Cognitive Aging : Role of Cardiovascular Disease Risk Factors

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Cognitive Aging: Role of Cardiovascular Disease Risk Factors

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SCIENTIFIC PRODUCTION

A. Publications (Appendix B)

Kaffashian S, Dugravot A, Nabi H, Batty GD, Brunner E, Kivimäki M, Singh-Manoux A. Predictive utility of the Framingham general cardiovascular disease risk profile for cognitive function: evidence from the Whitehall II study. *European Heart Journal* 2011;32 (18)

Kaffashian S, Dugravot A, Brunner E J, Kivimäki M, Sabia S, Ankri Joel, Kivimäki M, Singh-Manoux A. Midlife stroke risk and cognitive decline: A 10-year follow-up of the Whitehall II cohort study. *Alzheimer's & Dementia* 2012 [E-pub ahead of print]

Kaffashian S, Dugravot A, Elbaz E, Shipley M, Sabia S, Kivimäki M, Singh-Manoux A. Predicting cognitive decline; a dementia risk score vs. the Framingham vascular risk scores. *Neurology* [in press]

C. Oral and poster communications

1. Utilisation des scores de risque cardiovasculaire pour la prédiction du déclin cognitif. *Colloque CODDIM*. September 17, 2012. Paris.

2. Kaffashian S, Dugravot A, Elbaz E, Shipley M, Sabia S, Kivimäki M, Singh-Manoux A. Cardiovascular versus dementia risk scores for prediction of cognitive decline in midlife. *European Congress of Epidemiology*, September 5-8, 2012. Porto, Portugal.

3. Le rôle des facteurs de risques cardiovasculaire dans le vieillissement cognitif. *Colloque CODDIM*. October 20, 2011.Paris.

4. Kaffashian S, Dugravot A, Brunner E J, Kivimäki M, Sabia S, Ankri Joël, Kivimäki M, Singh-Manoux A. Ten-year stroke risk and cognitive decline in midlife. *World Congress of Epidemiology*. August 7-11, 2011. Edinburgh, Scotland.

5. Kaffashian S, Dugravot A, Nabi H, Batty GD, Brunner E, Kivimäki M, Singh-Manoux. Predictive utility of the Framingham General Cardiovascular Risk Profile for cognitive function. *American Academy of Neurology Annual Meeting*. April 9-16, 2011. Honolulu, Hawaii.

FRENCH SUMMARY OF THE THESIS

Contexte

La démence représente aujourd'hui un problème majeur de santé publique. L'espérance de vie continuant à augmenter, le nombre de personnes âgées qui développeront une démence est amené à augmenter rapidement dans les années à venir. De nombreuses études suggèrent l'existence d'une longue phase « préclinique » de la démence, durant laquelle des changements cognitifs et neuropathologiques subtils sont observés pendant plusieurs années avant même que des symptômes cognitifs et comportementaux se manifestent. Par conséquent, il est important d'étudier les déterminants du déclin cognitif à des âges précoces au cours du vieillissement.

De nombreuses études ont montré que les facteurs de risque et pathologies cardiovasculaires (par exemple, hypertension, hypercholestérolémie, diabète) sont associés au déclin cognitif. L'exposition au cours de la vie à des facteurs de risque cardiovasculaire est associée au vieillissement cardiaque et de la paroi artérielle qui sont à l'origine d'hypoperfusion, d'hypoxie et d'ischémie cérébrale dans des régions cérébrales vulnérables. L'hypoperfusion et l'hypoxie initient un déficit énergétique neuronoglial qui induirait la cascade physiopathologique conduisant aux lésions neurodégénératives.

De plus, c'est l'exposition à ces facteurs de risque au cours de la vie en particulier avant 65 ans qui contribue de manière plus importante au déclin cognitif. Par exemple, l'hypertension entre 40 et 60 ans semble liée aux capacités cognitives, tandis que cette association est affaiblie chez des sujets plus âgés. A ces résultats, s'ajoute un large consensus quant à la multiplicité des facteurs de risque cardiovasculaire et à leur agrégation qui pourrait être responsable d'une potentialisation de leurs effets délétères sur la fonction cognitive. Par exemple, chez les sujets de moins de 55 ans, l'accumulation des facteurs de risque cardiovasculaire, tels que l'obésité, l'hypertension et l'hypercholestérolémie, est associée à un risque augmenté de démence. Ainsi l'estimation du risque cardiovasculaire et des effets de ces facteurs sur la fonction cognitive nécessite une approche multifactorielle. Cette approche multifactorielle est régulièrement employée pour prédire les événements cardiovasculaires, tels que l'accident vasculaire cérébral (AVC) ou l'infarctus du myocarde, en utilisant des scores de risque comme les scores de risque de Framingham. Dans le contexte de la recherche sur le vieillissement cognitif, cette approche est relativement nouvelle.

Les objectifs de recherche

Ce travail de thèse s'intéresse à l'association entre les principaux facteurs de risque cardiovasculaire et le vieillissement cognitif au cours de la phase précoce du vieillissement. Il s'appuie sur trois aspects importants: la période d'exposition aux facteurs de risque cardiovasculaire (milieu de vie), le regroupement de ces facteurs, et l'association de ces facteurs de risque avec le vieillissement cognitif à partir d'une approche longitudinale utilisant des mesures répétées de la fonction cognitive sur une période de 10 ans.

L'objectif spécifique est d'examiner l'agrégation du risque cardiovasculaire avec un intérêt particulier pour les scores de risque cardiovasculaire. En effet, la relation entre les scores de risque cardiovasculaire et la fonction cognitive demeure peu étudiée. Par exemple, le score de risque cardiovasculaire global de Framingham est l'un des derniers scores développés dans l'étude de Framingham, mais son association avec les fonctions cognitives n'a jamais été examinée. De plus, le score de risque de démence CAIDE, proposé récemment et qui utilise des facteurs de risque mesurés a l'âge moyen de 50 ans pour prédire le risque de démence au cours des 20 années suivantes, reste lui aussi peu étudié par rapport au déclin cognitif avant la survenue de démence.

Les objectives spécifiques de cette thèse sont les suivants :

1. Etudier l'association entre le syndrome métabolique (au moins 3 des 5 critères suivants: obésité abdominale, taux de triglycérides élevé, taux du HDL cholestérol bas, hyperglycémie, hypertension) et la fonction cognitive (associations transversales) et le déclin cognitif sur 10 ans (associations longitudinales)

2. Etudier l'association de deux scores de risque de Framingham, le score de risque cardiovasculaire global (composantes: âge, sexe, tabagisme, diabète, tension artérielle systolique, cholestérol, HDL cholestérol) et le score de risque de Framingham pour l'AVC (composantes: âge, sexe, tabagisme, diabète, maladie cardiovasculaire, tension artérielle systolique, fibrillation atriale, hypertrophie ventriculaire gauche) avec la fonction cognitive et le déclin cognitif sur 10 ans. De plus, l'association avec chaque composante du score de risque est étudiée.

3. Comparer ces deux scores de risque cardiovasculaire avec le score de risque de démence CAIDE (composantes: âge, sexe, niveau d'études, tension artérielle systolique, indice de masse corporelle, cholestérol, activité physique, génotype *APOE-ε4*) afin de déterminer leur valeur prédictive respective. Cette partie de la thèse vise à établir si les scores de risque

cardiovasculaire peuvent être un moyen d'évaluer la cognition, en particulier le changement cognitif au fil du temps, dans une population en phase précoce de vieillissement.

La population d'étude et les données

Cette thèse s'appuie sur les données de la cohorte Whitehall II, une cohorte prospective mise en place en 1985 sur 10308 fonctionnaires âgés de 35 à 55 ans et employés dans 20 ministères à Londres lors de l'inclusion. Le premier recueil de données a été réalisé à l'aide d'un questionnaire et d'un examen clinique. Par la suite, un questionnaire postal a été envoyé à chaque phase et un examen clinique a été réalisé aux phases impaires. Les tests des fonctions cognitives ont été réalisés pour la première fois lors de l'examen clinique de la phase 5 (1997-1999) puis ont été répétés lors des phases 7 (2002-2004) et 9 (2008-2009). Ces tests sont adaptés à la population étudiée (âge moyen autour de 55 ans lors du premier recueil), et comprennent un test de raisonnement (Alice Heim 4, partie I), un test de mémoire verbale a court terme, deux tests de fluence verbale (fluence phonémique et sémantique), et un test de vocabulaire. Un score global a été calculé à partir de ces 5 tests. Pour les analyses de cette thèse, les facteurs de risque vasculaire étaient mesurés à la phase 5, coïncidant avec la première phase des données cognitives. Des analyses transversales et longitudinales ont été menées. Les analyses longitudinales ont été effectuées en utilisant des modèles mixtes. Pour comparer entre elles les associations avec différents scores de risque dans la dernière partie de la thèse, une méthode de 'bootstrap' a été employée.

Résultats

L'association entre le syndrome métabolique et la cognition

L'analyse comparant 517 personnes avec un syndrome métabolique et 4566 personnes sans au début du suivi a montré que les personnes présentant un syndrome avaient de plus faibles scores cognitifs dans les analyses transversales (p <0,001 pour l'ensemble des tests considérés). Après ajustement sur les facteurs sociodémographiques (âge, sexe, niveau d'études), les comportements de santé (tabagisme, consommation d'alcool, activité physique) et les symptômes dépressifs, les associations subsistent pour le score de mémoire (β =-0,10; intervalle de confiance à 95 % (IC 95%): -0,19, - 0,01 ; p =0,02), de vocabulaire (β =-0,08; IC 95% : -0,16, 0,02 ; p=0,03) et le score global (β=-0,09 ; IC 95% : -0,17, - 0,04 ; p=0,03). En revanche, dans les analyses

longitudinales, il n'y avait pas de différence de déclin cognitif en fonction de la présence d'un syndrome métabolique. Parmi les composantes du syndrome métabolique, seule l'hyperglycémie était associée à un déclin cognitif global plus rapide (β =-0,07; IC 95%: -0,13, 0,001 ; *p*=0,05).

L'association des scores de risque cardiovasculaire avec la cognition

Dans les analyses transversales, un risque cardiovasculaire élevé était associé à des scores plus faibles de mémoire et de cognition globale. Dans les analyses étudiant l'association entre les composantes du score de risque (pression artérielle systolique, cholestérol total, cholestérol HDL, diabète et tabagisme) et la cognition, la pression artérielle systolique, le cholestérol HDL et le tabagisme étaient associés à des scores cognitifs plus faibles. Dans les analyses longitudinales, une augmentation de 10% du risque cardiovasculaire était associée à un déclin cognitif plus rapide pour tous les tests, à l'exception du test de raisonnement. Par exemple, une augmentation du risque cardiovasculaire de 10% a été associée à un déclin plus rapide pour la cognition globale (β =-0,03 ; IC 95% =-0,04, -0,006 ; *p*=0,01). Concernant les composantes du score de risque, après prise en compte des variables sociodémographiques et des comportements de santé, le cholestérol total et le diabète étaient associés à un déclin cognitif plus rapide au cours des 10 ans de suivi.

Un risque d'AVC plus élevé était associé à des scores cognitifs plus bas dans les analyses transversales. Ces associations ont persisté après ajustement sur les facteurs sociodémographiques et les comportements de santé. Les analyses longitudinales ont montré que les personnes ayant le risque d'AVC le plus élevé présentaient un déclin cognitif plus rapide sur 10 ans pour l'ensemble des tests cognitifs considérés, à l'exception du raisonnement et de la mémoire. Par exemple, pour le score global, par rapport à un déclin moyen de -0,21 écart-type (ET) (IC 95%= -0,24, -0,19) sur 10 ans pour les participants dans le quartile de risque le plus faible, le déclin correspondant pour ceux dans le quartile de risque le plus élevé était de -0,25 ET (IC 95% =-0,28, -0,21) (*p* =0,02). Parmi les composantes de ce score de risque, le diabète et l'hypertrophie ventriculaire gauche étaient indépendamment associés à un déclin cognitif plus rapide au cours du suivi.

Comparaison des scores de risque cardiovasculaire avec le score de risque de démence de CAIDE

Les résultats de cette partie de thèse comparant les deux scores de risque cardiovasculaire avec le score de risque de démence CAIDE ont mis en évidence une plus forte association transversale avec le score de risque de démence qu'avec les scores de risque cardiovasculaire, probablement lié à l'effet important du niveau d'études qui est une composante du score de démence CAIDE. En effet, plusieurs études ont montré que le niveau d'études élevé est associé de manière transversale avec de meilleures performances cognitives, tandis que l'éducation a un effet minimal sur le déclin cognitif. Les analyses longitudinales ont montré que les deux scores de risque cardiovasculaire étaient de meilleurs prédicteurs du déclin cognitif que le score de risque de démence. En effet, les scores de risque cardiovasculaire étaient associés au déclin cognitif dans tous les domaines, sauf pour la mémoire, tandis que le score de risque de démence était associé à un déclin plus rapide dans les tests de raisonnement, vocabulaire et cognition globale.

Conclusion

L'objectif principal de cette thèse était d'étudier les relations entre différentes mesures des facteurs de risque cardiovasculaire et la cognition et le changement cognitif au cours de 10 ans. Les analyses ont d'abord porté sur le syndrome métabolique, une entité multidimensionnelle incluant plusieurs facteurs de risque cardiovasculaire, et elles ont montré que le déclin cognitif sur 10 ans était similaire chez les personnes avec et sans syndrome métabolique. Ceci pourrait être dû à la définition du syndrome métabolique qui nécessite la présence de trois facteurs de risque parmi cinq. Or, chez les sujets moins âgés, qui ont généralement de faibles niveaux d'exposition aux facteurs de risque cardiovasculaire et métabolique, cette définition peut ne pas refléter adéquatement la continuité du risque et donc ne permet pas de distinguer les individus ayant un risque à la limite du seuil ou ceux ayant un seul facteur de risque.

Les résultats ont montré qu'un risque cardiovasculaire élevé est associé à un déclin cognitif plus rapide. Par conséquent, les deux scores de risque de Framingham développés pour prédire les événements cardiovasculaires peuvent être utilisés pour identifier les personnes susceptibles de présenter un risque plus élevé de déclin cognitif plus rapide. Les études utilisant des données de neuroimagerie ont rapporté des associations entre les scores de risque de Framingham et des marqueurs précliniques de maladie cérébrovasculaire, comme par exemple les calcifications des artères coronaires, l'augmentation de l'épaisseur intima-média carotidienne, des anomalies de la substance blanche et l'atrophie du cerveau. De tels changements structurels du

cerveau peuvent refléter un effet de l'exposition aux facteurs de risque cardiovasculaire et être associés au déclin cognitif. Les résultats de cette thèse fournissent une indication supplémentaire du rôle des facteurs de risque cardiovasculaire sur les trajectoires de déclin cognitif.

