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Does the Framingham cardiovascular disease risk score also have predictive utility for dementia death?

Does the Framingham cardiovascular disease risk score also have predictive utility for

dementia death? An individual participant meta-analysis of 11,887 men and women

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 ABSTRACT

Objective: Individual cardiovascular disease (CVD) risk factors are associated with dementia. For the first time, we investigated whether the Framingham CVD risk score – which comprises these multiple risk factors – was also associated with future dementia risk.

Methods: Individual participant meta-analysis of two large, general population cohort studies (N=11,887). For the purposes of comparison of the dementia results, we also examined the association between the Framingham CVD risk score and CVD-related death.

Results: Framingham CVD risk score was associated with dementia death (HR per 10% increased risk, 95%CI: 4.00, 2.44-6.56). Adjusting for age eliminated this association (1.04, 0.53-2.01); similarly, age explained 88% of the ability of the Framingham CVD risk score to predict CVD death.

Conclusions: The Framingham CVD risk score was no more strongly associated with future dementia than age. It therefore offers no added value in predicting dementia.

Introduction

Cardiovascular disease (CVD) and dementia represent a major disease burden worldwide. These conditions share a series of risk factors (hypertension, smoking, obesity, diabetes, and dyslipidaemia).[1] CVD itself, particularly multiple strokes, also appears to elevate dementia risk.[2] The Framingham Cardiovascular Disease Risk Score,[3] which comprises these risk factors, is a standard tool for assessing future risk of CVD in people who are apparently healthy. This raises the possibility that this risk score might also be useful in identifying people at increased risk of developing dementia. Since the Framingham CVD risk score is already commonly used in clinical practice, the implications of such an observation would be considerable.

While the Framingham CVD risk score has been shown to predict cognitive decline,[4] an aspect of dementia, to the best of our knowledge, there are no prospective studies examining the links between the Framingham CVD risk score and future dementia.[5] Accordingly, we meta-analysed individual-participant data from two large English population-based cohort studies.

Methods

Participants were taken from the Health Survey for England,[6] a series of annual, on-going, independent, general population-based cross-sectional studies that are representative of household-dwelling individuals in England in most years. Participants gave informed consent and ethical approval was obtained from the London Research Ethics Council.

The scientific focus of each survey changes year to year; risk factor data for calculating the Framingham CVD risk score[3] (age, sex, HDL-cholesterol, total cholesterol, systolic blood pressure, smoking, and diabetes) were available for surveys conducted in 1998 and 2003. Mortality follow-up of study members in these studies continued until death or 15th February

2008, whichever came first. Dementia- and CVD-related deaths[3] were identified from any mention on death certificates of the following codes: dementia – ICD-9 codes 290.0-290.4 (senile dementia, uncomplicated; presenile dementia; senile dementia with delusional or depressive features; senile dementia with delirium; or vascular dementia), 294.9 (unspecified persistent mental disorders due to conditions classified elsewhere), 331.0-331.2 (Alzheimer's disease; frontotemporal dementia; or senile degeneration of the brain), and 331.9 (cerebral degeneration, unspecified) and ICD-10 codes F01, F03, F09, G30, and G31; CVD – ICD-9 codes 410-414 (ischaemic heart disease), 428 (heart failure), 430-438 (cerebrovascular disease), 440 (atherosclerosis), and 443-445 (other peripheral vascular disease; arterial embolism and thrombosis; or atheroembolism) and ICD-10 codes I20-I25, I50, I60-I69, I70, I73, and I74.

Using similar methodology to previous studies,[7] we used Cox proportional hazards models to compute study-specific effect estimates with accompanying standard errors which we pooled in a random effects meta-analysis. We report unadjusted hazard ratios (HR) with accompanying 95% confidence intervals (CI) per 10% increase (disadvantage) in the Framingham CVD risk score in relation to dementia-related deaths following the convention in testing multifactorial predictive algorithms[8]. Models were also adjusted for age and sex. We also ran models examining the association between the Framingham CVD risk score and CVD-related death to compare the predictive utility of the score for dementia with its original purpose.

In addition, we conducted a number of supplementary analyses: including only individuals aged <75 years since the Framingham CVD risk score is recommended for use in this age-group; using the Framingham CVD risk score having substituted BMI for HDL- and total cholesterol;[3] and dropping any dementia-related deaths during the first two years of follow-up in order to assess reverse causality (49 dementia deaths). In a further sensitivity analysis, missing values for

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covariates were imputed with PASW statistics version 18.0 using five imputations. All other

statistical analyses were conducted using R version 2.15.0.

Results

From an initial sample of 21,945 participants, 1,997 did not consent to record linkage and 6,071

had missing data. Additionally, we excluded 1,990 with evidence of CVD at baseline. These

exclusions resulted in an analytic sample of 11,887 (mean[SD] age 54.0[13.2] years, range=35-95).

Individuals with missing data (N=6,056) were slightly older (55.2[SD=14.4] vs 54.0[13.2],

p<0.001) and somewhat more likely to be female (58.9% female vs 54.4%, p<0.001), the

statistically significant differences arising from a large sample size rather than any sizeable

absolute differences.

Of the 875 deaths during a mean (SD) follow up of 7.1 (2.6) years, 54 were dementia-related (13

Alzheimer disease, two vascular dementia, and 39 dementia sub-type not specified). The Figure

shows the relation of the Framingham CVD risk score with deaths from dementia and CVD.

