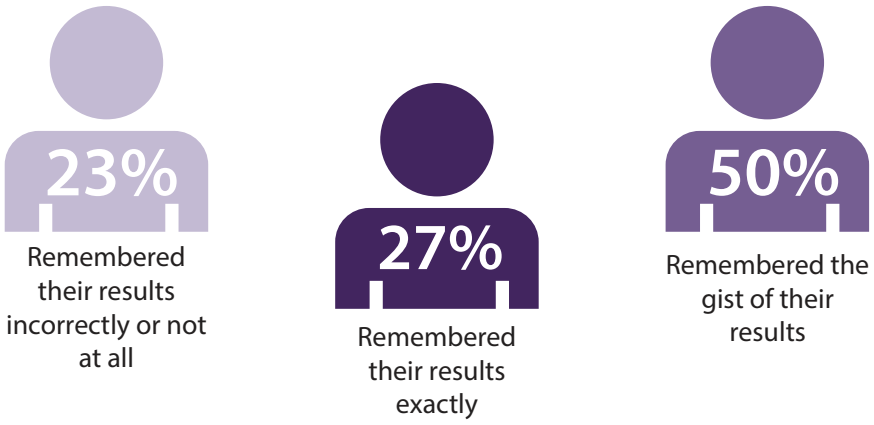
A recent published review of whether dementia testing for apparently healthy individuals is ever justified concluded that 'attention to life course risk reduction and support in the community for frail and cognitively impaired older adults is a better use of limited healthcare resources than introduction of unevaluated dementia screening programmes'[43]. This follows a number of earlier papers from healthcare professionals arguing that political drives to screen for pre-dementia or at-risk states are not evidence based and may do more harm than good[44–46].

In summary, there is insufficient evidence that use of dementia risk prediction models at population level would provide an acceptable balance of benefits to risks, given the number of potential harms and uncertainties across domains ranging from ethics to model validity, model utility and implementation.

Public attitudes towards dementia risk prediction and prevention

In the Risk Evaluation and Education for Alzheimer's disease (REVEAL) study, 162 asymptomatic adults from the United States who had a parent with LOAD had their own *APOE4* genotypes tested and were randomly assigned to either receive or not receive the results[47]. There were no differences in changes in overall anxiety, depression or test-related distress between the groups over time. However, after receiving their results, the *APOE4* negative subgroup had lower levels of test-related distress than the *APOE4* positive subgroup. People with high levels of emotional distress before undergoing the genetic test were also likely to have higher levels of emotional distress after disclosure of their *APOE4* results.

Qualitative follow-up work with 79 of the REVEAL participants showed that at 12 months, only 27% were able to recall their results correctly and 23% remembered nothing or remembered incorrectly, while 50% remembered the gist of the information given. Risk information was interpreted in light of their experiences of family members with AD, who in the family they suspected would get AD (e.g. based on family likenesses), and information gathered from a variety of sources including doctors, patient charities and the media. Knowing their *APOE4* genotype did not displace participants' uncertainty about their personal LOAD risk[40].



In a similar study carried out in Montreal among 40 first-degree relatives of people with LOAD, ideas about AD causation and prevention were mostly informed by family history and personal experience of caring for relatives with LOAD, with many participants unclear about how genetic testing would reveal new information[40].

Another survey of 4,036 participants from an online community of people interested in AD prevention research suggested that around 80% wanted genetic or biomarker testing (if it were paid for by insurance). However, 33% did not view a positive biomarker result as evidence of increased risk. As well as a lack of understanding about the meaning of test results, around 12% of people, worryingly, indicated that they would 'seriously consider suicide' if found to be to high risk for AD[48].

A recent focus group study of people in Spain and the UK, three quarters of whom had a first degree relative with AD, showed that there was initially high interest in learning information about personal AD risk. However, interest waned when people realised that biomarkers do not provide conclusive information and options to reduce disease risk were not available[49].