En comparant les scores de risque de Framingham avec le score de risque de démence CAIDE, il est apparu que les scores de risque de Framingham offriraient un meilleur moyen d'identifier les individus présentant un risque plus important de déclin cognitif. Cela pourrait s'expliquer par des différences dans la catégorisation des facteurs de risque qui composent les algorithmes des scores de risque Framingham et celui du score de risque CAIDE. Par exemple, la pression artérielle systolique comporte cinq catégories dans le score de risque de Framingham (<120, 120-129, 130-139, 140-159, ≥ 160 mm Hg), alors qu'elle n'en compte que deux (≤ 140 et > 140 mm Hg) dans le score de risque de démence de CAIDE. Cette catégorisation plus fine des facteurs de risque dans les scores de risque de Framingham permet de mieux rendre compte de la continuité du risque et offre une meilleure distinction des niveaux de risque, particulièrement pour les niveaux de risque modérés observés généralement chez les sujets les plus jeunes. D'un point de vue pratique, l'utilisation d'un score de risque de démence tel que le CAIDE n'est pas évidente, en particulier en raison de l'inquiétude associée à la démence; en conséquence, l'acceptabilité de son utilisation en particulier chez des adultes jeunes sera sans doute faible. En revanche, les scores de risque de Framingham sont déjà bien connus et généralement intégrés dans les systèmes de soins primaires. De plus, des études, y compris celles de cette thèse, ont montré l'utilité de ces scores dans le cadre du vieillissement cognitif. Par conséquent, ils peuvent être utilisés non seulement pour informer les personnes sur leur risque cardiovasculaire, mais aussi servir d'indication quant au risque de déclin cognitif.

Forces et faiblesses

Le principal point fort de ce travail de recherche est qu'il s'appuie sur des données longitudinales avec 3 mesures répétées de la fonction cognitive sur un grand échantillon de personnes suivies pendant 10 ans à partir d'un âge moyen de 55 ans. La principale limite concerne la représentativité de la cohorte Whitehall II par rapport à la population générale. Il s'agit d'une cohorte de fonctionnaires avec des emplois stables, mais également avec un profil de risque cardiovasculaire relativement faible. Il est donc possible que les associations rapportées ici aient

été sous-estimées. Cependant, il est peu probable que cette sous-estimation, si elle existe, ait affecté les résultats des analyses comparant les scores de risque.

Portée des résultats

Ce travail de thèse contribue à la réflexion sur le vieillissement cognitif en soulignant l'intérêt d'étudier les fonctions cognitives avant l'âge de la survenue de la démence. Les résultats montrent que les facteurs de risque chez des sujets de moins de 65 ans jouent un rôle important dans le vieillissement cognitif. De nombreuses maladies, dont les maladies cardiovasculaires et la démence, ont des étiologies communes. Il est donc raisonnable de prôner l'utilisation d'outils communs pour l'estimation de risque et aussi pour cibler les traitements pour diminuer ce risque.

De nombreux scores de risque cardiovasculaire sont déjà utilisés, notamment par les médecins généralistes, pour calculer le risque cardiovasculaire de leurs patients; l'utilisation de scores de risque cardiovasculaire est aussi préconisée dans de nombreuses recommandations de pratique clinique. Pour optimiser la prévention de l'apparition du déclin cognitif, la prise en compte des facteurs de risque cardiovasculaire pourrait représenter un axe d'intervention essentiel. L'impact de la modification des facteurs de risque cardiovasculaire sera sans doute plus bénéfique si elle intervient avant la phase préclinique des troubles cognitifs et de la démence.

Les futures recherches et guides cliniques devraient discuter de l'utilité de ces scores de risque pour informer du risque de déclin cognitif. Cela permettra non seulement d'informer mais également de traiter les personnes ayant un risque cardiovasculaire élevé, ajoutant un élan pour le traitement et le contrôle des facteurs de risque cardiovasculaire. La réduction de ces facteurs de risque est susceptible d'avoir un impact important dans la réduction du nombre des cas de déficit cognitif et de démence.

CHAPTER I: INTRODUCTION

I.1 Population aging

Over the last century, life expectancy has increased dramatically, contributing to the aging of the population. For the world as a whole, life expectancy increased by two decades since 1950; from 48 years in 1950-1955, to 68 years in 2005-2010; global life expectancy is set to rise further to 76 years during the current half century. The number of those over age 60 is projected to increase from 800 million today, representing 11% of the world population, to over 2 billion in 2050, representing 22% of the world population (United Nations Population Division, 2011). Although the world population is expected to increase 4 times from 1950 to 2050, the number of those aged 60 and over will increase by a factor of 10, and for those 80 and older, by a factor of 26 (United Nations Population Division, 2011).

Population aging may be seen as a human success story with the triumph of public health and advancements in medical science over diseases and injuries that had limited human life expectancy for centuries. However, despite the increase in life expectancy, disability-free life expectancy has not increased proportionately. This is reflected in the increase in the number of people living with non-communicable diseases including cardiovascular disease and dementia. Chronic and non-communicable diseases are currently responsible for nearly 60% of deaths and half of the loss of actual and effective life years due to disability or death (WHO, 2010). Furthermore, costs of care and treatment are relatively high for non-communicable diseases. The global burden and threat of non-communicable diseases constitutes one of the major challenges facing societies, therefore greater emphasis on disease prevention will be paramount in mitigating the increasing burden on individuals and the health care system.

I.1.1 Dementia: A public health challenge

Dementia is a clinical syndrome characterized by progressive decline in cognitive function. These cognitive changes are often accompanied by deterioration of mood, behavior, and personality that interfere with the individual's ability to perform everyday activities (Ritchie et al., 2002). Alzheimer disease (AD) is the most frequent type of dementia, accounting for 50-80% of all cases, followed by vascular dementia representing 20-30% of all dementia (Abbott, 2011). Other types include dementia with lewy bodies, frontotemporal dementia, and dementia secondary to another disease such as AIDS, Parkinson's, or Huntington's disease. However, traditional

diagnosis of dementia subtypes has been challenged by population based studies that suggest that different forms of dementia share underlying neuropathologies and provide evidence for the existence of a range of dementia associated brain pathologies ranging from pure vascular to pure AD; most dementia cases present a mixed state composed of features of more than one type of dementia, attributable to both vascular disease and neurodegeneration (Ritchie et al., 2002; Viswanathan et al., 2009).

Dementia is a principal cause of lower survival, disability and institutionalization at older ages, and has become a major challenge to public health and health care systems across the world. Incidence of dementia increases exponentially with age. The age-specific prevalence of dementia roughly doubles every 5 years from approximately 1.5% in 60-69 year olds to 40% in those over 90 years of age. An expert panel estimated that the global prevalence of dementia in people aged 60 years and over was 3.9%, with some regional variations ranging from 1.6% in Africa to 5.4% in western Europe and 6.4% in North America (Ferri et al., 2005). In 2010, there were 35.6 million people living with dementia worldwide, a figure that is set to increase to 65.7 million by 2030 and 115.4 million by 2050 (Ferri et al., 2005). Personal burden of dementia is also great due to progressive deterioration in various cognitive abilities including memory and language skills, cognitive processing speed, reasoning and judgment, and problem solving. Further impairments such as personality changes, behavioral and emotional problems including agitation, delusions and hallucinations often lead to loss of autonomy. The disability weight for dementia has been estimated to be higher than any other health condition after spinal cord injuries and terminal cancer (Ferri et al., 2005). Recent global estimates put medical and social service costs associated with dementia care at roughly equivalent to 1% of the world's gross domestic product (GDP), an estimated US $ 604 billion in 2010. If all economic factors remain unchanged, these costs are predicted to increase by 85% by 2030 and to become one of the biggest economic strains for health-care systems and communities worldwide (Alzheimer's Disease International, 2010).

In addition, informal care giving and social care provided by community care professionals and residential home care contribute to over 40% of total worldwide costs. In high income countries, between one third and one half of people with dementia live in resource and cost-intensive residential care facilities. However, because dementia is under diagnosed and the majority of those diagnosed with dementia are receiving inadequate care (Brayne et al., 2007;

Holsinger et al., 2007), the true costs and burden of disease associated with dementia is believed to be larger than current estimates. As the global aging populations and the rising life expectancy will bring an increase in the number of people with dementia, there is a growing need to understand the disease. Effective preventive and health-care planning strategies are paramount to curb individual and societal burden of dementia.

I.1.2 Cognitive aging and preclinical phase of dementia

Aging is characterized by increasing inter-individual differences in functional decline. The disparities in patterns of decline suggest that in addition to normal aging, other age-related processes are involved. With aging, there is a marked and progressive increase in cerebrovascular pathologies. At the same time there is a great overlap between normal aging and pathological aging of the brain as it is unclear what exactly constitutes pathological aging. However, as cognitive abilities involving acquired knowledge and vocabulary often grow or remains relatively unchanged with aging, there is a general deterioration in cognitive processes requiring processing speed and memory. Concurrently, the brain shows an increase in neurodegenerative plaques, atrophy, and vascular damage; few individuals reach advanced age with no or little neuropathological damage (Brayne, 2007).

The wide distribution of cognitive profiles and differences in cognitive trajectories across the life span, are largely influenced by a combination of individual's demographic and life time experiences and exposure to risk factors, health behaviors, and chronic diseases. With growing emphasis on life-course health and disease trajectories, there is an interest to determine the point at which individual cognitive trajectories begin to diverge. Although it was previously suggested that there is little cognitive decline before the age of 60 (Hedden et al., 2004), emerging evidence suggests that cognitive decline may be evident as early as in the fourth decade of life (Singh-Manoux et al., 2012). Therefore, it is increasingly important to study determinants of cognitive aging starting at younger ages.

Studies of risk factors for cognitive impairment have mostly examined cognitive impairment and dementia at older ages, focusing on overt or clinical cognitive symptoms. One important limitation of these studies is the reliance on diagnostic categories of dementia and mild cognitive impairment (MCI) that are constantly changing and do not capture the complex and dimensional nature of cognitive impairment (Stephan et al., 2007). Thus, the focus is starting to shift to a continuum of cognitive change and long-term cognitive decline and to identify the

beginning of the transition from healthy aging to dementia. This shift has largely resulted from converging evidence from numerous prospective and longitudinal studies pointing to a 'sub-clinical' phase of dementia, whereby subtle cognitive and neuropathological changes are observed several years before overt cognitive and behavioral symptoms become apparent (Amieva et al., 2008; Galvin et al., 2005; Grober et al., 2008; Hall et al., 2000; Johnson et al., 2009; Twamley et al., 2006). Dementia itself represents only the end stage of a process of gradual cognitive decline resulting from several years of accumulation of pathological changes in the brain (Hachinski, 2008). These cognitive changes may appear as early as 22 years before clinical diagnosis of dementia (Elias et al., 2000). In addition, there may be a turning point in the transition from normal aging to preclinical dementia marked by a sharp inflection point followed by accelerated cognitive decline in multiple domains (Johnson et al., 2009).

A great limitation of current epidemiological research on cognitive aging has been its focus on cohorts over the age of 65. Studies based on older adults can only address questions on later-life risk factors and do not inform on questions related to early or midlife risk factors. Moreover in such studies, the extent of exposure to risk factors and subclinical states before the onset of dementia cannot be reliably examined. Where there is long delay between exposure and disease and where exposures have common etiologies and change in one may result in change in other exposures, longitudinal studies based on well characterized cohorts offer a rare opportunity to study these relationships. Such longitudinal studies in which individuals are followed over time risk factors can be measured early and changes in risk factors can be studied in relation to changes in the outcome.

Studies conducted in older populations are subject to a number of different biases that may affect interpretation of results. These include selection biases both prior to and post study entry and reverse causation. Studies based on elderly populations include individuals who have necessarily survived competing causes of death. This may introduce a selection bias prior to study entry since mortality rates increase with age and the exposure is also related to mortality. The inconsistencies in studies examining cardiovascular disease (CVD) risk factors in the elderly, some reporting a decrease in risk related to individual CVD risk factors are in part related to this bias. For example, in a review of prospective studies, relative risk of dementia among smokers compared with non-smokers was reported to attenuate with age (Hernan et al., 2008). Similarly, association of blood pressure with vascular disease and cognitive outcomes have been shown to

be modified by age; while high blood pressure in middle age is associated with increased risk of cognitive deficits, this association in late life is reversed (Euser et al., 2009). In addition, selection bias after study entry as a result of death and drop out is frequent in longitudinal studies of aging. But studies on the elderly are more prone to this bias due to higher mortality rates and because those who die or drop out during the course of the study are more likely to have lower cognitive function and faster decline compared to those who remain in the study (Euser et al., 2008). Therefore analyses based on surviving participants, that do not take into account such missing data (missing not at random) would lead to biased estimates of the importance of putative risk factors (Hernan et al., 2008; Hogan et al., 2004). In contrast, studies conducted on populations who are younger at baseline and not subject to high mortality rates and competing causes of death, these biases are significantly minimized.

In aging studies involving older participants, reverse causation is of particular concern. It is well known that some of the association between CVD risk factors and cognition is bidirectional whereby CVD risk factors affect cognition through various mechanisms leading to cerebral damage; changes in cognition or physical function may also influence CVD risk factors through health behaviors (e.g. diet, smoking, physical activity). Studies based on a younger population that have a longitudinal design to examine these risk factors early, before they have exerted their effects, and monitoring trajectories of change in cognition will enable differentiation of these effects.

Advances in biochemical and imaging techniques have resulted in identification of several chemical and imaging biomarkers characterizing the dementia disease process. Biomarker abnormities typically precede clinical and cognitive symptoms of dementia and thus are particularly useful in detecting early pathological changes in the brain (Jack, Jr. et al., 2010). These include measures of cerebral atrophy and white matter hyperintensities, cerebrospinal fluid (CSF) tau, and CSF beta-amyloid (Aβ), all hallmarks of Alzheimer's disease pathology but also of aging (Rodrigue et al., 2009; Rodrigue et al., 2012). These well accepted biomarkers of Alzheimer's disease have been used in diagnostic procedures with high sensitivity and specificity (Lewczuk et al., 2004). However analyzing CSF biomarkers is time consuming and costly, and requires invasive procedures (i.e. lumbar puncture) and thus their use is currently limited.

Identifying risk factors and their effect on the trajectories of cognitive decline will allow capturing the true continuum of cognitive change across the life course, and avoid use of diagnostic categories, and may also provide better opportunities for treatment and prevention.

I.2 Major risk factors for cognitive impairment and dementia

Risk factors for cardiovascular disease have been found to be associated with cognitive impairment and dementia. Non modifiable factors include age, sex and ethnicity, and genetic risk factors (e.g. APOE, PICALM, CLU, CR1, BIN1, etc.). Modifiable risk factors include socioeconomic factors (education, occupational position), life style factors (physical activity, smoking, alcohol intake, diet), medical and chronic conditions (traumatic head injury, depression, thyroid dysfunction), and CVD risk factors and vascular disease (hypertension, hypercholesterolemia, diabetes, stroke etc) (Figure 1). Cardiovascular disease risk factors form the largest and most important group of modifiable risk factors for cognitive impairment and dementia (Barnes et al., 2011; Gorelick et al., 2011; Viswanathan et al., 2009).