Higher Framingham CVD risk score was associated with increased risk of dementia death: each

10% increase (disadvantage) was associated with a 4.00-fold (95%CI 2.44-6.56) increase in the

risk of dementia death (p_{trend}<0.001). Adjusting for sex increased the magnitude of the association

(HR 5.08; 3.50-7.37; p_{trend}<0.001). Age is part of the Framingham CVD risk score algorithm, but

because dementia is age-related (HR per year increase: 1.21; 1.17-1.24) we additionally controlled

for age in these analyses whereupon the association between the Framingham CVD risk score

and dementia was eliminated (age-adjusted HR 1.04; 0.53-2.01; p_{trend}=0.91).

Using CVD-related death as the outcome of interest also showed a substantial attenuation of the

relationship after age-adjustment although, unlike dementia, there was still evidence of increased

CVD risk. Thus, a higher Framingham CVD risk score was associated with 3.76-fold (95%CI 2.63-5.39; p_{trend}<0.001) increased risk of CVD death per 10% increase in Framingham CVD risk score before, and 1.34-fold (0.73-2.45; p_{trend}=0.34) risk after, age-adjustment.

None of the supplementary analyses, mentioned above, altered our conclusions. Restricting the models to individuals aged <75 years (N=10,828; 12 dementia deaths, 128 CVD deaths) gave an unadjusted HR for dementia death of 3.96 (95%CI 0.92-16.99, p_{trend}=0.064) and an age-adjusted HR of 0.96 (0.04-22.2, p_{trend}=0.98). The unadjusted HR for the association between the Framingham CVD risk score-BMI and dementia death (N=14,148; 53 dementia deaths) was 3.23 (95%CI 1.08-9.71; p_{trend}<0.001). Dropping any deaths during the first two years of follow-up (49 dementia deaths) resulted in an unadjusted HR for dementia death of 2.34 (95%CI 0.46-11.84; p_{trend}=0.30) and an age-adjusted HR of 0.37 (0.01-9.78; p_{trend}=0.55).

Accounting for missing data by multiple imputation did not appreciably change the results: association between the Framingham CVD risk score and dementia death, unadjusted HR 3.63 (95%CI 2.78-4.73; p_{trend}<0.001), age-adjusted HR 1.13 (0.83-1.53; p_{trend}=0.45); association between the Framingham CVD risk score and CVD death, unadjusted HR 3.47 (2.93-4.11; p_{trend}<0.001), age-adjusted HR 1.34 (1.05-1.71; p_{trend}=0.017).

Discussion

The aim of the present analyses was to examine whether the Framingham CVD risk score was useful in predicting future risk of dementia. In a large population sample of adults who were free from CVD at study induction, we found an association between elevated Framingham CVD risk score and an increased risk of dementia death that was greater in magnitude than the relationship between Framingham CVD risk score and CVD-related death. However, the Framingham CVD

risk score-dementia relation was lost when age was added to the multivariable model. While age also explained 88% of the ability of the Framingham CVD risk score to predict CVD it did not completely remove the association.

As described, there is evidence of an association between the Framingham CVD risk score and cognitive decline.[4] To our knowledge, this is the first large-scale prospective population-based study to examine the association between the Framingham CVD risk score and dementia, and certainly the first to use individual participant meta-analysis methodology.

Any mention of dementia on a death certificate resulted in a death being classified as dementia-related. This is appropriate as dementia may well not be the immediate cause of death but an important contributory factor. Classifying cause of death according to death certification is a common methodology in population-based studies. Under-reporting of dementia on death certificates seems to be improving—a recent memory clinic study found that 71.5% of 502 patients with probable Alzheimer disease had dementia correctly recorded on their death certificates.[9] Autopsy studies confirm that death certification of CVD is satisfactory for the purposes of epidemiological research.[10]

None of the additional analyses essentially altered the findings of the study. However, dropping dementia-related deaths in the first two years of follow up did reduce the magnitude of the association between the Framingham CVD risk score and dementia death suggesting that part of the observed association between the risk score and dementia may relate to participants suffering from undiagnosed subclinical CVD at baseline. Approximately a third of participants (33.8%) had data missing for one or more variable necessary for calculating the Framingham CVD risk

score. However, accounting for missing data by multiple imputation had little effect on the results and therefore the missing data are unlikely to have resulted in bias.

While cardiovascular disease risk factors have been linked to cognitive decline[4] and dementia risk,[1] these results suggest that, importantly, the Framingham CVD risk score was no more strongly associated with future dementia than age. It therefore offers no added value in predicting dementia. Therefore, though CVD risk factors may play a role in dementia aetiology, future research attention should also focus on non-CVD risk factors and risk markers for dementia, including changes in Aβ42 levels in cerebrospinal fluid,[11] metabolic alterations in PET scans,[12] and possibly also biomarkers related to immune function, endocytosis and amyloid-precursor proteins.[13-15]

Conflict of interest

The authors declare no conflict of interest

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Table 1. Characteristics of the 1998 and 2003 Health Surveys for England

	1998	2003	Total
N (complete data for all variables)	6656	5321	11887
Participants with missing data (%)	2721 (29.0)	3335 (38.9)	6056 (33.8)
Age (mean [SD])	54.0 (13.4)	54.0 (12.9)	54.0 (13.2)
range	35-95	35-94	35-95
Female (%)	53.9	55.1	54.4
Years of follow-up (mean [SD])	9.1 (1.6)	4.5 (0.5)	7.1 (2.6)
Number of deaths	713	162	875
Dementia deaths	50	4	54
Cardiovascular disease deaths	252	49	301
Ischaemic heart disease deaths	134	27	161
Cerebrovascular disease deaths	82	19	101

Figure 1. Association of Framingham CVD Risk Score with Dementia[1] and CVD[2] Death over a Mean 7.1-year Follow-up

Hazard ratios (95% confidence intervals) are per 10% increase (disadvantage) in the Framingham CVD risk score in men and women who were free from dementia and CVD at baseline in the 1998 and 2003 Health Surveys for England (N = 11,887).