Studies of public attitudes towards dementia prevention also highlight the complex associated practical and ethical issues, particularly in the context of low general understanding about dementia. A systematic review of 34 population surveys carried out between 2012 and 2017 across Europe, the United States, Eastern Asia, Israel and Australia found that public knowledge of the potential for prevention and treatment of dementia is poor, though there was some evidence of improvement over time[50].

In summary, individuals are often interested in genetic testing for future disease risk. Research has shown that these individuals do not generally experience adverse psychological outcomes when receiving their test results from a trained professional. However, there are many challenges involved in both estimating and communicating disease risk accurately from genetic information[51], especially when public understanding of the condition is low.

It has also been noted that the scientific community's ability to generate a research evidence base to inform policy and practice around genetic testing for future disease risk is being overwhelmed by the rate of scientific discoveries and commercial efforts to market genetic tests direct to consumers[51].

4. Current landscape of dementia risk prediction models

Overview of current risk prediction models

Numerous dementia risk prediction models have been developed, largely for research, but with the hope that they could eventually be used to target interventions or trials to those at highest risk. A systematic review carried out in 2010[52] described over 50 dementia risk prediction models that were heterogeneous in terms of their accuracy, the variables included, follow up time, and the outcome predicted. This review concluded that none were fit for the purpose of dementia risk prediction due to methodological weaknesses of the studies, and the lack of unbiased evaluation.

A follow up systematic review published by the same research group in 2015[53] identified an additional 21 dementia risk prediction models published in the intervening time period. Again, the models were highly variable in terms of the variables included. The review authors described five categories of models:

- Demographic only models incorporating factors such as age, sex, education and ethnicity
- Cognitive models incorporating cognitive test scores with or without subjective memory complaints or demographic data
- Health variables and health risk indices e.g. information on cardiovascular risk factors
- Genetic risk scores including *APOE4* and other risk variants e.g. CLU
- Multivariable models typically incorporating demographic, health and lifestyle measures

While this review showed that the field of dementia risk prediction modelling has progressed to incorporate non-traditional dementia risk factors (such as diet and physical function) and a wider variety of genetic information into models, there was still a lack of evidence to support the use of any particular model for dementia risk prediction in population settings.

A recent systematic review from 2018 described similar categories of dementia risk prediction models subdivided into four intended uses[54].

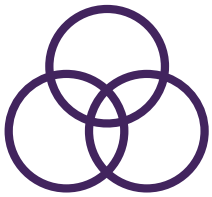
- These were late life risk models for the general population
- Midlife risk models for the general population
- Models for patients with diabetes
- Models for predicting conversion of mild cognitive impairment to Alzheimers disease

Again, it was noted that comparing the accuracy of models was hampered by variability in the age and risk factor profile of the population under study, as well as varying sample sizes, dementia diagnostic criteria and length of follow up.

Overall, these systematic reviews, along with expert perspectives, highlight the need for published external validations of existing dementia risk prediction models. As well as considering how well models predict dementia risk in particular populations (e.g. stratified by age), authors emphasised the need for research to focus on other aspects of dementia risk prediction such as its public acceptability, the cost and feasibility of gathering data for calculating risk, and the ethical and social implications[53,54].

Evaluating dementia risk prediction models

The 2012 paper *Risk prediction models: a framework for assessment* identified three domains to guide the assessment of a risk prediction model[55]. These are:

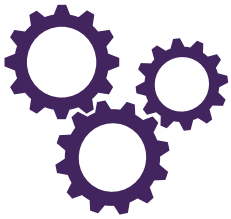


The context in which a model will be used

- Purpose, clinical or public health context, population and disease
- Availability of intervention(s) and thresholds for use
- Risks and costs associated with the test and treatments

The performance of the model itself

- Quality and applicability of data upon which the model was built
- Performance metrics
- External validation



Issues related to limplementation

- Service delivery, feasibility and acceptability
- Cost effectiveness
- Unintended benefits and harms

Of these, statistical issues related to the performance of the model tend to receive most attention in dementia risk prediction literature. However, evaluating model performance is hampered by the variable methods used and the lack of technical standards for reporting model performance. Several aspects of model performance need to be considered:

- **Internal validity** of a risk prediction model refers to how well it performs in the population in which it was developed.
- **External validity** refers to testing how generalizable the is model for use in other similar populations. It is commonly considered a stronger test for prediction models than internal validation as it addresses transportability rather than reproducibility of the model[56].