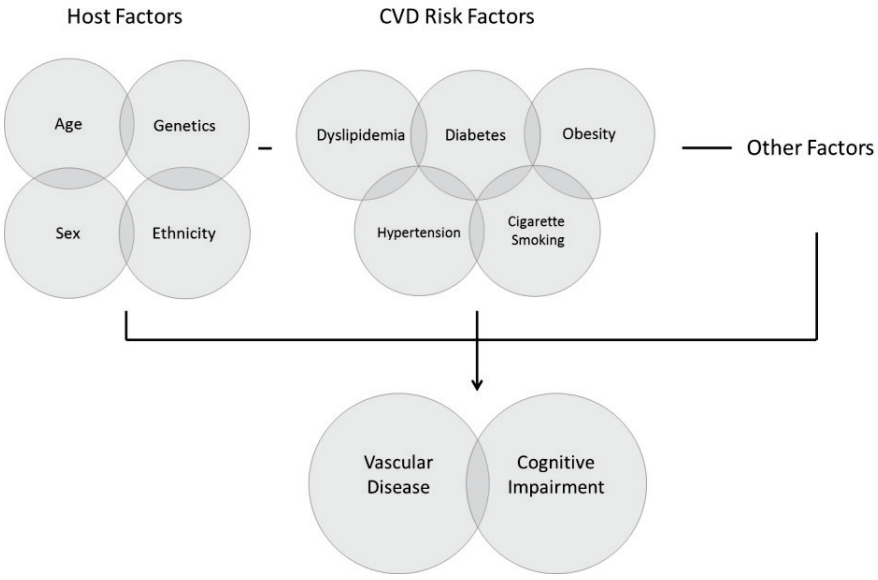

Figure 1. Schematic interplay of factors involved in cognitive impairment

I.2.1 Vascular contribution to cognitive impairment and dementia

Vascular contributions to cognitive impairment and dementia are now widely acknowledged. Traditional diagnostic categories of dementia distinguished vascular dementia from Alzheimer's disease, as the pathologic mechanisms underlying these two conditions were considered separate

or mutually exclusive. Vascular dementia was thought to be secondary to vascular disease and Alzheimer's disease, was regarded as a purely degenerative disorder. However, pathological studies have repeatedly demonstrated a significant overlap between Alzheimer's and vascular disease pathologies (Schneider et al., 2007; Schneider et al., 2009). There is now overwhelming evidence that CVD risk factors not only increase risk of vascular cognitive impairment, they also predispose to Alzheimer's disease (Gorelick et al., 2011). While Alzheimer pathology is more common in the aging brain, it nearly always coexists with vascular pathology (Strozyk et al., 2010). A study of more than 450 donated brains in the MRC Cognitive Function and Aging Study (CFAS) found Alzheimer type pathology (plaques) in nearly all of them and identified vascular damage in four fifths of brains of individuals with dementia (Wharton et al., 2011). In the Nun Study, among those with Alzheimer pathology, those with additional vascular pathology (small lacunes and silent infarcts) were considerably more likely to have dementia (Snowdon et al., 1997). Neurodegenerative mechanisms often interact and affect the course of cognitive impairment and dementia (de la Torre, 2002; de la Torre, 2004; Kivipelto et al., 2002; Viswanathan et al., 2009). Dementia is more likely to be present when vascular and AD lesions coexist (Langa et al., 2004). Multiple CVD risk factors including hypertension, diabetes and hypercholesterolemia have been found to promote conversion from mild cognitive impairment to Alzheimer's disease and their treatment associated with reduced risk of Alzheimer's disease (Li et al., 2011). Vascular pathology can be additive with Alzheimer pathology in impairing cognition. In persons with Alzheimer's disease, presence of CVD risk factors is associated with accelerated cognitive decline (Helzner et al., 2009; Kume et al., 2011; Li et al., 2010a; Regan et al., 2006). Even when vascular lesions and Alzheimer pathology such as white matter changes, do not lead to dementia by themselves, their cumulative load is likely to lead to dementia. For example, in patients with asymptomatic Alzheimer pathology who have both stroke and white matter changes, the period of preclinical Alzheimer's disease might be shortened, implying faster conversion to clinical dementia (Pasquier et al., 1997).

Cardiovascular disease risk factors exert their deleterious effects on cognition through both vascular mechanisms related to cerebral microvasculature, and non vascular or degenerative mechanisms such as amyloid deposition (Kalaria, 2010) (Figure 2). These processes develop in parallel and are interconnected through complex dynamic pathways that disrupt the neurovascular unit and its functions. Direct structural damage to the brain in the form of cortical and

hippocampal atrophy and neuronal loss can result from silent brain infarcts and stroke linked to CVD risk factors (Pinkston et al., 2009).

Other important mechanisms involved in cerebral tissue damage are those that compromise endothelial function and the blood brain barrier in the brain. In the normal brain, cerebrovascular autoregulation protects the brain from fluctuations in perfusion pressure by keeping cerebral blood flow constant within a range of blood pressures. In addition, trafficking of molecules across the blood brain barrier is controlled by tight junctions between cerebral endothelial cells and specialized membrane transporters. Cardiovascular disease risk factors such as hypertension and insulin resistance disrupt this homeostasis of the cerebral microenvironment by interrupting cerebral blood flow leading to alteration of microvascular structure and disruption of endothelium dependent responses. Similarly, high cholesterol levels leading to arterial stiffness and intima thickening can cause hypoperfusion, disruption of cerebral blood flow, and weakening of endothelial functions leading in turn to impaired cerebral metabolism and neuronal death (Gorelick et al., 2011).

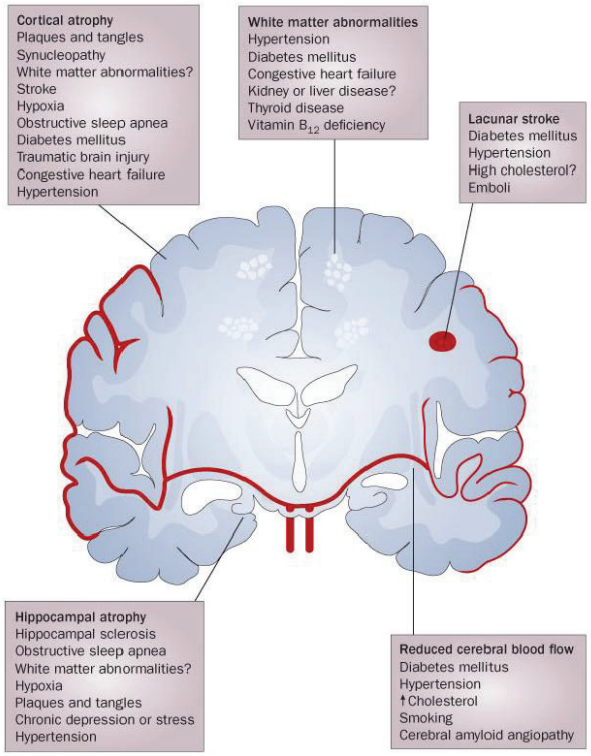

Figure 2. Neuropathological changes linked to cognitive impairment (Source: Fotuhi M, et al. Changing perspectives regarding late-life dementia. *Nat Rev Neurol* 2009 (5), p 653).

Disruption of cerebral blood flow is also indicated in amyloid pathology whereby transport and clearance of β amyloid becomes impaired resulting in deposition of β amyloid plaques in the brain (amyloid angiopathy). A potent vasoconstrictor, β amyloid leads to further disruption of the cerebral blood flow causing cortical and hippocampal atrophy. Elevated circulating levels of β amyloid promote inflammation and oxidative stress that also play a role in white matter changes in the brain (Gomis et al., 2009). In addition, metabolic disturbances linked to factors such as diabetes and dyslipidemia lead to imbalance of certain enzymes involved in protein phosphorylation (e.g. protein kinases and protein phosphatases). A consequence of these imbalances is hyperphosphorylation of tau, a protein abundant in the neurons that stabilizes microtubules. The resulting aggregation of hyperphosphorylated tau in the form of neurofibrillary tangles is associated with neuronal cell death and is a characteristic feature of Alzheimer pathology (Figure 3) (Ballard et al., 2011).

The association of CVD risk factors, brain lesions, and cognition is complex and the precise pathogenic processes involved in this association remain to be determined. Regardless of underlying mechanisms, there is compelling evidence for the causative role of these risk factors in the development of various brain pathologies such as atrophy, white matter abnormalities and β amyloid plaques, and their association with concurrent or long-term cognitive deficits. The following sections present the evidence regarding the association of major CVD risk factors with cognitive impairment and dementia, as well as a brief overview of putative mechanisms involved in these associations.

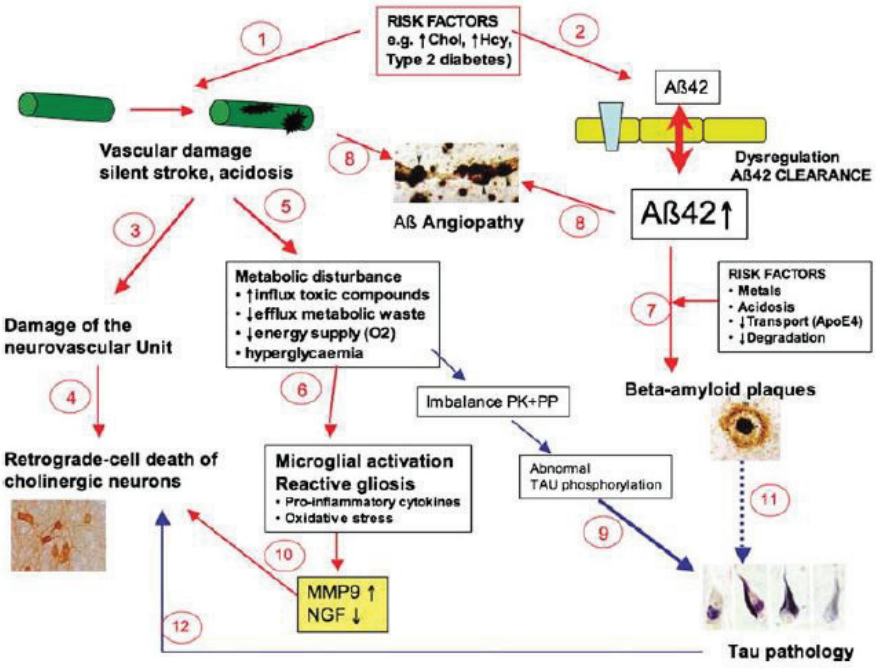

Figure 3. Proposed pathway leading to Alzheimer disease pathology involving both vascular and neurodegenerative processes. It is hypothesized that chronic mild exposure of different (vascular) risk factors may play a role in the development of Alzheimers disease. These factors are e.g. hyperhomocysteinemia, hypercholesterolemia or type 2 diabetes. This leads to damage of the neurovascular brain capillaries leading to silent strokes and acidic conditions (1) or to a dysregulation of β-amyloid at the blood-brain barrier resulting in increased β-amyloid (1–42) levels in the brain (2). The cerebrovascular dysfunction may result in a damage of the sensitive neurovascular unit (3). The subsequent retrograde-induced cell death of cholinergic neurons correlates with the lack of cortical or hippocampal acetylcholine (4). Metabolic disturbances (e.g. enhanced influx of toxic compounds, reduced efflux of metabolic waste, or reduced energy supply) may induce neuroinflammation (5) and microglial activation and reactive gliosis (6). Different risk factors (such as metals, reduced pH, reduced transport or degradation of β-amyloid) may result in aggregation of beta-amyloid and plaque deposition (7). The cerebrovascular damage and dysfunctional β-amyloid clearance result in deposition of β-amyloid (angiopathy) in brain vessels (8). It is suggested that metabolic disturbances cause an imbalance of specific protein kinases (PK) or phosphatases (PP), resulting in abnormal tau phosphorylation, which finally cause the tau pathology (9). Microglia inflammation enhances matrix metalloproteinase-9 (MMP9) and cause a dysfunction of the metabolism of nerve growth factor (NGF) with a reduced bioavailability for cholinergic neurons, supporting their cell death (10). Tau pathology may on the other hand also be caused by β-amyloid plaque deposition (11) or may contribute to neuronal cell death (12). (Source: Humple C. Chronic mild cerebrovascular dysfunction as a cause for Alzheimer's disease? *Exp Gerontol* 2010 (46), p 225-232)

Cardiovascular and cerebrovascular disease

The existence of a link between dementia and cerebrovascular and cardiovascular diseases such as atherosclerosis, coronary heart disease, and stroke has been suggested because these diseases share conventional risk factors (Casserly et al., 2004; de la Torre, 2002; Kivipelto et al., 2001b; Waldstein et al., 2010) as summarized below:

Heart disease

Several studies have reported an independent relationship between atherosclerosis (carotid intima media thickness, carotid plaques, peripheral artery disease) and dementia. A longitudinal study of 6,647 participants of the Rotterdam study with a mean follow-up of 9 years found carotid atherosclerosis to be associated with an increased risk for any dementia type (van et al., 2007). In the same way, arterial stiffness has been associated with cognitive impairment (Hanon et al., 2005a; Waldstein et al., 2008).

Major complications of atherosclerosis, such as coronary heart disease (CHD) and congestive heart failure have also been associated with cognitive deficits and dementia. In the Cardiovascular Health Study that followed over 3000 individuals over 5.4 years, the incidence of dementia was higher in those with prevalent coronary artery disease (Newman et al., 2005). In the Whitehall II Study, history of CHD was associated with lower cognitive performance in middle-aged adults (Singh-Manoux et al., 2008b). Coronary artery disease has also been found to be associated with neuropathological hallmarks of Alzheimer's disease in apolipoprotein E (*APOE) ε4* allele carriers (Beeri et al., 2006). Similarly, congestive heart failure has been shown to be associated with higher prevalence of dementia (Qiu et al., 2006a), cognitive impairment (Cacciatore et al., 1998; Vogels et al., 2007a; Vogels et al., 2007b), and worse immediate and long-term memory (Almeida et al., 2012). The potential pathways linking heart failure to cognitive impairment include hypotension and associated low cardiac output that in turn lead to cerebral hypoperfusion (Zuccala et al., 2001). Multiple cerebral emboli that are often a complication of heart failure can also lead to cerebrovascular pathology and play a role in neurodegenerative processes (Cohen et al., 2007).

Stroke and silent infarctions

One in 3 individuals will experience stroke, dementia, or both (Hachinski et al., 2006). Stroke is followed by a significant decline in cognitive function (Kase et al., 1998). Epidemiological studies have reported a several fold increased incidence of dementia after stroke (Barba et al., 2000; Desmond et al., 2002a; Ivan et al., 2004; Leys et al., 2005; Pendlebury et al., 2009). Post stroke dementia leads to especially high mortality rates in stroke patients (Barba et al., 2002; Desmond et al., 2002b). Prevalence of dementia in people with a history of stroke is about 30% (Leys et al., 2005). Diagnosis of dementia after stroke is greater immediately after the

stroke. In the first year after stroke the prevalence of dementia ranges from 7% in population based studies, to 40% in studies of hospital based patients (Pendlebury et al., 2009). In addition, recurrent stroke leads to greater cognitive decline after a first stroke (Srikanth et al., 2006). Incident rates of dementia are three times higher for recurrent stroke compared with first ever stroke with a rise in incidence after each recurrent stroke (Pendlebury et al., 2009). This is in line with the stepwise progression of cognitive deficits associated with vascular dementia (VaD) (Pendlebury et al., 2009). Even silent brain infarcts double the odds of developing dementia (Vermeer et al., 2003). In the absence of dementia, cognitive impairment is three times more common in people who have had a stroke than in those who have not (Linden et al., 2004).

While some studies have found a role for CVD risk factors such as diabetes, hypertension, and smoking in the link between stroke and subsequent dementia risk (Henon et al., 2001), others have not (Gamaldo et al., 2006; Ivan et al., 2004). In these studies, although stroke was consistently found to increase risk of dementia, individual stroke risk factors did not alter the impact of stroke on the risk of dementia. For example the joint presence of stroke and *APOE ε4* - the most important genetic risk factor for late-onset Alzheimer's disease, has been found to be associated with a greater risk of dementia, but this effect seems to be unmodified by *APOE* genotype. Thus, while cerebrovascular disease plays an important role in determining the presence and severity of dementia symptoms, vascular disease and stroke seem to lead to dementia via independent mechanisms.

