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Predicting cognitive decline: a dementia risk score vs. the Framingham vascular risk scores

Running title: risk scores for cognitive decline in late middle age

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Author Contribution

Ms. Kaffashian developed the analytical plan, performed statistical analyses and drafted the manuscript

Ms. Dugravot provided ongoing methodologic support and assisted in interpretation of results

Dr. Elbaz provided methodologic expertise and edited the manuscript

Mr. Shipley provided statistical expertise

Dr Sabia edited the manuscript

Dr. Kivimaki edited the manuscript

Dr. Singh-Manoux secured funding, provided ongoing guidance, co-developed the analytical plan, and provided input on all versions of the manuscript

All authors edited and approved the final version of the manuscript

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Abstract

Objective: Our aim was to compare two Framingham vascular risk scores with a dementia risk score in relation to 10-year cognitive decline in late middle age.

Methods: Participants were men and women with mean age 55.6 years at baseline, from the Whitehall II study, a longitudinal British cohort study. We compared the Framingham General Cardiovascular Risk Score and the Framingham Stroke Risk Score with the CAIDE Dementia Risk Score that uses risk factors in midlife to estimate risk of late-life dementia. Cognitive tests included were reasoning, memory, verbal fluency, vocabulary and global cognition, assessed three times over ten years.

Results: While higher cardiovascular risk and higher stroke risk were associated with cognitive decline in all tests except memory, higher dementia risk was associated with greater decline in reasoning, vocabulary and global cognitive scores. Compared with the dementia risk score, cardiovascular and stroke risk scores showed slightly stronger associations with 10-year cognitive decline; these differences were statistically significant for semantic fluency and global cognitive scores. For example cardiovascular risk was associated with -0.06 SD (95% CI= -0.08, -0.05) decline in the global cognitive scores over 10 years while dementia risk was associated with -0.03 SD (95% CI= -0.04, -0.01) decline (difference in β coefficients =0.03; bootstrapped 95 % CI = 0.01, 0.05).

Conclusions: The CAIDE dementia and Framingham risk score predict cognitive decline in late midlife but the Framingham risk scores may have an advantage over the dementia risk score for use in primary prevention both for assessment of cognitive decline and targeting of modifiable risk factors.

Along with attempts to identify risk factors for dementia there is increasing interest in studying predictors of cognitive decline as it is now widely accepted that dementia has a long preclinical phase. Vascular risk factors and disease are hypothesized to be the key risk factors for dementia and adverse cognitive outcomes.¹⁻⁵ Mid- rather than late-life vascular risk is seen to be important for late life cognitive impairment and dementia.^{2, 5-9} Moreover, individuals may be at higher risk of cognitive impairment from accumulation of risk with the clustering of risk factors being associated with the risk of dementia in a cumulative manner.^{7, 10}

Recognizing the role of multiple risk factors, a number of mostly cross sectional and prospective studies have examined the utility of risk scores to assess risk of cognitive impairment and dementia.¹¹⁻¹⁸ The Framingham cardiovascular risk algorithms, in particular the Framingham Stroke Risk Profile (FSRP), initially developed to predict cerebrovascular disease, have been shown to be associated with brain pathology and cognitive dysfunction.^{11, 13, 14, 16, 17} A dementia risk score based on the CAIDE study that uses midlife risk factors for prediction of late life dementia has recently been proposed.¹⁵ However, whether it predicts cognitive decline better than the Framingham risk scores remains unknown. To our knowledge, there has been no attempt so far to compare risk scores in predicting cognitive decline in midlife. The objective of this study is to compare two well known Framingham risk scores, the Framingham stroke and general cardiovascular risk scores with the CAIDE dementia risk score in relation to cognitive decline over 10 years.

METHODS

Study population. Data were drawn from the Whitehall II study, an ongoing prospective cohort study established in 1985 on 6895 men and 3413 women, aged 35-55 years.¹⁹ The study design consists of a self administered questionnaire approximately every 2.5 years and a clinical examination every 5 years. Cognitive tests were introduced at phase 5 (1997/99) and repeated at

phase 7 (2002/04) and phase 9 (2007/09). Phase 5 constitutes baseline of the present study, concurrent with the first cognitive measure.

Standard protocol approvals, registrations, and patient consents. All participants provided written informed consent. Ethical approval for the Whitehall II study was obtained from the University College London Medical School committee.