Key measures of model performance are:

- **Calibration,** which refers to whether a model can correctly estimate the average risk of dementia of a group of people. Agreement between the risk predicted under the model and the observed frequency of the condition under study can be evaluated using calibration plots[57] and assessing the mode intercept (alpha) and slope (beta)[56].
- **Discrimination,** which refers in this context to how well a risk score can differentiate between participants who will and will not develop dementia[57]. A model that discriminates well will accurately rank individuals' risks in relation to the population as a whole. Discriminative ability is commonly quantified with a concordance statistic (or C-statistic)[56]. For a binary endpoint such as being at high risk of dementia or not, the C-statistic is identical to area under the receiver operating characteristic (ROC) curve (AUC) which plots the sensitivity against 1-specificity for consecutive cut offs of predicted risk.
- **Clinical usefulness,** which can be measured by decision-curve analysis, where the net true positive classification rate is displayed by using a model over a range of thresholds[56].

While newer statistical developments in model performance assessment such as reclassification of individuals into high and low risk categories have been proposed[58], these have not yet been widely adopted in the reporting of dementia risk prediction models.

How valid are existing dementia risk prediction models?

How well do existing dementia risk prediction models perform using these measures? In the 2015 systematic review, only four risk prediction models had been externally validated[53,57], which had increased to eight models or scores by the 2018 systematic review[54]. Of these eight models, five were designed to predict dementia among general populations, either in midlife (one model) or later life (four models).

The tables in the **appendix** show the five models with their relative performances for predicting future dementia risk. The remaining three validated models were intended for use in specialist populations (diabetes – two models; people with MCI – one model; data not shown).

C-statistics reported for multivariable models of dementia risk prediction among general populations ranged from 0.49 to 0.84. C-statistics of 0.81-0.89 were reported for a model based upon cognitive test score alone, although this model performed best among people with existing memory complaints. One systematic review used AUC values of 0.9-1, 0.7-0.9 and <0.7 to represent high, moderate and low accuracy respectively[54]. However, the cut off at which a C-statistic or AUC score is deemed acceptable depends upon the purpose of a risk score.

For provision of general health education and lifestyle advice, a value of 0.7-0.8 can be acceptable[59], though it is highly questionable whether a risk score is needed at all for this purpose as this will involve potential cost to individuals with unknown benefits. Stricter requirements might be needed for risk scores aimed at entering people into clinical trials of drugs with potentially severe side effects or referral to specialist clinics for extensive testing[59].

If the dementia risk prediction model is intended for health purposes, then, depending on the context for use, it could be classified as a medical device. This would mean that the model would have to satisfy certain performance requirements, demonstrating scientific and clinical validity in the population for which it is intended.

A strong age effect was seen, i.e. the same models performed differently in different age groups. For example, the ANU-ADRI model was relatively valid (C-statistic 0.74) for individuals with a baseline age of ≥53 years, but performed less well in a population aged ≥75 years (C-statistic 0.64). Similarly the DRS, which aimed to predict the risk of dementia at five years, showed a C-statistic of 0.84 for individuals aged 60-79 years compared to 0.56 for those aged 80 years and over – the age group at highest dementia risk.

In general, prognostic models aiming to predict future dementia risk perform better in younger age groups. However, in younger populations with low dementia prevalence, using existing models would lead to large numbers of false positives being identified[43]. In addition, whilst some models have been validated in different ethnic groups (e.g. the BDSI; see Table 1), further work is needed to test models in multiple populations including those of different ages and ethnicities.