Cerebral infarctions and stroke lead to cognitive impairment and dementia through direct damage to brain regions such as thalamus and thalamo-cortical projections (Pendlebury et al., 2009). They can also lead to Alzheimer pathology by inducing inflammatory responses, increasing extracellular Aβ deposition, and hypoperfusion. The latter can lead to over-expression of cyclin-dependent kinase 5 (CDK5) that is implicated in synapse formation and synaptic plasticity critical to learning and memory (Cheung et al., 2008). Abnormal CDK5 activation is associated with neuronal apoptosis and abnormal phosphorylation of tau which in turn contributes to the formation of Neurofibrillary Tangles (NTFs), a primary marker of Alzheimer's disease (Weishaupt et al., 2003).

Several studies have examined the influence of cognitive decline existing prior to stroke on the risk of post-stroke dementia (Barba et al., 2000; Gamaldo et al., 2006; Henon et al., 2001; Reitz et al., 2008). Most of these studies suggest that cognitive decline prior to stroke is frequent

and may account for some of the dementia syndromes after stroke (Barba et al., 2000; Gamaldo et al., 2006; Henon et al., 2001). The first of such studies carried out in a cohort of 202 stroke patients found that the risk of post-stroke dementia increased in patients with pre-stroke cognitive decline. In this study diabetes mellitus, silent infarcts and cognitive disturbances prior to stroke were independent predictors of post-stroke dementia (Henon et al., 2001). A similar study examining risk and determinants of dementia following a clinically overt stroke in a prospectively followed cohort of elderly men found that in patients with cognitive impairment, the occurrence of stroke led to dementia in almost all cases; when cognitive impairment did not precede the stroke, there was no increase in the risk of subsequent dementia. The investigators concluded that dementia after stroke may be partly determined by cognitive impairment that exists prior to stroke. It is likely that preexisting Alzheimer's disease pathology or asymptomatic cerebrovascular disease that is then substantiated by the stroke is implicated in these observations (Gamaldo et al., 2006). In contrast to these reports, an analysis of the large population based Rotterdam study found that incident stroke doubled the risk of dementia independent of prestroke level of cognitive function and prestroke rate of cognitive decline (Reitz et al., 2008).

These findings point to the complex link between vascular risk leading to stroke, and the cognitive deficits that ensue. Stroke can be the main cause or a precipitating factor of dementia, or they may share common etiological bases. However there is convincing evidence to suggest that the effects of stroke on cognition are through mechanisms other than those of other potential CVD risk factors, and that stroke exerts its effects on dementia risk independently of these risk factors (Reitz et al., 2008). The strong association of post stroke dementia with number of strokes and stroke characteristics (e.g. size of infarct) provides further evidence for the central causal role of stroke itself above and beyond the underlying exposure to CVD risk factors. In other words, although exposure to CVD risk factors may increase susceptibility to the impact of stroke on cognition, the stroke event itself has an immediate and consequential effect on the absolute risk of dementia (Pendlebury et al., 2009). Although it is difficult to disentangle the effects of CVD risk factors and stroke on cognition, preventing stroke is likely to significantly reduce the risk of dementia (Jin et al., 2008).

Atrial fibrillation and left ventricular hypertrophy

Atrial fibrillation is a common cardiac arrhythmia (irregular heart rate). It is mostly asymptomatic, especially at early stages, but may lead to heart palpitations and chest pain, as well as congestive heart failure (Stewart et al., 2002). It is also an independent risk factor for stroke (Wolf et al., 1991a). Atrial fibrillation often remains undetected unless overt symptoms (e.g. heart palpitations or stroke) necessitate a physical examination. A quarter of patients with ischemic stroke who undergo magnetic resonance imaging are diagnosed with atrial fibrillation (Vermeer et al., 2003).

Findings from studies examining atrial fibrillation's association with cognitive function have been inconsistent (Forti et al., 2006; Mead et al., 2001; Miyasaka et al., 2007; O'Connell et al., 1992; Rastas et al., 2007; Sabatini et al., 2000). Some studies have reported that atrial fibrillation is associated with cognitive impairment and dementia independent of stroke or other CVD risk factors (Marzona et al., 2012; Ott et al., 1997). In addition, chronic atrial fibrillation in stroke-free patients has been associated with greater hippocampal atrophy that is related to memory impairment (Knecht et al., 2008). However, a systematic review of studies of atrial fibrillation and dementia concluded that while there is convincing evidence for the association between atrial fibrillation and increased risk of dementia in patients with a history of stroke, the link among those without a history of stroke is uncertain (Kwok et al., 2011). There is currently a dearth of longitudinal studies especially in non-elderly populations to clarify the association between atrial fibrillation and cognitive outcomes and its relation with underlying cardiovascular disease.

Left ventricular hypertrophy, another coronary risk factor and marker of cardiovascular disease refers to an extreme thickening of the myocardium of the left ventricle of the heart. While it may be a natural physiological reaction to strenuous physical activity, it can also be a pathological reaction to volume overload resulting from aortic insufficiency, regurgitant valvular heart disease and hypertension (Carabello, 1995; Gardin et al., 1997; Jilaihawi et al., 2003). The latter is the most studied risk factor for left ventricular hypertrophy which appears to be reversible with long-term reduction of blood pressure (Gardin et al., 2002).

Although left ventricular hypertrophy is closely associated with cardiovascular events such as myocardial infarction and congestive heart failure (Gottdiener et al., 2000; Levy et al., 1990; Levy et al., 1996; Verdecchia et al., 2001), only a handful of studies have evaluated its

relation to cognitive function, reporting an association between left ventricular hypertrophy and cerebral white matter lesions, cognitive impairment, and dementia (Elias et al., 2007; Scuteri et al., 2009; Selvetella et al., 2003; van Dijk et al., 2008). In the Framingham offspring cohort, left ventricular mass was inversely associated with cognitive performance. The attenuation of the observed associations after adjustment for CVD risk factors such as blood pressure suggested a mediating role of these factors in the relation between left ventricular hypertrophy and cognition (Elias et al., 2007). In contrast to these findings, a study of older adults reported an association between left ventricular hypertrophy and higher risk of poor cognitive performance and dementia independent of blood pressure levels (Scuteri et al., 2009).

Although atrial fibrillation and left ventricular hypertrophy are not often thought of as classic risk factors, they are receiving increasing attention as subclinical markers of cardiovascular disease - an intermediate state on the continuum from risk factors to clinically overt disease. They can also serve as an important indicator of long-term vascular burden representing degree and duration of exposure to CVD risk factors (e.g. hypertension). For example in the case of left ventricular hypertrophy, left ventricular mass correlates with degree of exposure to elevated blood pressure. While the role of these risk factors in detection and prevention of cardiovascular disease has been increasingly studied, their association with cognitive outcomes using longitudinal studies remains relatively unexplored.

Blood pressure

Hypertension is a key risk factor for stroke and CHD and many studies have assessed its link with cognition. However findings of cross sectional and longitudinal studies have at times been contradictory. These inconsistencies can be attributed to differences in methodology, specifically, the type of population studied, recruitment methods, the presence or absence of antihypertensive treatments, variation in the time between measurement of blood pressure and cognitive assessment, specific cognitive domain examined, and the age at which these parameters were assessed.

Cross sectional studies examining the association of hypertension with cognitive function have been extremely heterogeneous and were subject to different sources of methodological bias that have resulted in contradictory findings (Farmer et al., 1987; Seux et al., 1998). Cross sectional studies have given way to longitudinal investigations that are better suited and more

informative to examine this relationship. Some of the earliest longitudinal evidence for the association of hypertension and cognitive impairment emerged from analyses of the Framingham Heart Study that indicated a link between blood pressure levels and cognitive deficits 14 years later (Elias et al., 1993). Subsequently, a 20-year follow up study found that hypertension at age 50 was associated with cognitive impairment 20 years later (Kilander et al., 1998). Other research includes a 4-year follow up study of older adults, that reported greater risk of cognitive deficits in hypertensive patients; those untreated for hypertension had an even greater risk (Tzourio et al., 1999). A 6-year follow up of the large population-based ARIC study that followed 10,963 participants over 6 years also found an association between hypertension and cognitive impairment (Knopman et al., 2001).

Studies with longer follow up periods have found an association between hypertension and increased risk of dementia. A 25-year follow up of the Honolulu-Asia Aging Study cohort found that untreated hypertension in middle age increased risk of dementia later in life (Launer et al., 2000). Another study found that raised systolic blood pressure in midlife was associated with an increased risk of Alzheimer's disease, 21 years later (Kivipelto et al., 2001b). Although the majority of studies to date carried out in different populations have confirmed that individuals with cognitive impairment or dementia had generally higher blood pressure in midlife (Kivipelto et al., 2001a; Knopman et al., 2001; Unverzagt et al., 2011; Whitmer et al., 2005b), results concerning the association between late-life blood pressure levels and cognitive decline and dementia remain inconsistent (Glynn et al., 1999; Posner et al., 2002; Ruitenberg et al., 2001).

With increasing age, the effect of blood pressure on dementia risk is attenuated. This association may even become inverted suggesting a protective effect of higher blood pressure on cognition. Some studies have observed that blood pressure begins to decrease before clinical diagnosis of dementia and may decrease further as the disease advances (Hanon et al., 2005b; Qiu et al., 2005; Verghese et al., 2003). A study of persons 75 years and older, found that compared to individuals who were free of dementia, blood pressure was lower in those with a clinical diagnosis of Alzheimer's disease, and that the reduction in blood pressure was related to the severity of dementia (Guo et al., 1996). These results may present evidence of reverse causation due to neurovascular changes related to dementia including vessel stiffening due to atherosclerosis, weight loss, and presence of comorbidities such as heart failure that affect cardiac pump function leading to hypotension. In addition, presence of degenerative prefrontal lesions

associated with Alzheimer's disease can interfere with autonomic regulation of blood flow and may contribute to the fall in blood pressure (Obisesan, 2009).

Mechanisms through which arterial blood pressure in midlife can increase the risk of cognitive impairment and dementia relate to alterations of cerebral structure and function. Elevated blood pressure is associated with acceleration of atherosclerosis as well as medial thickening of cerebral vessels leading to cerebral white matter hypoperfusion, small vessel disease and infractions. It also affects vascular integrity of the blood-brain barrier and endothelial dysfunction. In turn these changes lead to protein excavation into the brain tissue causing cell damage and apoptosis, a reduction in neuronal or synaptic function, and an increase in extracellular Aβ accumulation resulting in cognitive deficits (Kalaria, 2010). Direct evidence from animal studies indicates that accumulation of Aβ is directly enhanced by hyperperfusion-induced vascular changes (Iadecola, 2004).

Lipids

The link between lipid levels and cognitive impairment depends on the type of lipid in question. Cholesterol, omega 3 fatty acids and triglycerides all affect the risk of cardiovascular disease. High levels of total cholesterol, low density lipoprotein (LDL) cholesterol and triglycerides raise the risk of cardiovascular disease, while high levels of high density lipoprotein (HDL) cholesterol are associated with a reduced risk of cardiovascular disease (Lloyd-Jones et al., 2010). The role of lipids in increasing the risk of dementia is debated and the exact mechanisms remain unclear. In relation to cognition, cholesterol is the most studied lipid as it is a known risk factor for atherosclerosis. High levels of circulating LDL cholesterol lead to carotid artery thickening and accumulation of plaques in arteries that aid production of β amyloid plaques and may also lead to silent infarctions (Panza et al., 2006). HDL cholesterol has a role in synapse maturation and plasticity and low levels have been linked to lower hippocampal volume (Michikawa, 2003; Wolf et al., 2004).

In cross sectional studies of older adults, the association of cholesterol and cognition is especially inconsistent. Early studies include a Finnish study of community elderly that reported an association between low serum total cholesterol and Alzheimer's disease, independent of *APOE* genotype (Kuusisto et al., 1997). Another cross sectional study of 1449 community elderly showed an inverse association between total cholesterol with incident Alzheimer's disease, again

independent of *APOE* genotype (Romas et al., 1999). In contrast, another study found that high total cholesterol was associated with Alzheimer's disease only in individuals who lacked the *APOE ε4* allele (Evans et al., 2000). The French Three-City study reported an association between higher total cholesterol levels and increased risk of non-Alzheimer's disease type dementia (Dufouil et al., 2005).

Results of prospective and longitudinal studies regarding the association between cholesterol levels and dementia are also somewhat conflicting. Most studies that assess cholesterol levels in midlife have indicated association between high cholesterol levels and increased risk of cognitive impairment or dementia (Kivipelto et al., 2002; Notkola et al., 1998), whereas some studies that consider cholesterol levels later in life have not found the same associations (Reitz et al., 2004; Tan et al., 2003). Analyses of the Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) study have shown raised midlife cholesterol levels greater than 6.5 mmol/L to be associated with increased risk of Alzheimer's disease, and hypercholesterolemia and *APOE* genotype to confer an additional risk in this association (Kivipelto et al., 2002). In addition, in a study of middle aged individuals followed up for an average of 21 years, high total cholesterol levels were associated with increased risk of MCI (Kivipelto et al., 2001a). Similarly, a long follow-up study of members of the Kaiser Permanante cohort reported an association between raised cholesterol levels measured in midlife (greater than 6.2 mmol/L) and diagnosis of Vascular Cognitive Impairment (VCI) and dementia 30 years later (Solomon et al., 2009).

Studies conducted in older populations point to different patterns of associations between lipid levels and risk of cognitive deficits and dementia. Investigations based on the Framingham study did not find an association between raised cholesterol levels and incident dementia (Tan et al., 2003). Similarly, an 18-year follow up study of a cohort of adults 70 years and older found increasing total cholesterol levels to be associated with a reduced risk of dementia (Mielke et al., 2005). A similar trend for a protective effect of increased serum total cholesterol and MCI was observed in a 3.5 year follow up study of older adults between 65 and 84 years of age (Solfrizzi et al., 2004).

These findings clearly demonstrate the importance of trajectory of serum cholesterol and the timing of its measurement over the life course in relation to the underlying course of cognitive impairment and dementia. A number of studies have noted a more marked progressive decrease

in serum cholesterol levels from midlife, in patients with dementia compared to those without (Solomon et al., 2007; Stewart et al., 2007). The reason for this observation may be related to the disease process and ongoing dementia pathology whereby several years before the apparition of clinical dementia, blood pressure and body mass index (BMI) may begin to decline, sometimes as a result of poorer nutritional status (Panza et al., 2006). Similar to the shift in blood pressure profiles with increasing age, here too, decreased cholesterol in the elderly may be an effect and not a cause of dementia. Regardless of these divergent findings, emerging evidence from clinical and histopathological studies suggest that aberrations of lipid metabolism are clearly involved in the pathophysiology of dementia (Matsuzaki et al., 2011; Pappolla et al., 2003) and their midlife rather than late life levels are important for cognitive health (Reynolds et al., 2010).

Smoking

Although the earliest studies acknowledged smoking as a risk factor for atherosclerosis and cerebrovascular accidents that could lead to dementia (Shinton et al., 1989), many subsequent case control studies reported smoking as a protective factor against Alzheimer's disease, supporting the neuroprotective effect of nicotine (Brenner et al., 1993; Ferini-Strambi et al., 1990; Graves et al., 1991; Tyas, 1996). Thereafter, these findings were attributed to selection bias and involvement of the tobacco industry (Cataldo et al., 2010; Hernan et al., 2008). While a meta-analysis of cross sectional studies with funding from the tobacco industry found an inverse association between smoking and risk of dementia, an analysis of 14 cohort studies without such affiliations showed a considerable increase in risk of dementia associated with smoking (Cataldo et al., 2010).