Risk Scores

Framingham risk scores. The Framingham general cardiovascular disease risk profile and the Framingham stroke risk profile are multivariable risk factor algorithms that provide a sex-specific absolute risk of cardiovascular events. The Framingham risk scores have been shown to be valid measures of cardiovascular risk in the Whitehall II study population and strongly predict incidence of cardiovascular events.²⁰

The Framingham general cardiovascular disease risk score includes age, sex, systolic blood pressure, treatment for hypertension, high density lipoprotein (HDL) cholesterol, total cholesterol, smoking, and diabetes. The Framingham stroke risk score incorporates age, systolic blood pressure, treatment for hypertension, diabetes, smoking, prior cardiovascular disease (myocardial infarction, angina pectoris, coronary insufficiency, intermittent claudication or congestive heart failure), atrial fibrillation, and left ventricular hypertrophy .

Dementia risk score. The CAIDE dementia risk score was developed to predict late-life dementia based on midlife risk factors. Its components are age, education, sex, systolic blood pressure, body mass index, total cholesterol, physical activity, and *APOE* $\epsilon 4$ genotype.²¹ There are two versions of the dementia risk score, the difference being the inclusion of *APOE* in one version.²¹ In this study both versions of this dementia risk score were examined.

We used standard operating protocols to measure risk factors for the risk scores (see supplementary online material). Components for the three risk scores were drawn from

questionnaire and clinical examination data at phase 5 (1997/99); risk scores were calculated according to the original algorithms and scoring methods proposed by the authors of these risk scores.²¹⁻²⁴

Cognitive function

Cognitive function was assessed three times over 10 years. The cognitive test battery consisted of 5 standard cognitive tasks:

The Alice Heim 4-I (AH4-I) tests inductive *reasoning* measuring the ability to identify patterns and infer principles and rules.²⁵ It is composed of a series of 65 verbal and mathematical reasoning items of increasing difficulty. Participants had 10 minutes to complete this test.

Short-term verbal memory was assessed with a 20-word free recall test. Participants were presented with a list of 20 one or two syllable words at two second intervals and were asked to recall in writing as many of the words in any order. They had two minutes to do this test.

Two measures of verbal fluency were used: phonemic and semantic. Phonemic fluency was assessed via “S” words and semantic fluency via “animal” words.²⁶ Participants were asked to recall in writing as many words beginning with “S” and as many animal names as they could. One minute was allowed for each test.

Vocabulary was assessed using the *Mill Hill Vocabulary test* in its multiple-choice format, consisting of a list of 33 stimulus words ordered by increasing difficulty and six response choices.²⁷

A global cognitive score was created using all five tests described above by first standardizing the raw scores on each test to z-scores (mean=0; standard deviation (SD) =1) using the baseline mean and standard deviation values in the entire cohort at baseline for each test. Z-

scores were then averaged to yield the global cognitive score. To allow comparability across the tests, standardized score were used in the analysis.

Statistical analysis

The analyses involve two analytic samples. The first concerns the comparison of Framingham cardiovascular risk score with the dementia risk score and is based on participants free of cardiovascular disease (CHD or stroke) at baseline, with data on all components of risk scores. The second concerns the comparison of the Framingham stroke risk score with the dementia risk score based on individuals without a history of stroke or TIA who had data on all components of the risk scores.

Using linear mixed effects models we examined longitudinal associations of the risk scores with cognitive change over 10 years. Mixed effects models take into account intra-individual correlation inherent in repeated measures and have the advantage of using all available data over the 10-year follow-up period. The models included terms for risk (three sets of analyses for cardiovascular, stroke, and dementia risk score), time, and an interaction term between risk and time. Both the slope and intercept were fitted as random effects, allowing them to vary between individuals. Risk scores were modeled in two forms: in continuous form they were standardized after natural logarithmic (\log_e) transformation to correct the skewed distributions. In categorical form, three groups with comparable numbers were constructed with categories taken to represent low, intermediate and high risk for cardiovascular (<7 , 7 to <13 , and ≥ 13), stroke (<4 , 4 to <6 , and ≥ 6), and dementia (<7 , 7 to 8, and ≥ 9) risk scores. These risk groups are based on the risk distributions in our study samples. We compared the Framingham cardiovascular and stroke risk scores with the dementia risk score using the beta estimates associated with each pair of standardized risk scores by subtracting $\beta_{\text{Framingham CVD/stroke}}$ from $\beta_{\text{CAIDE dementia}}$. To test

whether this difference was statistically significant, a 95% confidence interval around the difference was calculated using a bootstrapping technique with 2000 resamplings.