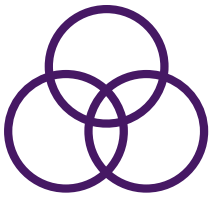
Other recent developments in dementia risk prediction modelling include the simplification of models to incorporate variables which are easily obtained, either from primary care records (e.g. the DRS) or from self-report[60]. The aim is to reduce the cost and expertise needed to calculate dementia risk scores.

Using dementia risk scores in clinical trial settings has also been explored[60]. The CAIDE score, in conjunction with neuropsychological testing, was used to identify an older Finnish population at risk of dementia for a trial of diet, physical activity, vascular risk monitoring and cognitive training, which showed a beneficial effect of this package on cognitive outcomes at 2 years[61]. This finding has not been shown in two other trials of similar interventions, over 3 and 6 years[62,63].

It seems clear from the literature that no single model will be suitable for dementia risk prediction across all populations and settings. Instead there have been calls for 'a set of models… for different purposes and contexts such as midlife versus late-life profiles, long-term versus short-term prediction and public health, primary care or specialized memory clinic use'[59].

5. Future research

It is important that future research does not just focus on developing and evaluating the performance of new models, but rather that it is a holistic process that takes into account the context in which a model might be used, as well as its potential value to society. The following suggestions for future research were drawn both from expert interviews and academic literature:

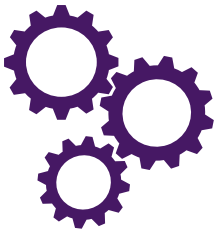


To address issues of medical context

- The natural history of dementia and dementia at-risk states at different ages is still poorly understood. There is a need for better stratification of groups at high risk and a better understanding of likely trajectories of change among these groups, recognising the complexity of risk
- Research is needed into the psychological, behavioural and societal effects of giving people a dementia risk score
- Research is needed into the effectiveness (and cost effectiveness) of interventions to prevent dementia. If randomised controlled trials of some interventions are not possible, alternative options should be used to develop the evidence base e.g. stepwise implementation and evaluation
- Trials are needed of the effect of providing advice or interventions to high-risk groups versus whole populations, and identifying exactly who would benefit from which support or interventions

To address issues with models

- Models aiming to predict dementia risk should be age-appropriate and based upon long-term dynamic follow up data on both predictors and outcomes[72]. They need to consider a broad range of fixed and modifiable predictors, as well as how to define predictors and weigh the costs and benefits of including expensive invasive biomarkers in models
- Evidence is needed on the best approaches to dementia risk prediction model development, including the role of machine learning over traditional epidemiological approaches, as large amounts of high quality, well phenotyped data are generated through projects such as the European Prevention of Alzheimer's Dementia (EPAD) study[73]
- Models and their performance metrics need to be reported in a standardised way, including key information about the population in whom the model was built, for example following guidelines such as the TRIPOD statement[74]
- It would be useful to have a set of criteria to judge the quality of risk prediction standards
- Models need to be externally validated. There is a need to consider how tests perform in true populations at risk



To address implementation issues

At present, implementation research for dementia risk prediction is premature: there are broader questions around the utility of testing that first need to be addressed. Nevertheless, research into implementation of risk prediction tools for other conditions such as cardiovascular disease may offer useful insights for policymakers in the future, especially by examining:

- The ethical, legal and social aspects of disease risk prediction, as well as the balance of costs and benefits for an individual and society
- The most suitable target populations for risk prediction tools
- The most effective ways to communicate risk and to link risk communication to behaviour change, which are not well understood
- The provider barriers and facilitators to implementing risk prediction tools in practice
- How best to design models with end users in mind, e.g. using data available in routine electronic health records or embedding tools within existing interfaces
- The regulatory challenges associated with using dementia risk prediction models for health purposes

6. Conclusions

The use of models to predict the development of future dementia in the general population (as opposed to identify individuals with signs of early disease) is currently confined to research rather than clinical settings.