Prospective studies on dementia free cohorts have provided compelling evidence for the association of smoking with cognitive deficits and dementia (Debette et al., 2011; Merchant et al., 1999; Ott et al., 1998). Of note are findings of the Honolulu-Asia Aging Study that reported a dose-dependent association between midlife smoking and dementia; risk of dementia in this cohort increased with increased pack-years of cigarette smoking. Furthermore, neuropathologic data from autopsied brains revealed an increase in the number of neutritic plaques with smoking level (Tyas et al., 2003). A meta-analysis of 19 prospective studies concluded that risk of incident dementia was nearly two times greater in smokers compared to those who had never smoked (Anstey et al., 2007). In older adults free of dementia, smoking may accelerate cognitive decline.

One study found that annual decline in Mini Mental State Examination (MMSE) scores in older adults without dementia was greater in current smokers compared to former smokers, and former smokers compared to those who never smoked (Ott et al., 2004). Smoking in midlife has also been consistently shown to be associated with lower cognitive performance and faster cognitive decline (Kalmijn et al., 2002; Knopman et al., 2001; Richards et al., 2003b; Sabia et al., 2008; Sabia et al., 2012).

Smoking can affect cognition through both vascular and neurodegenerative mechanisms. It has a considerable role in promoting atherosclerosis and cerebrovascular disease and is also linked to white matter changes, brain atrophy and hypoperfusion (Debette et al., 2011; Meyer et al., 1999), all linked to cognitive deficits. Neurodegenerative mechanisms include increased inflammatory immune system responses leading to oxidative damage through activation of phagocytes. Increased oxidative stress may cause neuronal degeneration and plaque formation.

Physical activity

Physical exercise is widely promoted to improve physical health, and there is emerging consensus regarding its association with cognitive deficits and dementia (Morgan et al., 2012). The role of exercise in cognitive health is multifactorial; several mechanisms have been proposed. Physical activity reduces the rate and severity of CVD risk factors such as obesity, hypertension and diabetes mellitus each of which is independently associated with cognitive impairment. In addition, exercise improves synaptic plasticity and aerobic fitness by increasing cerebral blood flow and oxygen extraction. Neuroimaging studies suggest that aerobic fitness in older adults is associated with less grey matter loss. Higher aerobic fitness levels have also been shown to be associated with larger hippocampus volume. In addition, exercise may improve cognition by upregulating brain derived neurotrophic factors and synaptic proliferation. Increased physical activity has been linked to decreased neocortical atrophy independent of atherosclerosis and brain infarcts (Nagahara et al., 2009).

The majority of epidemiological studies have reported that physical activity at various ages is associated with a lower risk of cognitive impairment and dementia later in life. Physically active elderly have slower rates of cognitive decline compared to those who are inactive (Laurin et al., 2001; Yaffe et al., 2001). In midlife, physical activity is associated with lower risk of cognitive impairment and dementia in late life (Rovio et al., 2005). The few studies that have

examined the role of early life physical activity have also reported that physically inactive teenagers and young adults have poorer cognitive performance and higher prevalence of cognitive impairment later in life (Dik et al., 2003; Middleton et al., 2010; Richards et al., 2003a).

Body mass index and adiposity

Early studies of the relation of BMI to cognition and dementia reported that low BMI was a risk factor for brain atrophy and dementia (Grundman et al., 1996; White et al., 1996; White et al., 1998). Others reported a U-shaped relationship between BMI and cognition in younger individuals and an inverse association in older persons (Luchsinger et al., 2007b). These observations have been attributed to the age at which BMI was assessed; the association of BMI with the risk of dementia seems to be modified by age. Weight loss caused by cognitive impairment (e.g. due to malnourishment or depression) is often observed in the years preceding dementia onset (Gustafson et al., 2009; Luchsinger et al., 2007b). Some studies suggest that weight reduction during early Alzheimer's disease is caused by the reduction in lean body mass and not adiposity (Burns et al., 2010). Even obese individuals may lose up to 50% of their body weight in the years prior to clinical diagnosis of dementia (Wang, 2002).

More recently, prospective studies with longer follow up periods and younger participants at baseline have largely shown higher BMI in midlife to be a risk factor for cognitive impairment and dementia (Gustafson, 2006). A 27-year longitudinal population-based study showed a positive association between BMI in midlife and risk of dementia independent of other CVD risk factors (Whitmer et al., 2005a). Another study with an 18-year follow up reported an increase of 36% in Alzheimer's disease risk for every 1 point higher BMI at 70 years (Gustafson et al., 2003). Further, both overweight and obesity in midlife have been shown to independently increase the risk of both Alzheimer's disease and vascular dementia (Xu et al., 2011). In addition to BMI, central obesity in midlife measured by waist circumference thought to be a better marker of adiposity than BMI, has similarly been associated with increased risk of dementia in old age (Luchsinger et al., 2007a; Whitmer et al., 2008).

There are several possible mechanisms underlying the association between obesity with cognitive impairment and dementia. Some are through vascular pathways, relating to increased cerebrovascular risk associated with adiposity, and some are through inflammatory pathways. Obesity is associated with vascular and coronary endothelial dysfunction, carotid artery wall

thickening and arterial stiffness, ventricular hypertrophy, increased sympathetic activity, high cardiac output, and platelet aggregation. In addition higher adiposity leads to an altered inflammatory state. Adipose tissue is the largest endocrine organ that secretes inflammatory cytokines and growth hormones (e.g. adipocytokines, interleukins, and C-reactive protein). For example, leptin, an adipocytokine is involved in deposition of amyloid β-42 which plays a role in neurodegenerative processes (Gustafson, 2006).

Type 2 diabetes

There is some inconsistency in the studies of prevalence of dementia in individuals with diabetes (Akomolafe et al., 2006; Leibson et al., 1997; Ott et al., 1999a; Tyas et al., 2001; Yoshitake et al., 1995). However, most of these studies were carried out in populations of older adults and factors such as survival bias and failure to account for the duration of diabetes may have affected their results. Findings from incidence studies have been more consistent suggesting that dementia is 50 to 100% more likely in individuals with diabetes. This association appears to be stronger for patients with vascular dementia than Alzheimer's disease (Biessels et al., 2006). There is also some evidence that *APOE ε4* carriers with diabetes are at an additional risk of cognitive deficits (Peila et al., 2002; Xu et al., 2004).

Further longitudinal studies have largely confirmed the positive association between type 2 diabetes and risk of cognitive impairment and dementia. A meta-analysis of longitudinal studies examining the relationship between type 2 diabetes and Alzheimer's disease found that it increases the risk of Alzheimer's disease by 54% (Profenno et al., 2010). In addition, studies based on midlife assessment of diabetic status have reported similar association between diabetes and increased risk of late life cognitive impairment and dementia (Kivipelto et al., 2001b; Whitmer et al., 2005b). In one study, midlife diabetes was shown to double the risk of dementia three decades later (Schnaider et al., 2004). In non-elderly populations without dementia, diabetes is associated with greater cognitive decline (Debette et al., 2011; Knopman et al., 2001) as well as subclinical cerebrovascular pathology (Debette et al., 2011; Knopman et al., 2011).

Diabetes is an established risk factor for cardiovascular disease and is often accompanied by other risk factors such as hypertension and dyslipidemia. Therefore it may lead to cognitive deficits through vascular mechanisms such as those related to ischemic cerebrovascular disease. It can, in addition, affect cognitive function independent of its role as a CVD risk factor. Impaired

glycemic control, both hyperglycemic and hypoglycemic states, and hyperinsulinaemia can affect cognition. For example, insulin appears to stimulate Aβ secretion and at the same time inhibit degradation and clearance of Aβ from the brain by competing with Aβ for insulin degrading enzyme (IDE) (Qiu et al., 2006b). This pathway appears to be particularly important; insulin resistance even in the absence of diabetes has been found to be associated with Alzheimer's disease (Luchsinger et al., 2004; Xu et al., 2007). Histopathological evidence from autopsy and imaging studies have provided evidence for both neurodegenerative and vascular markers of dementia, showing that diabetic individuals have more evident cerebral amyloid angiopathy, greater hippocampal atrophy (Peila et al., 2002), and lacunar infarcts compared to non diabetic persons (van et al., 2006).

Metabolic syndrome

The metabolic syndrome is a constellation of five cardio-metabolic abnormalities that include abdominal obesity, elevated triglycerides, low HDL cholesterol levels, hypertension and hyperglycemia (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults., 2001). It has been associated with an increased risk of atherosclerosis, ischemic heart disease and cerebrovascular disease including silent brain infarctions (Bokura et al., 2008; Kwon et al., 2006; Kwon et al., 2009). Although there is substantial evidence for the association of individual components of the metabolic syndrome and cognitive impairment, few studies have examined the link between the metabolic syndrome itself, and cognitive impairment or dementia. Even fewer studies have examined whether the metabolic syndrome offers a higher predictive value for cognitive deficits and dementia than its individual components.

Studies of the link between metabolic syndrome and cognition have been largely based on older populations. In participants of the Longitudinal Aging Study Amsterdam (LASA), 65 years and older, metabolic syndrome was associated with poorer cognitive functioning particularly in those with higher levels of inflammatory markers (Dik et al., 2007). In another population-based study of older adults (69 years and older) those with metabolic syndrome had twice the odds of having Alzheimer's disease than those without (Vanhanen et al., 2006). The few studies with prospective or longitudinal design have reported an association between metabolic syndrome with dementia (Kalmijn et al., 2000; Raffaitin et al., 2009) and cognitive decline (Yaffe et al., 2004; Yaffe et al., 2007). In the French Three-City study, metabolic syndrome in individuals 65 years

and over had a negative impact on global cognitive decline after 4 years (Raffaitin et al., 2011). In addition, middle aged adults with persistent metabolic syndrome over 10 years have poorer cognitive functioning in late midlife (Akbaraly et al., 2010). Furthermore there is some evidence to suggest that the composite measure of the metabolic syndrome is associated with a greater risk of cognitive impairment and cognitive decline than its individual components (Raffaitin et al., 2011; Yaffe et al., 2004; Yaffe et al., 2007).

Genetic risk factors

Dementia, in particular Alzheimer's disease is highly heritable but genetically complex. A number of genes related to vascular disease that lead to an increase in susceptibility for sporadic Alzheimer's disease have been identified. The first such gene to be discovered was *APOE* that is located on chromosome 19 and occurs in three common alleles (ε2, ε3, ε4). APOE protein is a major constituent in very low-density lipoproteins that plays a role in lipid metabolism and the transport of cholesterol among various cells including neurons. Plasma levels of APOE have been shown to depend upon *APOE* genotype (Yasuno et al., 2011). An allelic variant of the *APOE ε4* has been found to be associated with atherosclerosis and coronary artery disease (Eichner et al., 2002). This association is thought to be particularly related to increased levels of total cholesterol and LDL cholesterol.

The ε4 variant of the *APOE* is the largest known genetic risk factor for familial and sporadic late-onset Alzheimer's disease and is associated with early onset Alzheimer's disease in a dose-dependent manner (Blacker et al., 1997; Henderson et al., 1995; Hsiung et al., 2004; Myers et al., 1996) and also predicts rate of cognitive decline in Alzheimer's disease (Martins et al., 2005). In addition, *APOE ε4* carriers have been reported to have higher rates of cognitive decline than non carriers (Caselli et al., 2007). Age related memory decline in *APOE ε4* carriers diverges from that of non-carriers before the age of 60 years despite normal clinical status in relation to dementia (Caselli et al., 2009).

While the exact mechanisms of the effect of APOE on the brain remain to be fully determined, several pathways leading to *APOE ε4* mediated amyloid aggregation and clearance and tau hyperphosphorylation have been proposed (Panza et al., 2006; Yanagisawa, 2002). Other prevailing evidence suggests APOE's role in homeostasis of cholesterol and phospholipids,

synaptic plasticity, neuroinflammation, amyloid metabolism, accumulation of neurofibrillary tangles and neuronal survival (Kim et al., 2009; Poirier et al., 2008).

APOE genotype may also modulate the association between CVD risk factors and dementia. Numerous studies suggest that the association between dementia and heart disease (Hofman et al., 1997), stroke (Slooter et al., 1997), hypertension (Qiu et al., 2003), and diabetes (Peila et al., 2002) may be particularly strong among *APOE ε4* carriers. One study reported that persons with stroke who were *APOE ε4* negative had two times higher odds of developing dementia, while those with stroke who were *APOE ε4* carriers had 15 times higher odds of dementia (Llewellyn et al., 2010). Other studies suggest an additive or synergistic effect of *APOE* and CVD risk factors and disease on dementia (Jin et al., 2008) and cognitive decline (Yasuno et al., 2012). These findings points to the complex interplay between *APOE* and CVD risk through different and potentially independent mechanisms leading to brain pathology and cognitive impairment.

Although for two decades, *APOE* remained the most robustly replicated gene for Alzheimer's disease, the recent advent of genome-wide association studies (GWAS) has uncovered additional risk marker alleles for Alzheimer's disease but they have also confirmed that *APOE* is the single most important genetic risk gene for late onset Alzheimer's disease (Ikram et al., 2012). In addition to the rare autosomal dominant mutations (*APP*, *PSEN1*, *PSEN2*), and *APOE* as a common variant with moderate to large effect on risk of Alzheimer's disease, early GWA studies emerging in 2007 identified over 500 common variants with smaller effects (Coon et al., 2007; Grupe et al., 2007; Reiman et al., 2007; Bertram et al., 2007). However not all have been subsequently replicated in other studies partly due to lack of power in most studies to detect small genetic effects (Colhoun et al., 2003). Recently large-scale GWA studies and meta-analyses combining data from over 40000 individuals have provided compelling evidence for the association of four susceptibility genes (*PCALM, CLU*, *BIN1, CR1*) and Alzheimer's disease (Lambert et al., 2009; Harold et al., 2009; Seshadri et al., 2010) . Following these studies, another five loci (*ABCA7*, *MS4A6A*/*MS4A4E*, *EPHA1*, *CD33*, and *CD2AP*) were discovered (Hollingworth et al., 2011; Naj et al., 2011), although the functional variation contributing to Alzheimer's disease susceptibility at these newly identified loci remains to be fully characterized. However, potential disease related functional effects may include pathways related to amyloid clearance, lipid processing and transport, endocytosis and intracellular

trafficking and inflammatory responses (Hollingworth et al., 2010). For example *APOE* and *CLU* are both brain apolipoproteins; *PICALM* and *BIN1* are involved in cell membrane trafficking, and *CR1, CD33,* and *EPHA1* affects the immune system (Morgan et al., 2011).

Much of the heritability of Alzheimer's disease remains unexplained suggesting that many more genetic variants are still to be discovered. Gene-gene and gene-environment interactions, effects that are difficult to study as they necessitates very large datasets to carry out GWA studies, are also likely to explain much of the missing heritability of Alzheimer's disease (Ikram et al., 2012). However, genetic research has already made substantial breakthroughs in unraveling the genetic architecture of Alzheimer's disease pointing to biological pathways not previously implicated in Alzheimer's disease pathology. Further advances in genetic sequencing techniques will continue to refine our understanding of the genetic architecture of Alzheimer's disease. Moreover, with the continued recognition of the preclinical phase of dementia and increasing availability and characterization of the time course of various preclinical biomarkers or endophenotypes (e.g. CSF measures of β amyloid and phosphorylated tau) during the preclinical phase, it will be possible to perform large-scale genetic studies on these endophenotypes (Ikram et al., 2012).

