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DEMENTIA RISK ASSESSMENT AND RISK REDUCTION USING CARDIOVASCULAR RISK FACTORS

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SUMMARY

Given the poor efficacy of disease modifying treatments and evidence that Alzheimer's Disease (AD) pathophysiology begins in middle-age, efforts to reduce the substantial disease burden have shifted towards preventative intervention in midlife. Up to a third of all AD(the commonest cause of dementia) is attributable to modifiable cardiovascular risk factors. A tool for predicting risk of future dementia using only cardiovascular risk factors has been validated and the effect of lifestyle modification on future cognitive decline is under investigation. In the UK, the QRISK3 risk calculator is used to quantify 10-year risk of cardiovascular disease. Lifestyle changes and lipid modifying therapy are recommended to patients based on their risk score. We will compare the emerging evidence for dementia risk assessment and risk reduction using cardiovascular risk factors with the evidence used to support the implementation of QRISK3 for cardiovascular disease risk assessment and intervention. This will guide future research to determine whether cardiovascular risk assessment can also be used to inform patients of risk of future dementia and advise on risk reduction strategies, in a primary care setting.

Key words: *Alzheimer's disease – dementia – screening - primary prevention*

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INTRODUCTION

In 2014 there were 835,000 people in the UK living with dementia and in our aging population, the prevalence and socio-economic burden of dementia are increasing (Alzheimer's Society 2014). Treatments targeting symptomatic stages of diseases that cause dementia (e.g. Alzheimer's disease) provide limited symptom relief and do not slow disease progression (Buckley 2015). As AD pathology begins decades before the onset of dementia, there is potential to prevent or delay symptom onset through intervention in mid-life (Barnes 2011, Ritchie 2010). Detection of subtle cognitive changes or early stages of a disease process causing dementia may facilitate intervention before the onset of frank symptoms. It is hoped that early intervention will improve patient outcomes and reduce disease burden. However, neurocognitive tests do not provide sufficient sensitivity or specificity for early dementia to qualify for use as a screening tool, and detection of disease biomarkers such as amyloid-beta plaques may be too invasive or expensive for screening purposes. In the absence of a practical test to quantify risk of future dementia using signs of early disease, emerging research may support an alternative means of assessing risk. A reliable quantification of patients' risk of future dementia may be achieved using cardiovascular risk factors such as age, gender, education and physical activity. Following the principles for disease screening set out by Wilson and Jungner (1968), patient's risk of future dementia should not be disclosed without offering a proven means of risk reduction. Risk assessment should always be accompanied by recommendation of an evidence-based intervention that reduces patients' risk. Several studies have found that multi-domain lifestyle interventions including diet and exercise, have beneficial effects on cognition in later life (Rosenberg 2018). Using QRISK3 and the UK National Vascular Risk Management Programme (UKNSC 2012) as a model for risk stratification, disclosure of information and evidence based intervention, we will consider whether current evidence can support implementation of a programme for dementia risk assessment and reduction using cardiovascular risk factors.

ASSESSING RISK OF FUTURE DEMENTIA

Screening is defined by The United Kingdom National Screening Committee (UKNSC) as "the process of identifying individuals who may be at higher risk of a disease or condition amongst large populations of healthy people". At present, The UKNSC does not recommend screening for dementia (UKNSC 2015). They highlight the poor sensitivity and specificity of neurocognitive test batteries used to diagnose dementia and Mild Cognitive Impairment (UKNSC 2015). High false positivity rates make the use of such tests unethical. Dementia is a syndrome associated with several diseases including Alzheimer's disease, Vascular dementia, and Lewy body dementia, each with a separate pathology. Hence, it may be possible to screen for dementia or for the onset of a particular disease process. The UKNSC states; 'In order to offer enough information to allow anyone invited to screening to make an informed choice, we would first need to understand how dementia develops". Alzheimer's disease (AD) is the most common cause of dementia, contributing to 60-80% of cases. AD patho-

logy is known to begin decades before the onset of dementia (Ritchie 2015). Therefore, it is theoretically possible to detect pathological changes that precede the onset of cognitive decline (Jack 2010). The potential to detect early AD using specific disease biomarkers (e.g. amyloid-PET and hippocampus volume) is under investigation (Ritchie 2012), but the cost and/or invasiveness of candidate tests may make them inappropriate for use in screening.