Although our focus was on risk scores as measures of aggregate risk, in subsidiary analyses we examined the associations of individual components to determine whether the associations with 10-year cognitive change were driven by a few risk factors. Additionally, we examined whether the association between the risk score and 10-year cognitive change, remained after adjusting separately for each component of the risk score. Although the beta coefficient in this case would not be meaningful, the corresponding p-values can provide an indication of whether the associations may be attributable to a single risk factor. Analyses were performed using SAS (SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 7830 (75.9%) of the original 10308 participants of the Whitehall II study participated in phase 5 (1997/99) when cognitive tests were introduced to the study. Comparison of the Framingham cardiovascular score and CAIDE dementia risk scores was based on 4374 participants (3162 men, 1212 women); comparison of Framingham stroke risk score and CAIDE dementia risk score involved 5157 individuals (3651 men, 1506 women) (Table 1). Mean dementia risk was 6.8 (SD=2.3). Mean cardiovascular and stroke risk (%) were 12.4 (SD=8.8) and 4.5 (SD=3.6) respectively. The correlation between cardiovascular and dementia risk was 0.51, and between stroke and dementia risk it was 0.38 ($p<0.05$). Approximately 74% of participants had cognitive data at all three phases and 18% at two phases. Compared to individuals not included in these analyses, the analytic samples consisted of younger and more educated individuals. For example in the first comparison sample mean age was 55.2 years vs. 56.9 years at phase 5, $p<0.001$; 28% vs. 24.1% had a university degree, $p<0.001$.

Table 2 presents 10-year cognitive change associated with dementia and cardiovascular risk. Higher cardiovascular risk was associated with faster cognitive decline in global cognitive score and all tests except memory; dementia risk was associated with faster decline in reasoning, vocabulary and global cognitive score. For dementia risk, mean 10-year decline in global cognitive score was -0.35 SD (95% CI=-0.39, -0.32) in the high risk group compared to -0.31 SD (95% CI=-0.33, -0.28) in the low risk group. Similarly, those in the high cardiovascular risk group had greater 10-year decline in global cognition (-0.40 SD; 95% CI=-0.43, -0.37) compared to those in the low risk group (-0.26 SD; 95% CI=-0.28, -0.23). The cardiovascular risk score compared with dementia risk was associated with faster decline in semantic fluency (difference in β coefficients=0.05; 95 % CI = 0.02, 0.08) and global cognitive score (difference in β coefficients =0.03; 95 % CI = 0.01, 0.05).

Comparison of dementia and stroke risk with 10-year cognitive change revealed similar results (Table 3). Higher stroke risk was associated with cognitive decline in all tests except memory; higher dementia risk was associated with greater decline in reasoning, vocabulary and global cognitive score. For dementia risk, mean 10-year decline in global cognitive score was -0.27 SD (95% CI=-0.29,-0.24) in the high risk group compared to -0.22 SD (95% CI=-0.24, -0.21) in the low risk group. For stroke risk, the corresponding high risk group had greater mean 10-year decline in global cognitive score (-0.31 SD; 95% CI=-0.34, -0.29) compared to the low risk group (-0.21 SD; 95% CI=-0.23, -0.19). There were slightly stronger associations between stroke risk compared to dementia risk with decline in semantic fluency (difference in β coefficients=0.04; 95 % CI = 0.02, 0.06) and global cognitive scores (difference in β coefficients=0.02; 95 % CI = 0.01, 0.04). Similar associations were observed using model 2 of the CAIDE dementia risk score that incorporates *APOE* genotype (see web tables e-1 to e-3).

Our subsidiary analyses revealed multiple components of the risk scores to be associated independently with 10-year cognitive decline. These included diabetes, total cholesterol, left ventricular hypertrophy, and *APOE* $\epsilon 4$. (Web tables e-4 to e-7). In addition, all associations between risk measures and 10-year decline in global cognitive scores remained after adjustment for each risk score component, suggesting that multiple components of the risk scores were involved in these associations.