In summary, a range of CVD risk factors and diseases have been associated with cognitive outcomes. However, the association of major CVD risk factors with cognitive outcomes varies with age, and the evidence for this association appears to be more consistent when the risk factors are measured in midlife. In the case of blood pressure and dyslipidemia, the observed interaction with age clearly illustrates that timing of such measures is critical. Numerous studies have established that midlife CVD risk factors constitute particularly important risk factors for cognitive health and have highlighted the importance a life-course approach to studying these risk factors (Debette et al., 2011; Kivipelto et al., 2001b; Reynolds et al., 2010; Stewart et al., 2007; Vuorinen et al., 2011; Xu et al., 2011). Indeed, population attributable risk of dementia for CVD risk factors measured at middle-age (40 to 65 years) is estimated to be higher than when they are measured in late life (65 years and over) (Kloppenborg et al., 2008). The reason for these findings may be due to the involvement of different biological mechanisms at different ages but also the inability to establish length of exposure to the risk factor. When CVD risk factors are measured in late life, it is impossible to determine the start and course of exposure. Thus in studies examining

CVD risk factors and cognition, age at exposure and duration of exposure are both critical variables.

I.2.2 Cardiovascular disease risk factors and cognition: importance of risk aggregation

Cardiovascular disease risk factors seldom exist alone. For example diabetes, insulin resistance, dyslipidemia and hypertension often coexist and it is difficult to separate their effects in observational studies. Most of the studies described above, examined the independent association between one CVD risk factor and cognitive impairment or dementia disregarding other co-occurring risk factors. Studies that took other CVD risk factors into account in their analyses simply adjusted for these risk factors but often lacked data for all major risk factors. Thus, this approach does not consider the possibility that CVD risk factors can cluster and increase CVD risk in an additive or synergistic manner. Several studies are beginning to explore the association of aggregation of CVD risk factors with cognitive impairment and dementia. One study found clusters including hypertension and heart disease increased the risk of Alzheimer's disease, and that the risk increased with the number of risk factors (Luchsinger et al., 2005).

In midlife, clustering of CVD risk factors including obesity, hypertension and hypercholesterolemia have been found to increase the risk of dementia in an additive manner. Individuals with all three risk factors had nearly 6 times higher risk of dementia after 21 years, compared to those with no risk factors (Kivipelto et al., 2005). Another study reported that multiple CVD risk factors at midlife substantially increased risk of dementia later, in a dose-dependent manner (Whitmer et al., 2005b). In addition, as previously discussed, the concept of metabolic syndrome intends to capture the common clustering of CVD risk factors and has been shown to confer greater risk of cognitive decline than its individual components (Yaffe, 2007).

I.3 Risk assessment and risk Scores

The concept of risk assessment using multiple risk factors simultaneously was initially developed by the Framingham Heart study over 50 years ago. Recognition of the role of major risk factors for cardiovascular disease, and their tendency to cluster and interact to increase cardiovascular risk, led to the creation of multivariable risk prediction models. The goal of risk assessment models is to determine the combination of factors that is most predictive of future risk of the outcome. In practice, they provide a quantitative estimate of risk, or the probability of a person experiencing the outcome (e.g. coronary heart disease) within a given time frame (e.g. next 10

years). Based on their risk, individuals may then be categorized as being at high, moderate or low risk of developing the condition (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults., 2001). The Framingham study has developed many risk scores for the prediction of different outcomes including specific cardiovascular and cerebrovascular diseases such as atrial fibrillation, coronary heart disease, congestive heart failure, and stroke (D'Agostino, Sr. et al., 2008; Wilson et al., 1998; Wolf et al., 1991b). These risk scores have been adapted for use in primary care in various user-friendly forms such as charts, computer programs and online tools and have been adopted in clinical practice guidelines and recommendations (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults., 2001). Their aim is to identify at risk asymptomatic individuals and tailor therapeutic strategies based on their risk profile.

Although cardiovascular risk scores are among the most widely known and validated risk scores, risk prediction models are not specific to cardiovascular diseases. In reality, almost all diseases and health-related outcomes are multifactorial and require multivariable risk assessment models to optimize risk prediction and improve targeting of preventive and treatment strategies; where there is a need to assess risk of disease (e.g. diabetes mellitus, osteoporosis, depression, breast cancer) or other health-related outcome (e.g. falls in the elderly), risk assessment models and risk scores may be used (Gail et al., 1989; Kanis, 2002; Noble et al., 2011). In addition to their role in screening and primary prevention, risk scores may be used in secondary prevention of disease, for example to assess risk of stroke or death after atrial fibrillation, depression after stroke, or cardiovascular disease in patients with type 2 diabetes (Berg et al., 2009; van et al., 2012; Wang et al., 2003).

With the increasing emphasis on primary prevention, many research groups have used their study cohorts to develop prediction models. For common diseases in particular, there may be dozens of risk scores available, aimed at various users including both patients and physicians. With research and advances in laboratory and imaging techniques, novel risk factors and markers for different diseases continue to be identified. Some risk scores are subsequently updated to incorporate these risk factors in order to refine and improve predictive performance of the model. However most risk assessment tools are underused because they have not been validated in populations other than that used to develop the model, or they require information on risk factors that are not routinely available to the user (Muller-Riemenschneider et al., 2010; Noble et al.,

2011). Other barriers to their routine use in primary care include time constraints, lack of physician knowledge or perceived accuracy of the risk score, and lack of accompanying recommendations to guide decision making for risk modification (Muller-Riemenschneider et al., 2010).

In addition, although studies have commonly compared two or more existing risk scores, particularly in the cardiovascular field (Coleman et al., 2007; Collins et al., 2009; Gale et al., 2009; Jensen et al., 2012; Ketola et al., 2010; Liu et al., 2004), very few systematic reviews and comparative studies to date, have evaluated relative effectiveness and predictive utility of all available risk scores for an outcome (Brindle et al., 2006; Noble et al., 2011; Stephan et al., 2010). While it is unlikely that there is one risk score that performs best across all populations and settings, even in similar settings evidence for use of a particular risk score is often lacking.

I.3.1 Risk scores for dementia

Various prediction models for dementia have been proposed, mainly for use in the older population (Barnes et al., 2009a; Hensel et al., 2007a; Hensel et al., 2007b; Hensel et al., 2007c; Hogan et al., 2000; Holtzer et al., 2008; Jungwirth et al., 2009; Nakata et al., 2009; Reitz et al., 2010). These risk prediction models have used a variety of approaches: cognitive models are based only on cognitive profiles using one or more neuropsychological tests believed to be good predictors of future dementia; health based models are derived from demographic (age, sex, education), life style (physical activity), cardiovascular (blood pressure, cholesterol level) and genetic (*APOE* allele) factors; multifactor models use a combination of neuropsychological testing, health based factors, neuroimaging, and sometimes self reported memory difficulties (Stephan et al., 2010). However, major differences in the methods used to develop these risk model such as study cohort, neuropsychological tests used, dementia outcomes considered (Alzheimer's disease, Vascular dementia or mixed subtypes), and follow up times make these risk models incomparable. Furthermore, these risk indices are of limited use due to lack of external validation outside the sample from which they were derived, and most, particularly the single factor models, have only low to moderate predictive accuracy (sensitivity and specificity <90%) (Stephan et al., 2010).

Two dementia risk assessment tools that address some of the constraints of the previous risk models have recently been developed (Brandt et al., 2011; Reitz et al., 2010). The Summary risk score for the prediction of Alzheimer's disease in elderly persons uses demographic (age,

sex, education, ethnicity), and CVD risk factors (*APOE ε4* genotype, history of diabetes, hypertension, smoking, HDL cholesterol levels, and waist to hip ratio) to estimate risk of late-onset Alzheimer's disease, and has moderate to high predictive accuracy (Reitz et al., 2010). The other, an internet-based dementia risk assessment tool (DRA) that uses demographic (age, sex, education), medical history (hypertension, diabetes, stroke, traumatic brain injury, Parkinson's disease, epilepsy etc), perceived cognitive functioning, and emotional symptoms (depression and anxiety) aims to provide a brief self-assessment tool that does not require a clinical assessment (Brandt et al., 2011).

A dementia risk score designed to be administered to middle-aged adults (40 to 64 years) has also been developed (Kivipelto et al., 2006). This Midlife dementia risk score is based on the Finnish Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study and uses a combination of demographic (age, sex, education), behavioral (physical activity), cardiovascular (obesity, hypertension and hypercholesterolemia) and genetic (*APOE* genotype) risk factors to predict risk of dementia 20 years later. This dementia risk prediction model has moderate sensitivity (0.77) and specificity (0.63) but its validity and reliability in other populations are yet to be established. One study evaluating the performance of this dementia risk score found that it predicted cognitive impairment after 15 years in a middle-aged (50-64 years) dementia free population (Reijmer et al., 2011b). Nonetheless, its focus on midlife rather than late life risk factors makes it particularly helpful in early identification of high-risk individuals and providing intervention options for risk factor modification.

As early identification of individuals who are at high risk of dementia gains increasing importance, the need to improve dementia risk prediction models becomes vital. At the same time, there is a need to strike a balance between predictive accuracy of risk models for dementia and their feasibility for use in primary care. For example, the Late-Life Dementia Risk Index that was recently developed to be a 'gold-standard' for predicting dementia risk in late life, has higher predictive accuracy than most other dementia risk models. Although it may offer a more in-depth approach to dementia screening, it is impractical to administer in most settings as it requires several measures (e.g. cerebral MRI and carotid artery ultrasound) that are not readily available or may be time-consuming and costly to obtain (Barnes et al., 2009a; Barnes et al., 2009b). As a result, this and other dementia risk scores remain unsuitable for use in most clinical settings or population based studies.

Due to their limitations and the lack of evidence for benefit of general screening, dementia risk scores are not formally advocated for assessing the risk of dementia in the general population (Brayne, 2007). Furthermore, despite the recognition of the importance of early identification of cognitive impairment and consensus based recommendations, there are no commonly agreed standards for identifying cognitive impairment in its early stages (Hachinski et al., 2006).

I.3.2 Other risk scores for cognitive assessment

Although commonly used cardiovascular risk scores were not originally developed to predict cognition, as the role of cardiovascular risk factors in the development of cognitive impairment and dementia is increasingly recognized, their use for assessment of cognitive outcomes is increasingly noted. Moreover, cardiovascular risk scores may offer a somewhat more feasible approach to risk assessment since many are well known, have been repeatedly validated (for cardiovascular outcomes) in different populations, and use readily available information to estimate risk.

The Framingham cardiovascular risk scores (e.g. for stroke and CHD) may be particularly suitable for this purpose due to their established reliability, extensive validation and their refined scoring system. Unlike indices that stratify risk into discrete broad categories (e.g. low, moderate, and high risk categories) (Barnes et al., 2009a), in the Framingham scoring system individual risk factors are additive in their predictive power and cumulative global risk is determined based on number and level of each risk factor (Wilson et al., 1998). Thus the continuous nature of risk is captured by the risk index. While accumulation of multiple risk factors may increase the risk of a cardiovascular event short term, long-term exposure to a single risk factor may confer similar or higher risk. The Framingham risk indices allow determination of risk for different time frames, for example, 10-year or 30-year risk of general cardiovascular disease (D'Agostino SR et al., 2008; Pencina et al., 2009). This makes the Framingham risk scores particularly useful to assess cardiovascular risk in individuals who may have only moderately elevated (i.e. subclinical) risk factors that may confer similar risk as having one greatly elevated risk factor. The Framingham Stroke Risk Profile (FSRP) has been shown to predict onset and progression of subclinical atherosclerosis (DeFilippis et al., 2011), and may thus be useful in assessing mild or subclinical vascular risk.

Few studies to date have evaluated cardiovascular risk scores in relation to cognition (Brady et al., 2001; Elias et al., 2004a; Llewellyn et al., 2008; Seshadri et al., 2004; Unverzagt et

al., 2011). In the earliest study, the FSRP predicted 3-year decline in semantic verbal fluency in a sample of 235 older men (Brady et al., 2001). Among 2175 stroke and dementia free participants of the Framingham Offspring Study, higher 10-year risk of stroke as determined by the FSRP was associated with poorer performance on multiple cognitive tests including abstract reasoning, visual spatial memory, visual organization, concentration, visual scanning and tracking (Elias et al., 2004a). In the same cohort, those with higher stroke risk had lower total cerebral brain volume ratio (TCBVr) determined from quantitative MRI (Seshadri et al., 2004). Similarly, among the participants of the English Longitudinal Study of Aging (ELSA), aged 50 years and over, higher stroke risk using a modified version of the FSRP was associated with poorer performance on tests of immediate and delayed verbal memory, semantic verbal fluency, and processing speed (Llewellyn et al., 2008). Finally, in a 4-year follow up study of a large and diverse cohort of individuals who were cognitively normal at baseline, increased stroke risk as measured by the FSRP was associated with incident cognitive impairment (Unverzagt et al., 2011).

There is arguably a dearth of studies evaluating the predictive utility of cardiovascular risk scores in assessment of cognition using a longitudinal design. The studies described above, all using the FSRP, have important limitations including their cross sectional design (Elias et al., 2004a; Llewellyn et al., 2008) and small selective study population and short follow up time (Brady et al., 2001). The study with the longer follow up period (4 years) and repeated measures used a single cognitive test to determine incident cognitive impairment (Unverzagt et al., 2011).

I.4 Research objectives

The overall objective of this thesis is to study the association of major CVD risk factors in relation to cognitive aging. It draws on three important points: 1) timing of assessment of risk factors 2) clustering of CVD risk factors 3) longitudinal assessment of cognition using repeated measures.

A number of cross sectional and prospective studies based on the Whitehall II study, the cohort studied in this thesis have examined associations between midlife cardiovascular risk factors and disease in relation to cognition (Akbaraly et al., 2010; Britton et al., 2004; Sabia et al., 2008; Sabia et al., 2009; Singh-Manoux et al., 2003; Singh-Manoux et al., 2005; Singh-Manoux et al., 2008a; Singh-Manoux et al., 2008b). However, longitudinal examination of cognition in relation to CVD risk factors has recently become possible with the completion of the third phase

of cognitive assessment. The association of some life style related risk factors (smoking) with long-term cognitive change has subsequently been examined (Sabia et al., 2012). While the focus of this thesis is on the conjoint influence of multiple risk factors and measures of aggregate CVD risk (i.e. risk scores), longitudinal associations between individual risk factor components of the risk scores (e.g. blood pressure and cholesterol levels) are also reported and as such provide the first longitudinal examination of these risk factors in this cohort. This work therefore addresses some major gaps in the literature by examining the role of major CVD risk factors in a middle aged population and cognitive change over a long time period (10 years) with a specific focus on risk assessment and use of cardiovascular risk scores. Specific objectives are:

1) To examine the association of the metabolic syndrome with cognitive function and decline. The metabolic syndrome comprised of 5 cardiovascular risk factors has been proposed as a construct capturing clustering of risk factors and has been associated with increased risk of cardiovascular events but its association with longitudinal cognitive decline remains unexamined.
2) To examine the association between cardiovascular risk as measured by two well known risk scores; the Framingham General Cardiovascular Risk Profile, and the Framingham Stroke Risk Profile, with cognitive function and cognitive change over 10 years. In addition, the association between the individual components of the risk scores and cognition will be assessed.
3) To compare the aforementioned cardiovascular risk scores with the CAIDE dementia risk score to determine their respective predictive utility. Neither cardiovascular risk scores nor the dementia risk score have been adequately studied in non-elderly populations and their relative performance remains unknown. This part of the thesis aims to establish whether cardiovascular risk scores may be a better means of assessing cognition, particularly cognitive change over time, in a middle aged population.