AN ALTERNATIVE DEMENTIA RISK ASSESSMENT USING CARDIOVASCULAR RISK FACTORS

In the absence of a reliable test for all cause dementia or a practical means of detecting early AD pathology, there may be a proxy method to assess risk of future dementia using known dementia risk factors. Although a precise mechanism for AD has not been determined, several inherited and environmental factors are known to affect the probability and time of symptom onset. Accounting for non-independence of risk factors, up to a third of AD cases worldwide may be attributable to modifiable risk factors including diabetes, hypertension, obesity, smoking, and cognitive and physical inactivity (Norton 2014). The CAIDE (Cardiovascular Risk Factors, Aging, and Incidence of Dementia) Dementia Risk Score was developed to predict later life dementia using cardiovascular risk factors (Sindi 2015). CAIDE provides a predictive risk score without the need for genetic testing or invasive testing. The multifactorial risk assessment includes age, hypertension, hypercholesterolemia, physical inactivity, obesity and educational level. Inclusion of Apolipoprotein E ε4 status, the most significant of all known genetic risk factors for AD, did not increase predicative value (Sindi 2015). This simple test is therefore available at minimal cost and minimal risk to the patient, and avoids the ethical complexity associated with genetic testing.

ASSESSING CARDIOVASCULAR RISK IN THE UK

Following the UK National Screening Committee' s recommendation for a National Vascular Risk Management Programme in 2006, there is a system in use within the UK National Health Service for assessing 10-year risk of cardiovascular disease (UKNSC 2012). This involves a risk calculation tool, QRISK3 (Hippisley-Cox 2017) which has been validated in 7.9 million adults aged between 25 and 84. QRISK3 includes the following cardiovascular risk factors: age, ethnicity, deprivation, systolic blood pressure, body-mass index, total-to-HDL cholesterol ratio, smoking, coronary heart disease in a first-degree relative younger than 60, presence of type 1 or type 2 diabetes, treated hypertension, rheumatoid arthritis, atrial fibrillation, stage 3, 4 or 5 chronic kidney disease, systolic blood pressure variability, migraine, corticosteroid use, systemic lupus, atypical antipsychotic use, severe mental illness, and erectile dysfunction. Patient data is collected in primary care and risk scores are shared with patients, according to NICE recommendations to clinical practitioners (NICE 2016). Patients identified as being at high risk of future cardiovascular disease are offered evidence-based interventions to reduce their risk of cardiovascular events. Patients are firstly advised on lifestyle modification and where appropriate, engage in a discussion on lipid modification therapy (NICE 2016).

Considering the QRISK3 protocol as a precedent for implementation of risk stratification, disclosure of information and evidence based intervention in a UK population, we will consider whether current evidence can support a similar programme for dementia. The Wilson and Jungner criteria for screening programmes were published in 1968 and continue to influence the requirements for disease screening (Wilson 1968). Although the proposed dementia risk assessment is not a screening programme (because it would measure the burden of risk factors rather than attempting to detect signs of a disease process), the Wilson and Jungner criteria provide a useful framework to assess its validity. Guided by these criteria, it is critical that a dementia risk assessment offers 1.) a suitable test that is acceptable to the public and 2) an effective intervention for those identified as high-risk to reduce their risk of developing disease. We will take each of these criteria in turn and use QRISK3 as a benchmark to assess the potential for dementia risk assessment in the UK.