DISCUSSION

In this longitudinal study we found all three risk scores examined to be associated with 10-year decline in multiple cognitive tests. However, cardiovascular and stroke risk displayed stronger associations with cognitive decline than dementia risk. Both cardiovascular and stroke risk were associated with decline in all cognitive tests except memory; dementia risk was not associated with decline in memory and phonemic and semantic fluency.

A notable strength of this study is its longitudinal design with repeated cognitive measurements over a 10-year follow-up period as well as assessment of multiple cognitive domains. In this comparative analysis, we could not test the relative discrimination and calibration of the risk scores since the outcome did not consist of a categorical event. However, we adopted an alternative approach to compare associations of the risk scores with 10-year cognitive decline using bootstrapped confidence intervals.

Limitations of our study include the occupational nature of the cohort of office based employees that may not be entirely representative of the general population. In addition, since our analytic samples consisted of participants with a more favorable demographic and risk profile, reported associations between risk scores and 10-year cognitive decline may

underestimate the strength of associations in the general population. However, this is unlikely to affect comparability of the risk scores.

The differences between the dementia and Framingham risk scores may be related to several factors. Since they were developed to predict different outcomes, differences in the development and validation processes of the two risk scores are of importance. The inclusion of education in the dementia risk score also differentiates this risk score from the two vascular risk scores. Education, a marker of cognitive reserve, is associated with cognitive performance and risk of dementia²⁸⁻³⁰ but not the rate of cognitive decline.^{31, 32} Indeed in our study, of all components of the dementia risk score, education had the strongest association with cognitive performance at baseline (results not reported) even though it was not associated with 10-year cognitive decline. The dementia risk score was developed to detect clinically diagnosable dementia and it is possible that the education component in the risk score has a major influence in driving the prediction of dementia. In contrast, the Framingham cardiovascular and stroke risk scores are composed mainly of vascular risk factors that may make them more sensitive at assessing sub-clinical cognitive decline.

Vascular risk factors in midlife have been consistently linked to structural brain aging, cerebral pathology such as brain atrophy and white matter abnormalities, as well as cognitive decline in processing speed and executive function.^{5, 16, 33-35} Our findings of an independent association of several components of the risk scores (diabetes, total cholesterol, left ventricular hypertrophy) with cognitive decline suggest a cumulative effect of these risk factors on cognition. Notably, diabetes which is a component of the two Framingham risk scores showed the strongest independent association with 10-year cognitive decline. Therefore inclusion of this and other important vascular risk factors in the Framingham risk scores also distinguishes these risk scores from the dementia risk score.

Moreover, vascular risk factors as scored by the Framingham risk algorithms represent a wider range of categories. For example systolic blood pressure has five categories in the Framingham cardiovascular risk score (<120, 120-129, 130-139, 140-159, \geq 160 mm Hg) but only two categories (\leq 140 and $>$ 140 mm Hg) in the dementia risk score. The wider range of risk factor categories in the Framingham risk scores better captures the continuous nature of risk, distinguishing moderately elevated levels of the risk factor as well as the higher risk imparted by multiple marginal risk factors, which is especially pertinent at younger ages when risk factor levels are generally lower.

The majority of dementia risk scores are for use in the elderly population, often require a clinical assessment, and most have low to moderate predictive validity.³⁶ The CAIDE dementia risk score addresses many constraints of previous dementia risk scores by including easily measurable risk factors at midlife. However, it is rarely used and has not been validated in other populations perhaps due to the dearth of studies on dementia that have also assessed midlife risk factors. In practice, integration of a dementia risk score especially in primary care settings may not be realistic or practical at present. First, although this dementia risk score is not intended to state whether or not an individual will be demented or non-demented in the future, the potential for individuals to perceive their dementia risk estimation as such still exists. Therefore, acceptability of dementia risk evaluation would expectedly be low due to the anxiety associated with cognitive impairment and dementia. Furthermore, in an already overtaxed general practice setting, it would be unrealistic to expect clinicians to add yet another screening tool to their practice and patient care.

The Framingham heart study has devised many risk assessment tools with good to excellent performance in relation to cardiovascular outcomes. Subsequently, great effort has been invested, both to improve these risk scores and to validate them in diverse populations, some very

different from the Framingham population, indicating universality in the assessment of cardiovascular risk across nations.³⁷ Framingham risk scores have been used in clinical practice guidelines and are amongst the most recognized and utilized risk scores both in research and primary care where various office-based and online risk calculators are widely accessible.