CHAPTER II: METHODS

II. 1 Study population

This thesis is based on data from the Whitehall II study, a prospective occupational cohort study set up in 1985 as a follow-up to the original Whitehall study that was established in 1960 in London (Marmot et al., 2005). The target population of the Whitehall II study was all civil service workers (n=14121), aged 35 to 55 years working in London offices of 20 Whitehall departments between 1985 and 1988. Among those invited, 73% (n=10308; 6895 men and 3413 women) accepted to participate. Compared to responders, non-responders at baseline (phase 1) had a mortality hazard double that for responders. Age and sex adjusted all-cause mortality hazard ratio for phase 1 non-responders was 2.3 (95 % CI=1.73, 2.39) (Ferrie et al., 2009). This excess mortality may be driven by various common causes of ill-health, caring or accessibility but since this information is not available for non-responders at baseline of the Whitehall II study, it is not possible to further examine characteristics of non-responders at baseline (Ferrie et al., 2009).

Phase 1 of the study (1985-1988) involved a medical examination and a self-administered questionnaire that collected sociodemographic data, health behaviors and psychosocial and social participation, work characteristics, medical history, and general health information. The clinical examination collected anthropomorphic and biological measures including height, weight, blood pressure, glucose, lipids etc. Over the follow-up, measures of subclinical cardiovascular disease using ultrasound, electrocardiograms, various biological markers of cardiovascular disease (e.g. fibrinogen, factor VIIc), and genotyping (e.g. *APOE*) were also performed. Subsequent phases alternated between a mailed questionnaire only (Phases 2 (1988-1990), 4 (1995-1996), 6 (2001) and 8 (2006)), and mailed questionnaire plus a clinical examination (Phases 3 (1991-1994), 5 (1997-1999), 7 (2002-2004), and 9 (2008-2009)). Regular contacts are maintained with the cohort to track changes in health states and optimize data collection. From phase 4 onwards, a brief telephone questionnaire was administered to non-responders and starting from phase 7 home screenings by trained study nurses were offered to participants who could not travel to the clinic. Cognitive assessments were added to the clinical examination at phase 5 and were repeated at phases 7 and 9 (Figure 4). The University College London Research Ethics Committee reviewed and approved the study, and each participant gave written informed consent.

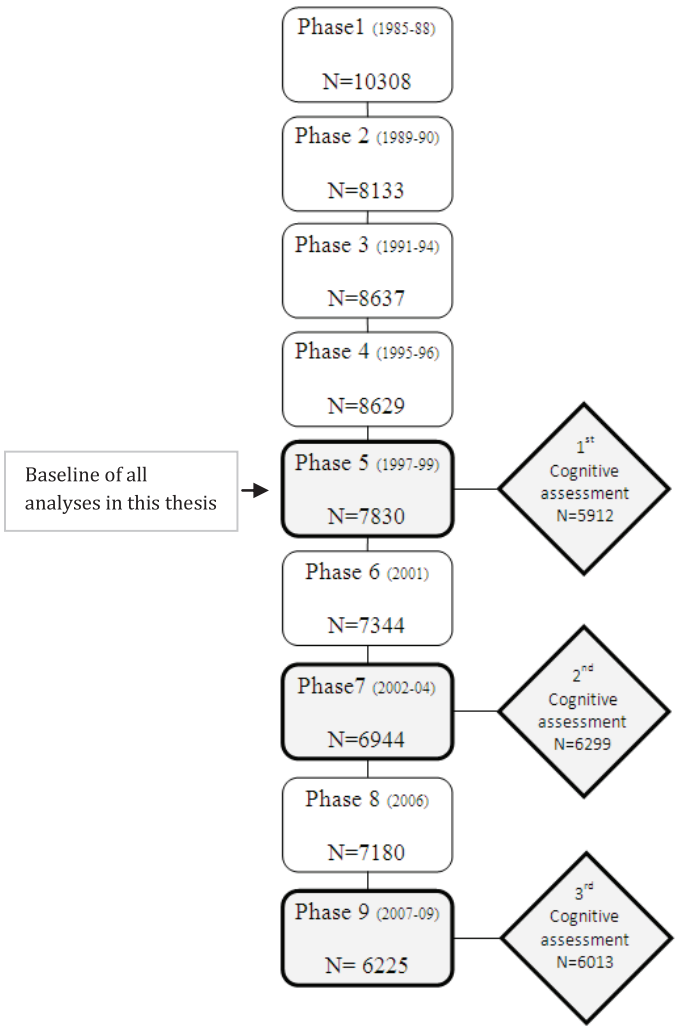

Figure 4. Phases of data collection in the Whitehall II study

II.2 Measures

II.2.1 Assessment of cognition

The cognitive test battery was chosen to be appropriate for use in this middle aged population. At the three phases of cognitive assessment-phases 5, 7, and 9, participants had a mean age of 56 years (range: 45 to 69), 61 years (range: 50-74), and 66 years (range: 55-79) respectively. The cognitive test battery is composed of five tests chosen to assess cognition in various distinct domains that were administered to participants who gave informed consent (i.e. who were not cognitively impaired). A brief description of each test appears below:

The Alice Heim 4-I (AH4-I) is composed of a series of 65 verbal and mathematical reasoning items of increasing difficulty (Heim AW, 1970). It tests inductive reasoning, the ability to identify patterns and infer principles and rules. Participants were given 10 minutes to answer as many questions as they could. Therefore the time dependent nature of the test concurrently assesses speed of reasoning which may be expected to decrease with age.

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

Verbal fluency was assessed using 2 tests; one for phonemic and the other for semantic fluency. Phonemic fluency was assessed via "S" words and semantic fluency via "animal" words. 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* administered in its multiple-choice format with 6 response choices. It consists of a list of 33 stimulus words requiring word matching and word definition, ordered by increasing difficulty (Raven, 1965). Participants were given 10 minutes for this test. Since it is a test of language skills learned and practiced over a life-time it is relatively unaffected by increasing age.

In addition to these five tests, The Mini Mental State Examination (MMSE) (Folstein et al., 1975), a test of global cognitive function, was administered at phase 5 to participants over the age of 60, and to all participants at phases 7 and 9. Although this test has been widely used in studies of cognitive aging, its use in this middle aged cohort is limited due to strong ceiling effects. At phase 5 nearly one third of participants achieved the maximum score of 30 on this test and thus the low degree of variability in scores does not allow an effective examination of inter-individual differences in cognitive performance. As the cohort ages, the MMSE is used to detect participants with possible MCI or dementia.

A score representing global cognition was created for the current analyses, using the five tests described above. For each test separately, raw scores were first standardized into z-scores (mean=0; standard deviation (SD) =1) using the baseline (phase 5) mean and standard deviation values in the entire cohort. Z-scores were then averaged to yield the global cognitive score.

Global scores constructed in this manner have been used in previous studies to minimize extent of measurement error on the individual tests (Wilson et al., 2010). In addition, since studies on cognition often use different cognitive tests, a global score would allow better comparability of results among studies. All participants with at least one cognitive measure over the three phases were included in the longitudinal analyses. Approximately 76% (n=7830) of the original participants of the Whitehall II study participated in phase 5 (questionnaire, clinical examination, or both) of the study when cognitive tests were introduced and 75% of these participants underwent cognitive testing (Table 1). Cognitive scores at phases 5, 7 and 9 are presented in Table 1.

Table 1. Cognitive scores at the three phases

		Phase 5 (n=5912)	Phase 7 (n=6299)	Phase 9 (n=6013)
Cognitive test	Range	Mean score (SD)		
Reasoning (AH4-I)	0-65	46.6 (11.2)	43.7 (11.2)	43.4 (11.2)
Memory	0-20	6.9 (2.4)	6.8 (2.4)	6.2 (2.3)
Semantic fluency (animals)	0-35	16.4 (4.2)	15.7 (4.1)	15.3 (3.9)
Phonemic fluency (Swords)	0-35	16.9 (4.5)	15.6 (3.9)	15.2 (3.8)
Vocabulary (Mill Hill)	0-33	24.9 (4.5)	24.9 (4.5)	25.2 (4.3)

II.2.2 Assessment of cardiovascular risk

Risk factors were drawn from questionnaire and clinical examination data at Phase 5. Their measurement was based on standard operating protocols as follows:

Venous blood was collected after either an 8 hour fast for participants presenting in the morning, or at least 4 hours after a light, fat free breakfast for those presenting in the afternoon. Serum for lipid analyses was refrigerated at -4^{o}C and assayed within 72 hours.

Diabetes was defined as a fasting glucose level $\geq$ 7.0 mmol/L or a 2 hour post-load glucose $\geq$ 11.1 mmol/L or reported doctor diagnosed diabetes, or use of diabetes medication (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus., 2003). Fasting blood glucose was measured using the glucose oxidase method (Cooper., 1973) on a YSI model 2300 StatPlus Analyzer (mean coefficient of variation 2.9-3.3%).

Cholesterol levels were measured using a Cobas FARA centrifugal analyzer (Roche Diagnostics System, Nutley, New Jersey).

HDL cholesterol levels were measured by precipitating non-HDL cholesterol with dextran sulfate-magnesium chloride with a centrifuge and measuring the cholesterol levels in the supernatant.

Serum triglyceride was determined by an enzymatic colorimetric method (glycerol phosphate oxidase-phenol + aminophenazone).

Systolic blood pressure (SBP) was measured twice, with the participant in the resting position after a 5-minute rest using a Hawksley random-zero sphygmomanometer (Lynjay Services, Worthing, United Kingdom). The average of the two readings was taken to determine systolic blood pressure. Information on use of *antihypertensive medication* was obtained from the questionnaires. It included use of diuretics, beta blockers, ACE-inhibitors, and calcium channel blockers.

Body mass index (BMI) was calculated as weight (kilograms) / height (meters) squared.

Atrial fibrillation and *left ventricular hypertrophy* diagnoses were based on a standard 12-lead ECG and the Minnesota Code Classification system for Electrocardiographic findings (atrial fibrillation: code 3-1 for High Amplitude R-waves; LVH: code 8-3-1 for Arrhythmias).

Cigarette smoking status was categorized into current smokers or past/non smokers.

APOE genotype was determined for a subset of participants (n=6156) using a standard polymerase chain reaction (PCR) assay of DNA extracted from blood using the salting out method (Miller et al., 1988).

Metabolic Syndrome

Metabolic Syndrome was defined according to the National Cholesterol Education Program-Adult Treatment Panel III criteria (2001), which requires the presence of three or more of the following cardio-metabolic parameters: (1) large waist circumference (women >88 cm and men >102 cm); (2) elevated triglycerides (≥150 mg/dL); (3) elevated blood pressure (>130 mm Hg systolic or >85 mm Hg diastolic blood pressure, or use of antihypertensive medication); (4) low HDL cholesterol (men <40 and women <50 mg/dL); (5) hyperglycemia (≥ 110 mg/dL or non fasting glycemia ≥200 mg/dL or antidiabetic medication) (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults., 2001).

Framingham General Cardiovascular Risk Profile

The Framingham general cardiovascular disease risk profile is a sex specific multivariable risk factor algorithm designed for use in primary care to assess general CVD risk. It provides an estimate of absolute risk of a first CVD event in individuals 30 to 74 years old without a CVD or a history of CVD at baseline. The CVD outcome includes coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, and heart failure (D'Agostino, Sr. et al., 2008). Its development was based on the prediction of 1174 CVD events over a 12-year follow up period involving 8491 participants (mean age 49 years) of the Framingham Heart study. Mathematical CVD risk functions were calculated using Cox proportional hazards regressions where CVD risk factors were related to the incidence of a first CVD event during a maximum of 12 years of follow up (D'Agostino, Sr. et al., 2008). These functions were then used to estimate 10-year absolute risk of CVD. Two models were developed, one based on all traditional risk factors and the other based on non-laboratory-based predictors. The components are:

- Age
- Diabetes
- Smoking
- Treated and untreated Systolic Blood Pressure
- Total cholesterol
- HDL cholesterol
- BMI replacing lipids in a simpler model

Risk can be estimated directly from the Cox model using the general formula provided, or from a score sheet. Both methods generate similar estimates.

General formula:

$$\hat{p} = 1 - S_0(t)^{\exp(\Sigma_{i=1}^{p} \beta_i X_i - \Sigma_{i=1}^{p} \beta_i \bar{X}_i)},$$

Where $S_0(t)$ is baseline survival at follow up time t (t=10 years), β_i is the estimated regression coefficient, Xi is the log-transformed value of the ith risk factor if continuous, X_i is the corresponding mean, and p is the number of risk factors (D'Agostino, Sr. et al., 2008).

The score sheet (below) is an example of an office-based algorithm that can be used to calculate raw scores which can then be converted to 10-year risk or predicted probability of incident CVD expressed as a percentage.

CVD points for men

CVD Points							
Points	**Age**	**HDL**	**Total Cholesterol**	**SBP Not Treated**	**SBP Treated**	**Smoker**	**Diabetic**
-2		60 +		<120			
-1		50-59			0		
0	30-34	45-49	<160	120-129	<120	No	No
1		35-44	160-199	130-139			
2	35-39	<35	200-239	140-159	120-129		
3			240-279	160+	130-139		Yes
4			280+		140-159	Yes	
5	40-44				160+		
6	45-49						
7							
8	50-54						
9							
10	55-59						
11	60-64						
12	65-69						
13							
14	70-74						
15	75+						

CVD risk for men

CVD Risk					
Points	**10-Year Probability, %**	**Points**	**10-Year Probability, %**	**Points**	**10-Year Probability,%**
-3 or less	Below 1	5	3.9	13	15.6
-2	1.1	6	4.7	14	18.4
-1	1.4	7	5.6	15	21.6
0	1.6	8	6.7	16	25.3
1	1.9	9	7.9	17	29.4
2	2.3	10	9.4	18+	Above 30
3	2.8	11	11.2		
4	3.3	12	13.2		

CVD points for women

CVD Points							
Points	**Age**	**HDL**	**Total Cholesterol**	**SBP Not Treated**	**SBP Treated**	**Smoker**	**Diabetic**
<-3				<120			
-2		60+					
-1		50-59			<120		
0	30-34	45-49	<160	120-129		No	No
1		35-44	160-199	130-139			
2	35-39	<35		140-149	120-129		
3			200-239		130-139	Yes	
4	40-44		240-279	150-159			Yes
5	45-49		280+	160+	140-149		
6					150-159		
7	50-54						
8	55-59						
9	60-64						
10	65-69						
11	70-74						
12	75+						

CVD risk for women

CVD Risk					
Points	**10-Year Probability, %**	**Points**	**10-Year Probability, %**	**Points**	**10-Year Probability, %**
-2 or less	Below 1	6	3.3	14	11.7
-1	1.0	7	3.9	15	13.7
0	1.2	8	4.5	16	15.9
1	1.5	9	5.3	17	18.5
2	1.7	10	6.3	18	21.5
3	2.0	11	7.3	19	24.8
4	2.4	12	8.6	20	28.5
5	2.8	13	10.0	21+	Above 30

As with the definition of the risk score, we excluded those with a history of stroke or coronary heart disease (CHD) at phase 5; CHD was defined as non-fatal myocardial infarction and definite angina. Diagnosis of myocardial infarction was based on the MONICA criteria (Tunstall-Pedoe et al., 1994) and was obtained at clinical examinations at phases 1, 3 or 5 and records obtained from participant's general practitioner or the hospital. Angina was based on participant self-report of symptoms with corroboration in medical records of abnormalities on a resting electrocardiogram, an exercise electrocardiogram, or a coronary angiogram. History of stroke including a transient ischemic attack was self-reported. All risk factors were assessed at phase 5.