Development and validation of the CAIDE Dementia Risk Score in comparison to QRISK3

The CAIDE risk score was developed in a longitudinal study of 1409 participants, where 4% developed dementia over 20 years of follow-up (Kivipelto 2006). Future dementia was significantly predicted by age (≥47 years), education (<10 years), hypertension, hypercholesterolaemia, and obesity. Risk score values were assigned to candidate risk factors using β coefficients from logistic regression. An individuals' dementia risk score was calculated as the sum of these weighted risk scores, and ranged from 0-15. The CAIDE risk score provided a reliable prediction of future dementia, (area under receiver operating characteristic curve 0·77; 95% CI 0·71–0·83). Participants were then assigned a dementia risk category: 1.0% for those with a score of 0–5, 1.9% for a score of 6–7, 4.2% for a score of 8–9, 7.4% for a score of 10–11, and 16.4% for a score of 12–15. Applying a cut-off of scores ≥9 points, the risk score provided a sensitivity of 0·77, specificity of 0·63, and negative predictive value of 0·98 (Kivipelto 2006).

Like QRISK, the CAIDE score has been subsequently validated in a retrospective cohort study (Exalto

2014). The study aimed to validate the CAIDE Dementia Risk Score in a different population and determine whether addition of other risk factors (central obesity, depressed mood, diabetes mellitus, head trauma, lung function, or smoking) would improve prediction value. The study included 12,247 participants in the validation cohort, (mean age 46.4±4.4 years). Of these 12,247 participants, 9480 participants aged 40–55 years were included in analysis to determine whether the prediction accuracy was improved by adding other risk factors to the model. Among the included participants, 2767 participants (25%) were diagnosed with dementia. Harrell's C statistics, (a similar measure of discrimination to the area under receiver operating characteristic curve) shows that the CAIDE risk score was well replicated with a C statistic of 0.75, (similar to the original CAIDE C statistic of 0.78). It achieved a good prediction within different race groups and prediction was not improved by addition of other risk factors (central obesity, depressed mood, diabetes mellitus, head trauma, lung function, or smoking). The risk score was demonstrated to allow stratification of participants into groups with low and high risk of dementia in the next 40 years (Exalto 2014).

Table 1 provides a summary of the development and validation of CAIDE (Exalto 2014) compared to the most recent validation of QRISK3 (Hippisley-Cox, 2017). It is difficult to determine specific criteria for implementation of a risk score – current practice can be used as a guide but the current iteration of QRISK has been subjected to re-validation and improvement since induction into clinical practice. Indeed, QRISK (Hippisley-Cox 2007) was introduced to replace the less reliable Framingham score (Anderson 1991), which was validated in population with limited ethnic diversity and a high prevalence of cardiovascular disease (Hippisley-Cox 2007). Here, we will compare the CAIDE Dementia Risk Score to the most recent validation of QRISK3, as current practice and standards should form a sound basis for future recommendations. The most striking difference between development and validation of the risk prediction tools is the size of the derivation and validation cohorts. The original QRISK tool (QRISK) was derived in a cohort of 1.28million patients and the validation cohort comprised 0.61 million (Hippisley-Cox 2007). QRISK3 and CAIDE both achieve good prediction accuracy, but clinical application of the CAIDE Dementia Risk Score requires validation using a large database such as UK primary care records. Future validation of CAIDE should also consider the effect of comorbidities on risk of future dementia and include younger and older participants.

Table 1. Derivation and validation of QRISK3 and CAIDE Dementia Risk Score (Hippisley-Cox 2017, Exalto 2014)

	QRISK3	CAIDE
Study Design	Retrospective cohort study	Retrospective cohort study
Derivation		
n	7,889,803	9,480
Age	25-84 years	40–55 years
Outcome	Clinical record of CVS disease using ICD-10 codes for: TIA and related syndromes, angina pectoris, acute MI, subsequent MI, complications after MI, other acute ischaemic heart disease, chronic ischaemic heart disease, cerebral infarction, stroke not specified as haemorrhage or infarction	Clinical record of Dementia diagnoses using ICD-9 codes for: possible dementia (excluded in analyses to investigate prediction improvement from addition of risk factors) and specialist confirmed dementia
Statistical Methods	Cox's proportional hazards - Regression coefficients for each risk factor in women and men were used to weight risk factors in the final risk equation. Non-linear risk relationships were accounted for using fractional polynomials. Rubin's rules for multiple imputations of missing data were applied.	Logistic regression - β coefficients were used to assign scores for each risk factor. Individuals' risk score was obtained by summing the scores for the appropriate level of each of the risk factors.
Validation		
n	2,671,298	12,247
Statistical Methods	Harrell's C statistic and Kaplan-Meier estimates evaluated at 10 years. Analyses were stratified by: age, ethnic origin, comorbidity and treatment subgroups.	Harrell's C statistic and Kaplan-Meier estimates of observed 40-year population-level dementia risk. Analyses were stratified by race.
Results	The QRISK3 algorithm explained 59.5% of the variation in time to diagnosis of cardiovascular disease. For women, C statistic was 0.88, for men C statistic was 0.86.	The risk score allowed stratification of participants into those with 40-year low and high dementia risk. The CAIDE risk score C statistic was 0.75, similar to the original CAIDE C statistic of 0.78.