Many objections raised about dementia screening and early detection also apply to dementia risk prediction. This includes a lack of scientific validity of current dementia risk prediction tools for use across different populations, especially where dementia prevalence is low. The utility of dementia risk prediction in the absence of effective interventions for individuals identified as 'high-risk' is also unclear.

There remain unresolved ethical, legal and social questions about using risk prediction tools for dementia, and uncertainties over how health systems would be able to respond to increased demand for health advice generated by the use of such risk prediction tools; a clear understanding of the costs, benefits and uncertainties is lacking.

As the population ages, and dementia becomes an ever more urgent priority for health policymakers, there will undoubtedly be greater interest in identifying individuals at high risk of dementia.

Developments in statistical modelling and data science approaches, together with the growth of large high quality datasets, are likely to generate fresh insights into dementia pathogenesis[72]. The challenge will be to generate better evidence for the validity of risk prediction tools operating at different stages across the life-course, as well as the effectiveness and cost effectiveness of interventions to prevent or delay dementia among high-risk individuals.

Meanwhile current evidence suggests that adopting a population approach to promoting general brain health at all stages of life is likely to result in greater societal benefit[42,75].

Appendix - features and performance of five general population dementia risk prediction tools with data from external validation(s)

Cardiovascular risk factors, ageing and dementia (CAIDE) (64)

Features of model

Setting and population in which model was developed	Finland. Sample of 1,409 participants from the CAIDE cohort aged 39 to 64 years.
Aim of model	To use risk factors in midlife to predict risk of dementia in later life (mean follow up 20 years)
Type of model	Multivariable model
Predictors included in model	Demographics (age, sex, education) Health (cholesterol level, BMI, systolic BP) Genetics (*APOE4* where available)
Availability of model predictors	Cohort data

Performance of model in original development cohort(s)

C-statistic	0.78
Sensitivity analyses	None

Performance of model in external validation cohort(s)

Cohort 1	9,480 individuals from Kaiser Permanente aged 40 to 55 years (mean follow up 36 years) (68)
C-statistic	0.75
Cohort 2	Rush Memory and Aging Study (MAP)
C-statistic	0.49
Cohort 3	Kungsholmen project
C-statistic	0.53
Cohort 4	Cardiovascular Health and Cognition Study
C-statistic	0.57
Cohort 5	6,667 non-demented community-dwelling individuals from Rotterdam Study aged ≥55 years (57)
C-statistic	0.55

Australian National University AD Risk Index (ANU-ADRI)(65)

Features of model

Setting and population in which model was developed	Australia. Risk index developed by reviewing literature on risk and protective factors for AD. No development cohort.
Aim of model	To assess a person's risk of developing AD at 60 years or over
Type of model	Multivariable model
Predictors included in model	Demographics (age, sex, education) Health (BMI, diabetes, depression, high cholesterol, traumatic brain injury) Lifestyle factors (smoking, alcohol, physical activity, cognitive activity, fish intake) Social/environmental factors (social engagement, pesticide exposure)
Availability of predictors	Self report/cohort data

Performance of model in original development cohort(s)

C-statistic	Performance tested in three validation cohorts below
Sensitivity analyses	None

Performance of model in external validation cohort(s)

Cohort 1	903 individuals from Rush Memory and Aging Study (MAP), baseline age≥53 years
C-statistic	0.74*
Cohort 2	905 individuals from Kungsholmen project, baseline age ≥75 years
C-statistic	0.49
Cohort 3	2,496 individuals from the Cardiovascular Health and Cognition Study, baseline age ≥65 years
C-statistic	0.73*
Cohort 4	6,667 non-demented community-dwelling individuals from Rotterdam Study aged ≥55 years (57)
C-statistic	0.75

* Results reported for AD. Using only 6 variables which were available across all three cohorts, the C-statistics were 0.69, 0.67 and 0.73 respectively.