There are currently no effective treatments for dementia and population screening is not advocated because in the absence of disease modifying treatments there is no evidence that benefit of screening outweighs potential harm. However, with a shift from dementia as an outcome, to earlier stages of cognitive decline, there is great potential to affect cognitive outcomes and change the course of cognitive decline preceding dementia, with early targeting of modifiable vascular risk factors.^{38, 39} Although both the dementia and Framingham risk scores were developed with the aim of addressing multiple risk factors simultaneously, and providing an estimate of risk that is easy to understand, Framingham vascular risk scores (and other vascular risk scores used in primary care) provide a dual advantage over a dementia risk score both in terms of feasibility of use and potential for real benefit from vascular risk factor modification. At present patients are told their cardiovascular risk predisposes them to heart disease and stroke; in future they could also be told that they are at higher risk of cognitive decline.⁴⁰

While future research on cognitive impairment and dementia will likely identify additional risk factors and biomarkers to improve prediction models for cognitive impairment and dementia, there is compelling evidence at present for the role of vascular risk factors in affecting cognitive aging trajectories starting in midlife. Our study advocates the use of cardiovascular risk scores in primary care adding incentive for early identification and treatment of vascular risk factors.

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REFERENCES

- (1) Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology*. 2005;64:277-81.
- (2) Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szklo M, McGovern P, Folsom AR. Cardiovascular risk factors and cognitive decline in middle-aged adults. *Neurology*. 2001;56:42-8.
- (3) Knopman DS, Mosley TH, Catellier DJ, Sharrett AR. Cardiovascular risk factors and cerebral atrophy in a middle-aged cohort. *Neurology*. 2005;65:876-81.
- (4) Nash DT, Fillit H. Cardiovascular disease risk factors and cognitive impairment. *Am J Cardiol*. 2006;97:1262-5.
- (5) Debette S, Seshadri S, Beiser A, Au R, Himali JJ, Palumbo C, Wolf PA, DeCarli C. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. *Neurology*. 2011;77:461-8.
- (6) Kivipelto M, Helkala EL, Hanninen T, Laakso MP, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A. Midlife vascular risk factors and late-life mild cognitive impairment: A population-based study. *Neurology*. 2001;56:1683-9.
- (7) Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kareholt I, Winblad B, Helkala EL, Tuomilehto J, Soininen H, Nissinen A. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Arch Neurol*. 2005;62:1556-60.
- (8) Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik RJ. The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. *JAMA*. 1995;274:1846-51.
- (9) Xu WL, Atti AR, Gatz M, Pedersen NL, Johansson B, Fratiglioni L. Midlife overweight and obesity increase late-life dementia risk: a population-based twin study. *Neurology*. 2011;76:1568-74.
- (10) Luchsinger JA, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R. Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology*. 2005;65:545-51.
- (11) Brady CB, Spiro A, III, McGlinchey-Berroth R, Milberg W, Gaziano JM. Stroke risk predicts verbal fluency decline in healthy older men: evidence from the normative aging study. *J Gerontol B Psychol Sci Soc Sci*. 2001;56:340-6.
- (12) Brandt J, Rogerson M. Preliminary findings from an internet-based dementia risk assessment. *Alzheimers Dement*. 2011;7:e94-100.
- (13) Elias MF, Sullivan LM, D'Agostino RB, Elias PK, Beiser A, Au R, Seshadri S, DeCarli C, Wolf PA. Framingham stroke risk profile and lowered cognitive performance. *Stroke*. 2004;35:404-9.