Abbreviations – CVS: Cardiovascular, ICD: International Classification of Diseases, MI: myocardial infarction, TIA: Transient ischaemic attack

Intervention to reduce risk of future dementia due to cardiovascular risk factors

Echoing Wilson and Junger's stipulation that "there should be an accepted treatment for patients with recognised disease" (Wilson 1968), the UKNSC states that we should "be confident that early treatment will slow the progression or even prevent the disease" (UKNSC 2015). As AD pathology begins decades before the onset of dementia, there is potential to prevent or delay symptom onset through intervention in midlife (Barnes 2011, Ritchie 2010). A 10-25% reduction in 7 modifiable AD risk factors (diabetes, midlife hypertension, midlife obesity, smoking, depression, low cognitive activity and low physical activity) could potentially prevent as many as 3 million AD cases worldwide (Barnes 2011). Studies have found that multi-domain lifestyle intervention (e.g. diet and exercise) has beneficial effects on cognition in later life, regardless of Apolipoprotein E ε4 status (Solomon 2018). A recent a double-blind randomised controlled trial of 2654 individuals aged 60-77 years, used CAIDE Dementia Risk Scores as an indicator of dementia risk and investigated the effect of multi-domain lifestyle intervention in those with CAIDE scores ≥6 (Rosenberg 2018). The intervention included diet advice, exercise, cognitive training, and monitoring of vascular and metabolic risk factors. Cognition at baseline and 2-year follow-up was assessed using neuropsychological test battery Z-scores. The intervention had a significantly beneficial impact on cognition; scores were 25% higher in the intervention group than those of the control group. Although at a superficial level this may provide theoretical support for using CAIDE scores and lifestyle intervention as a means of reducing the incidence of dementia, the application of this evidence to dementia is limited. Better cognitive performance after 2-year follow-up does not reflect the incidence of dementia in the cohort. Although cognition is an important factor influencing the development of dementia (through the mechanism of "cognitive reserve"), the outcomes are not interchangeable.

In a large intervention study that did use incidence of dementia as the outcome measure, dementia incidence was not affected by a reduction in exposure to cardiovascular risk factors in an unselected cohort aged 70-78 (van Charante 2016). Better patient outcomes may be achieved through earlier, targeted intervention in cohorts identified as high-risk. Therefore, there is a need to identify middle-aged individuals at high risk of developing dementia and demonstrate dementia risk reduction using cardiovascular factors in this high-risk population. A meta-analysis of 263 studies with various interventions including cognitive training, physical activity, diet, dietary supplements, hormone therapy and pharmacological intervention (including antihypertensive therapy, lipid-lowering therapy and diabetes treatment) found no strong evidence for the effectiveness of such interventions on preventing or delaying age-related cognitive decline, MCI and clinical Alzheimer's-type dementia (Kane 2017). Although they found no consistent benefit from physical activity interventions in preventing cognitive decline, the authors concluded that the proportion of results reporting a benefit was unlikely to be due to chance and warranted investigation of a potentially significant relationship (Kane 2017). These findings provide an incentive for further research to determine whether interventions before the onset of dementia can improve patient outcomes and reduce disease burden. To support implementation of the proposed scheme (CAIDE risk assessment in an appropriate patient group), studies should demonstrate reduced incidence of dementia following reduction of cardiovascular risk (by lifestyle or pharmacological measures) in patients shown to have high CAIDE Dementia Risk Scores in mid-life.