Brief Dementia Screening Indicator (BDSI) (66)

Features of model

Setting and population in which model was developed	USA. Individuals with mean ages 71.3 – 72.9 years from four cohort studies: the Cardiovascular Health Study (CHS, n=2,794), Framingham Heart Study (FHS, n=2,411), Health and Retirement Study (HRS, n=13,889) and the Sacramento Area Latino Study on Aging (SALSA, n=1,125).
Aim of model	To predict 6 year risk of dementia (and enable primary care clinicians to identify high-risk older patients for targeted cognitive screening).
Type of model	Multivariable model
Predictors included in model	Demographics (age, education) Health (history of stroke, diabetes, BMI, depressive symptoms) Lifestyle (assistance needed with money or medication)
Availability of predictors	Cohort data

Performance of model in original development cohort(s)

C-statistic	CHS: 0.68 HRS: 0.76 FHS: 0.77 SALSA: 0.78
Sensitivity analyses	Performance by ethnicity (HRS) Whites 0.75 Blacks 0.70 Latinos 0.71 Performance by ethnicity (CHS) Whites 0.70 Blacks 0.65

Performance of model in external validation cohort(s)

Cohort 1	6,667 non-demented community-dwelling individuals from Rotterdam Study aged ≥55 years (57)
C-statistic	0.78

Dementia Risk Score (DRS) (38)

Features of model

Setting and population in which model was developed	UK. 930,395 patients aged 60-95 years without dementia or cognitive symptoms from 377 general practices in The Health Improvement Network (THIN)
Aim of model	To predict 5 year risk of first recorded dementia diagnosis for people aged i) 60-79 years ii) 80-95 years
Type of model	Multivariable models
Predictors included in model	i)For people aged 60-79 years Demographics (age, sex) Other (calendar year) Health (current depression, history of stroke/TIA, diabetes, atrial fibrillation, BMI) Medications (current use of aspirin, antihypertensives) Lifestyle (high alcohol consumption, smoking) Social (local area deprivation) ii) For people aged 80-95 years Demographics (age, sex) Other (calendar year) Health (depression, anxiety, stroke/TIA, diabetes, atrial fibrillation, BMI, systolic BP, lipid ratio) Medications (current use of aspirin, NSAIDs, anti-hypertensives) Lifestyle (high alcohol consumption, smoking)
Availability of predictors	Primary care records

Dementia Risk Score (DRS) (38) (continued)

Performance of model in original development cohort(s)

C-statistic	Performance tested in validation cohort below
Sensitivity analyses	

Performance of model in external validation cohort(s)

Cohort 1	264,224 individuals from 95 randomly chosen THIN practices that did not contribute to the development cohort (38)
C-statistic	i) 0.84
	ii) 0.56
Cohort 2	6,667 non-demented community-dwelling individuals from Rotterdam Study aged ≥55 years (57)
C-statistic	0.81

Free and Cued Selective Reminding Test (FCSRT-free recall)

Features of model

Setting and population in which model was developed	USA. Originally developed as a dementia screening test in a cross sectional sample of 50 nursing home residents (mean age 80.3 years), 25 without dementia and 25 with dementia according to DSM-III criteria (67)
Aim of model	Original aim: To correctly identify individuals with dementia. Has since been used for prediction of dementia risk from 2 to 5 years
Type of model	Cognitive test
Predictors included in model	Cognitive test score of free recall, cued recall and total recall
Availability of predictors	Data from cross-sectional study.

Performance of model in original development cohort(s)

C-statistic	Performance tested in external cohorts below
Sensitivity analyses	

Performance of model in external validation cohort(s)

Cohort 1	2,558 non-demented community-dwelling individuals from French Three Cities cohort (Bordeaux and Montpellier centres) aged ≥65 years (69)
C-statistic	i) 0.85 (3 years) ii) 0.81 (3-5 years) iii) 0.83 (5 years)
Cohort 2	194 non-demented primary care patients mean age 78.3 years (70)
C-statistic	0.81 (2.6 years)
Cohort 3	854 participants from Einstein Aging Study aged ≥70 years without dementia but with subjective memory complaints (71)
C-statistic	i) 0.87 (2 years) ii) 0.88 (3 years) iii) 0.89 (4 years)

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