- (14) Llewellyn DJ, Lang IA, Xie J, Huppert FA, Melzer D, Langa KM. Framingham Stroke Risk Profile and poor cognitive function: a population-based study. *BMC Neurol.* 2008;8:12.
- (15) Reijmer YD, van den Berg E, van SS, Dekker JM, Nijpels G, Stehouwer CD, Kappelle JL, Biessels GJ. Dementia risk score predicts cognitive impairment after a period of 15 years in a nondemented population. *Dement Geriatr Cogn Disord.* 2011;31:152-7.
- (16) Seshadri S, Wolf PA, Beiser A, Elias MF, Au R, Kase CS, D'Agostino RB, DeCarli C. Stroke risk profile, brain volume, and cognitive function: the Framingham Offspring Study. *Neurology.* 2004;63:1591-9.
- (17) Unverzagt FW, McClure LA, Wadley VG, Jenny NS, Go RC, Cushman M, Kissela BM, Kelley BJ, Kennedy R, Moy CS, Howard V, Howard G. Vascular risk factors and cognitive impairment in a stroke-free cohort. *Neurology.* 2011;77:1729-36.
- (18) Kaffashian S, Dugravot A, Nabi H, Batty GD, Brunner E, Kivimaki M, Singh-Manoux A. Predictive utility of the Framingham general cardiovascular disease risk profile for cognitive function: evidence from the Whitehall II study. *Eur Heart J.* 2011.
- (19) Marmot M, Brunner E. Cohort Profile: the Whitehall II study. *Int J Epidemiol.* 2005;34:251-6.
- (20) Kivimaki M, Shipley MJ, Allan CL, Sexton CE, Jokela M, Virtanen M, Tiemeier H, Ebmeier KP, Singh-Manoux A. Vascular Risk Status as a Predictor of Later-Life Depressive Symptoms: A Cohort Study. *Biol Psychiatry.* 2012.
- (21) Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *Lancet Neurol.* 2006;5:735-41.
- (22) D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study. *Stroke.* 1994;25:40-3.
- (23) D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation.* 2008;117:743-53.
- (24) Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke.* 1991;22:312-8.
- (25) Heim AW. *AH4: Group Test of General Intelligence.* Windsor United Kingdom: NFER-Nelson Publishing Company, Limited; 1970.
- (26) Borkowski JG, Benton AL, Spreen O. Word fluency and brain damage. *Neuropsychologica.* 1967;5:135-40.

- (27) Raven JC. *Guide to using the Mill Hill vocabulary test with progressive matrices*. London, UK: HK Lewis; 1965.
- (28) Evans DA, Hebert LE, Beckett LA, Scherr PA, Albert MS, Chown MJ, Pilgrim DM, Taylor JO. Education and other measures of socioeconomic status and risk of incident Alzheimer disease in a defined population of older persons. *Arch Neurol*. 1997;54:1399-405.
- (29) Ngandu T, von SE, Helkala EL, Winblad B, Nissinen A, Tuomilehto J, Soininen H, Kivipelto M. Education and dementia: what lies behind the association? *Neurology*. 2007;69:1442-50.
- (30) Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R. Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA*. 1994;271:1004-10.
- (31) Karlamangla AS, Miller-Martinez D, Aneshensel CS, Seeman TE, Wight RG, Chodosh J. Trajectories of cognitive function in late life in the United States: demographic and socioeconomic predictors. *Am J Epidemiol*. 2009;170:331-42.
- (32) Singh-Manoux A, Marmot MG, Glymour M, Sabia S, Kivimaki M, Dugravot A. Does cognitive reserve shape cognitive decline? *Ann Neurol*. 2011;70:296-304.
- (33) DeBette S, Beiser A, DeCarli C, Au R, Himali JJ, Kelly-Hayes M, Romero JR, Kase CS, Wolf PA, Seshadri S. Association of MRI markers of vascular brain injury with incident stroke, mild cognitive impairment, dementia, and mortality: the Framingham Offspring Study. *Stroke*. 2010;41:600-6.
- (34) Gorelick PB, Scuteri A, Black SE, DeCarli C, Greenberg SM, Iadecola C, Launer LJ, Laurent S, Lopez OL, Nyenhuis D, Petersen RC, Schneider JA, Tzourio C, Arnett DK, Bennett DA, Chui HC, Higashida RT, Lindquist R, Nilsson PM, Roman GC, Sellke FW, Seshadri S. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2011;42:2672-713.
- (35) Knopman DS, Mosley TH, Catellier DJ, Coker LH. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: the ARIC MRI Study. *Alzheimers Dement*. 2009;5:207-14.
- (36) Stephan BC, Kurth T, Matthews FE, Brayne C, Dufouil C. Dementia risk prediction in the population: are screening models accurate? *Nat Rev Neurol*. 2010;6:318-26.
- (37) Khalili D, Hadaegh F, Soori H, Steyerberg EW, Bozorgmanesh M, Azizi F. Clinical usefulness of the framingham cardiovascular risk profile beyond its statistical performance: the tehran lipid and glucose study. *Am J Epidemiol*. 2012;176:177-86.
- (38) Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol*. 2011;10:819-28.