In addition to lifestyle advice, patients identified as having high risk of cardiovascular disease using QRISK3 may be offered lipid-modifying therapy (NICE 2016). Clinicians are urged to promote cardiovascular risk reduction through lifestyle modifications in the first instance and advise patients that statin therapy is designed to supplement not replace such changes. Clinicians engage in a discussion with the patient on the risk and benefits associated with statins and come to a decision that is acceptable for the individual patient. In a systematic review including two randomised controlled trials and 26,340 participants, statins were found to have no effect on occurrence of Alzheimer's disease or dementia compared to placebo (McGuinness et al. 2016). However, age range in the cohort was 40 to 82 years and 11,610 participants were more than 70 years old. Targeted pharmacological intervention in a middle-aged high-risk cohort may have a beneficial effect on incidence of dementia.

Wilson and Jungner highlighted the potential for recommending intervention to falsely positive participants i.e. those who are not truly at high-risk of developing the disease (Wilson & Jungner 1968). There are benefits and risks associated with any intervention. However, lifestyle modification (a low risk intervention) and existing treatments to lower cardiovascular risk factors are known to provide greater benefit than harm for patients with high QRISK3 scores (NICE 2016). As there is overlap between the components of QRISK3 and CAIDE, patients with high QRISK3 scores are likely to have high CAIDE Dementia Risk Scores. There should be strong evidence to show that interventions recommended following risk assessment achieve a significant risk reduction, but at all events, adjusting the same cardiovascular risk factors should reduce patients' risk of stroke and myocardial infarction.

RECOMMENDATIONS FOR CLINICAL PRACTICE

Wilson and Jungner emphasised that "Facilities for diagnosis and treatment should be available". If validated in the UK, the infrastructure to support such a programme is almost already in place. Cardiovascular risk factors are routinely assessed in primary care and lifestyle modification programmes such as smoking cessation services and cardiac rehabilitation are available. We would be able to offer information and intervention to high-risk patients with the only additional cost being the increased access to those identified as high risk. NICE guidelines for completing the QRISK3 assessment indicate appropriate patient populations and how to navigate disclosure of results (NICE 2016). Clinicians are guided on how to engage in a joint decision making process with patients. Similar guidance should be available should a dementia risk assessment be introduced. Secondly, investigation is needed to determine whether informing patients of their risk of dementia can be ethically justified. Certainly, given that the patients would not be suffering from Dementia when assessed, there must be consideration given to keeping Dementia Risk scores private, and to proper confidentiality in record keeping (Arribas-Ayllon 2011). If the evidence continues to show that reduction of cardiovascular risk in individuals at high risk of dementia has a beneficial effect on long-term cognitive function, it would be a strong indication for inclusion of individuals at high risk of dementia in such programmes.

CONCLUSION

Dementia certainly fulfils the criteria of being an "important health problem", but current knowledge cannot support a conventional screening programme. Rather than testing a population for signs of early dementia or AD, we propose a dementia risk assessment similar to the existing cardiovascular risk assessment in the UK. At present, an appropriate population is informed of their risk of cardiovascular disease using QRISK3 (Hippisley-Cox 2007). Patients then have the choice of starting an evidence-based therapy to reduce their cardiovascular risk, modify their lifestyle, or do nothing. If future research supports lifestyle modification as an effective means of reducing risk of dementia, we could offer the same in the context of future dementia – assessing patients' risk of dementia using the CAIDE Dementia Risk Score and offering cardiovascular rehabilitation to reduce risk. However, further evaluation needs to be made as to the degree to which targeting cardiovascular risk factors actually reduces the risk of dementia. If we can reliably inform patients of their risk of dementia due to modifiable risk factors that are already routinely tested, and educate them on lifestyle changes that will reduce risk of cognitive decline, it would empower patients to make informed decisions to change their lifestyle to reduce their risk of dementia. Until a sensitive and specific test for early dementia or AD becomes available, we look forward to further evaluation of whether such an assessment will reduce the onset of dementia in our patients.

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Anna McKeever - application of cardiovascular risk assessment to screening for dementia.

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