- (39) de la Torre JC. Alzheimer's disease is incurable but preventable. *J Alzheimers Dis.* 2010;20:861-70.
- (40) Diener HC. Prevention of dementia should start 20 years before symptoms become apparent. *Eur Heart J.* 2011;32:2228-30.

Table 1. Characteristics of the study sample at baseline (phase 5)

Risk score components	Comparison 1 Framingham CVD vs. dementia risk score N=4374	Comparison 2 Framingham stroke vs. dementia risk score N=5157
<i>CAIDE dementia risk score</i>		
Age, y, mean (SD)	55.2 (5.1)	55.6 (5.9)
Men	72.3	70.8
Education <10 years	12.4	11.4
Systolic blood pressure > 140 mmHg	14.9	14.6
BMI >30 kg/m ²	12.8	13.8
Total cholesterol > 6.5 mmol/L	25.9	26.4
Physical activity, inactive	56.9	58.7
<i>Framingham risk scores</i>		
	<i>CVD</i>	<i>Stroke</i>
Age, y, mean (SD)	55.2 (5.1)	55.6 (5.9)
Men	72.3	70.8
Systolic blood pressure (mm Hg), mean (SD)	122.5 (15.9)	122.9 (16.4)
Antihypertensive medication use	11.8	12.7
Diabetes	4.0	4.1
Current smoker	10.1	9.8
Total cholesterol (mg/dL), mean (SD)	229.7 (40.4)	-
HDL cholesterol (mg/dL), mean (SD)	56.7 (15.3)	-
History of heart disease	-	5.6
Atrial fibrillation	-	1.8
Left ventricular hypertrophy	-	6.0

Values are percentages unless otherwise indicated. CVD= cardiovascular disease

Table 2. Associations of dementia and CVD risk (1997/99) with 10-year cognitive change (1997/99, 2002/04, 2007/09), N=4374

Cognitive test	Risk groups			<i>p trend</i>	Standardized risk	
	Low	Intermediate	High		β (95% CI)	Δ (95% CI) ^a
	10-year cognitive change (95% CI)					
Reasoning						
Dementia risk	-0.28 (-0.31, -0.26)	-0.35 (-0.38, -0.32)	-0.36 (-0.39, -0.33)	<0.001	-0.05 (-0.06, -0.03) ^{***}	
CVD risk	-0.26 (-0.29, -0.23)	-0.31 (-0.34, -0.28)	-0.41 (-0.44, -0.38)	<0.001	-0.06 (-0.08, -0.04) ^{***}	0.01 (-0.004, 0.03) ns
Memory						
Dementia risk	-0.24 (-0.28, -0.19)	-0.27 (-0.33, -0.22)	-0.26 (-0.32, -0.19)	0.46	-0.01 (-0.04, 0.01)	
CVD risk	-0.20 (-0.25, -0.15)	-0.29 (-0.34, -0.24)	-0.27 (-0.32, -0.21)	0.09	-0.03 (-0.06, 0.00)	0.02 (-0.02, 0.06) ns
Phonemic fluency						
Dementia risk	-0.34 (-0.38, -0.31)	-0.37 (-0.42, -0.33)	-0.36 (-0.41, -0.31)	0.42	-0.01 (-0.04, 0.01)	
CVD risk	-0.31 (-0.35, -0.27)	-0.36 (-0.40, -0.32)	-0.39 (-0.44, -0.35)	0.01	-0.03 (-0.06, -0.01) ^{**}	0.02 (-0.005, 0.05) ns
Semantic fluency						
Dementia risk	-0.29 (-0.33, -0.26)	-0.32 (-0.37, -0.28)	-0.29 (-0.35, -0.24)	0.85	0.001 (-0.02, 0.02)	
CVD risk	-0.31 (-0.35, -0.27)	-0.36 (-0.40, -0.32)	-0.39 (-0.44, -0.35)	<0.001	-0.05 (-0.07, -0.02) ^{***}	0.05 (0.02, 0.08)
Vocabulary						
Dementia risk	0.05 (0.03, 0.07)	0.004 (-0.02, 0.03)	-0.02 (-0.05, 0.01)	<0.001	-0.02 (-0.04, -0.01) ^{**}	
CVD risk	0.05 (0.03, 0.08)	0.03 (0.002, 0.05)	-0.02 (-0.05, 0.001)	<0.0001	-0.04 (-0.05, -0.03) ^{***}	0.02 (-0.004, 0.04) ns
Global cognition						
Dementia risk	-0.31 (-0.33, -0.28)	-0.36 (-0.39, -0.34)	-0.35 (-0.39, -0.32)	0.01	-0.03 (-0.04, -0.01) ^{**}	
CVD risk	-0.26 (-0.28, -0.23)	-0.34 (-0.37, -0.32)	-0.40 (-0.43, -0.37)	<0.001	-0.06 (-0.08, -0.05) ^{***}	0.03 (0.01, 0.05)

ns: not significantly different at $p < 0.05$.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

^a Difference in β coefficients: $\beta_{\text{Dementia risk}} - \beta_{\text{CVD risk}}$; bootstrapped 95% confidence intervals.

Table 3. Associations of dementia and stroke risk (1997/99) with 10-year cognitive change (1997/99, 2002/04, 2007/09), N=5157

Cognitive test	Risk groups			<i>p trend</i>	Standardized risk	
	Low	Intermediate	High		β (95% CI)	Δ (95% CI) ^a
	10-year cognitive change (95% CI)					
Reasoning						
Dementia risk	-0.28 (-0.30, -0.26)	-0.35 (-0.38, -0.32)	-0.37 (-0.40, -0.33)	<0.001	-0.05 (-0.06, -0.04) ^{***}	
Stroke risk	-0.27 (-0.29, -0.24)	-0.34 (-0.36, -0.31)	-0.42 (-0.45, -0.38)	0.001	-0.05 (-0.06, -0.03) ^{***}	0.00 (-0.02, 0.02) ns
Memory						
Dementia risk	-0.24 (-0.28, -0.20)	-0.27 (-0.32, -0.22)	-0.27 (-0.33, -0.20)	0.33	-0.02 (-0.04, 0.01)	
Stroke risk	-0.24 (-0.28, -0.20)	-0.27 (-0.31, -0.22)	-0.25 (-0.32, -0.19)	0.56	-0.03 (-0.06, 0.00)	0.01 (-0.01, 0.03) ns
Phonemic fluency						
Dementia risk	-0.34 (-0.37, -0.30)	-0.37 (-0.41, -0.33)	-0.37 (-0.41, -0.31)	0.27	-0.02 (-0.04, 0.01)	
Stroke risk	-0.32 (-0.36, -0.29)	-0.36 (-0.39, -0.32)	-0.42 (-0.47, -0.37)	0.003	-0.03 (-0.06, -0.01) ^{**}	0.01 (-0.01, 0.04) ns
Semantic fluency						
Dementia risk	-0.29 (-0.32, -0.26)	-0.34 (-0.38, -0.30)	-0.30 (-0.35, -0.26)	0.43	-0.01 (-0.03, 0.01)	
Stroke risk	-0.26 (-0.29, -0.22)	-0.33 (-0.37, -0.29)	-0.40 (-0.44, -0.34)	<0.001	-0.05 (-0.08, -0.03) ^{***}	0.04 (0.02, 0.06)
Vocabulary						
Dementia risk	0.05 (0.03, 0.07)	0.006 (-0.02, 0.03)	-0.03 (-0.06, -0.002)	<0.001	-0.03 (-0.04, -0.01) ^{***}	
Stroke risk	0.04 (0.03, 0.07)	0.02 (-0.001, 0.04)	-0.05 (-0.08, -0.02)	<0.001	-0.04 (-0.05, -0.02) ^{***}	0.01 (-0.004, 0.03) ns
Global cognition						
Dementia risk	-0.22 (-0.24, -0.21)	-0.27 (-0.29, -0.25)	-0.27 (-0.29, -0.24)	<0.001	-0.02 (-0.03, -0.01) ^{***}	
Stroke risk	-0.21 (-0.23, -0.19)	-0.26 (-0.28, -0.24)	-0.31 (-0.34, -0.29)	<0.001	-0.04 (-0.05, -0.03) ^{***}	0.02 (0.01, 0.04)

ns: not significantly different at $p < 0.05$.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

^a Difference in β coefficients: $\beta_{\text{Dementia risk}} - \beta_{\text{Stroke risk}}$; bootstrapped 95% confidence intervals.