Framingham Stroke Risk Profile

The Framingham stroke risk profile (FSRP) was developed to predict a sex-specific 10-year probability of stroke for individuals free of stroke at baseline. Its development was based on 427 stroke events observed over a 10-year follow up period in 5734 participants of the Framingham study cohort (D'Agostino et al., 1994; Wolf et al., 1991b). The FSRP is based on the following risk factors:

- Age
- Systolic blood pressure
- Use of hypertensive medication
- Diabetes mellitus
- Cigarette smoking
- Prior CVD (MI, angina pectoris, coronary insufficiency, intermittent claudication, congestive heart failure)
- Atrial fibrillation (as determined by ECG)
- Left ventricular hypertrophy (as determined by ECG)

Similar to the Framingham general CVD risk score, 10-year stroke risk can be obtained using the formula based on the Cox proportional hazards regression model, or from a score sheet (Wolf et al., 1991b). In our analyses, the equation was used to obtain predicted 10-year probability of incident stroke. This equation incorporates adjustment for use of hypertensive medication, made after the publication of the original equation. This was done after Framingham investigators observed that the effect of antihypertensive therapy was present only for systolic blood pressures between 110 to 200 mmHg. The original model was thus slightly modified and recalibrated (D'Agostino et al., 1994). The general form of the equation is similar to that for the general CVD risk score described above. For example to calculate the predicted probability that an individual will develop stroke within 10 years can be computed as follows:

For men:

$$L = (0.0505 \times \text{Age}) + (0.0140 \times \text{SBP}) + (0.3263 \times \text{Hyp Rx}) + (0.3384 \times \text{Diabetes}) + (0.5147 \times \text{smoking}) + (0.5195 \times \text{CVD}) + (0.6061 \times \text{AF}) + (0.8415 \times \text{LVH})$$

$$A = L - M$$

$B = e^{A}$

$p = 1 - (S(t))^{B}$

Regression coefficients are based on the Cox proportional hazards model. M is the mean value for the population, S indicates survival without stroke and t is the index of number of years (e.g. 0.9044 for 10 years).

The point system provides a simple means of estimating the FSRP especially in office-based settings.

Stroke points for men

Points											
	0	**+1**	**+2**	**+3**	**+4**	**+5**	**+6**	**+7**	**+8**	**+9**	**+10**
Age, y	54-56	57-59	60-62	63-65	66-68	69-72	73-75	76-78	79-81	82-84	85
Untreated SBP	97-105	106-115	116-125	126-135	136-145	146-155	156-165	166-175	176-185	186-195	196-205
Treated SBP	97-105	106-112	113-117	118-123	124-129	130-135	136-142	143-150	151-161	162-176	177-205
Diabetes	No		Yes								
Cigs	No			Yes							
CVD	No				Yes						
AF	No				Yes						
LVH	No					Yes					

Stroke risk for men

Stroke Risk					
Points	**10-Year Probability, %**	**Points**	**10-Year Probability, %**	**Points**	**10-Year Probability, %**
1	3	11	11	21	42
2	3	12	13	22	47
3	4	13	15	23	52
4	4	14	17	24	57
5	5	15	20	25	63
6	5	16	22	26	68
7	6	17	26	27	74
8	7	18	29	28	79
9	8	19	33	29	84
10	10	20	37	30	88

Stroke points for women

Points											
	0	**+1**	**+2**	**+3**	**+4**	**+5**	**+6**	**+7**	**+8**	**+9**	**+10**
Age, y	54-56	57-59	60-62	63-64	65-67	68-70	71-73	74-76	77-78	79-81	82-84
Untreated SBP		95-106	107-118	119-130	131-143	144-155	156-167	168-180	181-192	193-204	205-216
Treated SBP		95-106	107-113	114-119	120-125	126-131	132-139	140-148	149-160	161-204	205-216
Diabetes	No			Yes							
Cigs	No			Yes							
CVD	No		Yes								
AF	No				Yes						
LVH	No					Yes					

Stroke risk for women

Stroke Risk					
Points	**10-Year Probability, %**	**Points**	**10-Year Probability, %**	**Points**	**10-Year Probability, %**
1	1	11	8	21	43
2	1	12	9	22	50
3	2	13	11	23	57
4	2	14	13	24	64
5	2	15	15	25	71
6	3	16	16	26	78
7	4	17	17	27	84
8	4	18	18		
9	5	19	19		
10	6	20	20		

The Dementia Risk Score

The CAIDE dementia risk score was developed as a prediction tool for late-life dementia based on risk factor profiles present in middle age (Kivipelto et al., 2006). One thousand four hundred and nine participants (875 women and 534 men) of the population based Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study were first examined in midlife (mean age= 50.4 (SD)=6.0; range = 39 to 64 years) and re-examined 20 years later for signs of dementia; 4% developed dementia during follow up. A number of cardiovascular risk factors including life style and genetic risk factors were assessed separately in logistic regression analyses to determine their association with dementia. Due to limitations of sample size, commonly reported cut-off values were used to categorize all variables into two or three groups. Factors that were associated with dementia were retained and two-way interactions between variables were tested. The components of the risk score are:

- Age
- Sex

- Education
- Systolic blood pressure (SBP)
- Body mass index (BMI)
- Total cholesterol
- Physical activity
- *APOE ε4* genotype

From the final logistic regression model, β coefficients for each risk factor were used to assign risk scores. To achieve a simple scoring system, β coefficients were standardized and rounded to the nearest integer. The 20-year risk of dementia for an individual is obtained by summing the scores for the appropriate level of each risk factor. There are two versions of the dementia risk score, one is based on a model incorporating the *APOE* genotype (*APOE ε4* carriers vs. non carriers); the other does not include this factor. The range of possible scores is 0 to 15 for model 1, and 0 to 18 for model 2.

CAIDE risk score- model 1

	Score				
	0	**1**	**2**	**3**	**4**
Age, y	< 47			47-53	> 53
Sex	woman	man			
Education, y	≥ 10		7-9	0-6	
SBP	≤ 140		>140		
BMI	≤ 30		>30		
Total cholesterol	≤6.5		>6.5		
Physical activity *	active	inactive			

*physical activity at least twice a week lasting at least 20-30 min each time is considered active

CAIDE risk score- model 2

	Score					
	0	**1**	**2**	**3**	**4**	**+5**
Age, y	< 47			47-53		> 53
Sex	woman	man				
Education, y	≥ 10			7-9	0-6	
SBP	≤ 140		>140			
BMI	≤ 30		>30			
Total cholesterol	≤6.5	>6.5				
Physical activity	active	inactive				
***APOE ε4* status**	non-ε4		ε4			

*physical activity at least twice a week lasting at least 20-30 min each time is considered active

The risk score was further categorized into quintiles and the probability of dementia (%) was calculated in each quintile. The probability of dementia increased as the risk score became greater particularly in the highest categories. Each risk score level was then taken to represent a cut off and corresponding sensitivity and specificity values were obtained. Further cut off scores corresponding to the best predictive values were chosen to represent three dementia risk groups: low, intermediate, and high.

Probability of dementia by risk score categories

Model 1			**Model 2**		
Score	All/demented	Risk (95% CI)	Score	All/demented	Risk (95% CI)
0-5	401/41	1.0% (0.0,2.0)	0-5	293/1	0.3% (-0.3,1.0)
6-7	270/5	1.9% (0.2,3.5)	6-8	363/6	1.7%(0.3, 3.0)
8-9	312/13	4.2% (1.9,6.4)	9-10	264/12	4.6% (2.0, 7.1)
10-11	245/18	7.4% (4.1,10.6)	11-12	226/10	4.4% (1.7, 7.1)
12-15	122/20	16.4% (9.7,23.1)	13-18	172/28	16.3% (10.7, 21.9)

Kivipelto et al (2006). Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *Lancet Neurol.*, *5*(9), 735-741

Risk factor profiles by dementia risk group

	Low risk profile		**Intermediate risk profile**		**High risk profile**	
	Model 1 score=1	Model 2 Score=0	Model 1 score=10	Model 2 Score=10	Model 1 score=15	Model 2 Score=18
Age, y	<47	<47	47-53	47-53	>53	>53
Sex	woman	woman	woman	woman	man	man
Education, y	≥ 10	≥ 10	7-9	7-9	≤6	≤6
SBP	≤ 140	≤ 140	>140	>140	>140	>140
BMI	≤ 30	≤ 30	≤ 30	≤ 30	>30	>30
Total cholesterol	≤6.5	≤6.5	>6.5	>6.5	>6.5	>6.5
Physical activity	active	active	inactive	inactive	inactive	inactive
APOE ε4 status	-	non-ε4	-	non-ε4	-	ε4
Risk of dementia	0.13%	0.09%	6.91%	4.06%	35.55%	48.93%

Kivipelto et al (2006). Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *Lancet Neurol.*, *5*(9), 735-741

II.2.3 Covariates

A number of variables considered as potential confounders or mediating factors in the association between CVD risk and cognition were included in the analyses. Covariates were measured at phase 5, concurrent with the first cognitive assessment.

Demographic variables included age, sex, ethnicity, and marital status. Ethnicity was categorized into two groups; white and other ethnic groups. Marital status included two categories: married/cohabiting, or single/divorced/widowed. Education was measured as highest level of education achieved with three levels: (1) elementary or lower secondary, (2) higher secondary (A' levels, usually completed at age 18), and (3) university degree or higher. Occupational position, representing British civil service employment grade and defined on the basis of salary, was grouped into three categories: (1) high-senior administrators, (2) intermediate-executive, professionals or technical staff, and (3) low-clerical and office support staff.

Health and Life-style variables included depressive symptoms, physical activity and alcohol use. Depressive symptoms were assessed using the four-item depression subscale of the General Health Questionnaire (GHQ). Scores of 0 to 3 represented absence of depressive symptoms and 4 or higher represented presence of depressive symptoms. Alcohol consumption was assessed using questions on the number of alcoholic drinks consumed in the last 7 days. This information on "measures" of spirits, "glasses" of wine, and "pints" of beer and converted to number of units of alcohol with each unit corresponding to 8 g of ethanol. A standard measure of spirits and a glass of wine are considered to contain 8 g of alcohol and a pint of beer 16 g of alcohol. Alcohol consumption was categorized as: (1) none (0 units/week), (2) moderate (1-14 for women and 1-21 for men), and (3) heavy (>14 for women and >21 for men). Physical activity level was determined from phase 5 questionnaires that included 20-items on frequency and duration of participation in different leisure time physical activities (e.g. walking, general housework, cycling) that were used to compute hours per week of each intensity level and was categorized into three groups: (1) high (>2.5 hours/week of moderate or >1 hour/week of vigorous physical activity), (2) moderate (between 1 and 2.5 hours/week of moderate physical activity), and (3) low (<1 hour/week of moderate and <1 hour week of vigorous physical activity).

CHAPTER III: RESULTS

III.1 Composite measures of cardiovascular risk and cognitive outcomes

What is presented in the following sections is an examination of the association of constructs of CVD risk factor clustering in relation to cognition; namely, the metabolic syndrome, and two Framingham risk scores. Their examination consists of studying both cross sectional and longitudinal associations. In all analyses, phase 5 (1997-1999) constitutes baseline of the study; longitudinal analyses are based on three cognitive assessments from phase 5 (1997-1999), phase 7 (2002-2004), and phase 9 (2007-2009) of the Whitehall II study screening phases. In the final section, the two Framingham risk scores are compared with the CAIDE dementia risk score and their relative utility and practical implications of their implementation are discussed. For each section a short background and methodology is presented, followed by results, and a brief discussion specific to the analyses presented in the section.

III.1.1 Metabolic Syndrome

III.1.1.1 Background and Rationale

Metabolic syndrome (MetS), a constellation of CVD risk factors, is an independent predictor of cardiovascular and cerebrovascular events (Novo et al., 2012). While components of MetS are independently associated with increased cardiovascular risk, when they co-occur, they interact synergistically to raise cardiovascular risk through several mechanisms, such as promoting the development of atherosclerosis (Novo et al., 2012; Yaffe, 2007).

In relation to cognition, while the association between individual components of MetS and various cognitive outcomes including dementia is widely reported, such evidence for the association of MetS and cognition is relatively scarce. Most studies of MetS and cognition are based on older individuals (Raffaitin et al., 2009; Raffaitin et al., 2011; Reijmer et al., 2011a; Vanhanen et al., 2006; Yaffe et al., 2007; Yaffe, 2007); few have prospective or longitudinal designs (Akbaraly et al., 2010; Kalmijn et al., 2000; Raffaitin et al., 2011). Furthermore, only a handful of studies have examined whether or not MetS as a whole imparts greater risk of adverse cognitive outcomes than its individual components (Yaffe, 2007). In these studies MetS was associated with cognitive decline, and increased risk of incident dementia (Ho et al., 2008; Komulainen et al., 2007; Raffaitin et al., 2009; Raffaitin et al., 2011; Yaffe et al., 2007).

Moreover, persistent MetS over 10-years has been linked to poorer cognitive functioning in midlife (Akbaraly et al., 2010).

The association of MetS with cognitive decline starting in midlife remains unknown. The objective of this analysis is to examine the association of MetS with cognition (at baseline) and cognitive change over 10 years in a middle aged population.

III.1.1.2 Methods

These analyses are based on all participants of the Whitehall II study with complete data for MetS and all covariates at phase 5. Non-white participants were not included because of strong ethnic differences in the prevalence of MetS. In the Whitehall II study, 10% of white participants compared to 18.0% of non-white participants had MetS at phase 5, and there was a strong interaction with ethnicity in the association between MetS and cognitive scores (*p* for interaction=0.01).

Covariates included demographic and socioeconomic factors: age (centered at the mean), sex, marital status, education and occupational position. Health and life style factors were depressive symptoms, alcohol intake, physical activity, and history of coronary heart disease that included myocardial infarction or angina. A history of angina was identified through screening questionnaires and corroborated with medical records (presence of abnormalities in a resting electrocardiogram (ECG), an exercise ECG, or a coronary angiogram). Nonfatal myocardial infarction was defined following the World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Disease criteria, and ascertained using data from five yearly medical examinations, hospital records of acute ECGs and use of cardiac enzymes.

Although adjusting for *APOE* genotype was desirable, we did not adjust for this variable in the main analyses since only a subsample of study participants had these data and restricting the analyses to these participants would have resulted in the exclusion of approximately 700 participants from the analyses. However the proportion of *APOE ε4* carriers among individuals with and without MetS was similar; 27.1% (n=1066) of those without MetS and 30.0% (n=146) of those with MetS were *APOE ε4* carriers (*p*=0.21).

Statistical analyses

Baseline characteristics of participants with and without MetS were compared by analysis of variance for means comparisons, and χ^2 tests for proportions. In cross sectional analyses that

included participants with cognitive measures at phase 5, the association of MetS with cognitive scores (z-scores) at baseline was examined using linear regression. First a basic unadjusted model was constructed. Adjustment for covariates was performed in two steps: first a model adjusted for age and sex; then a model further adjusted for other sociodemographic variables and health and life style factors. There were no strong interactions between individual covariates and MetS (all *p* values <0.10).

In longitudinal analyses linear mixed effects models were used to estimate cognitive change using three cognitive measures over 10 years (phases 5, 7, and 9). Participants with at least one cognitive measure over 10 years were included in these analyses. Models included fixed effects for time, the main effect term for MetS and interactions between time and MetS where the main effect represents its effect at time 0 (baseline) and the interaction between the variable and time represents the effect of the variable on change in cognitive score over time. Both slope and intercept were fitted as random effects, allowing individuals to have different cognitive scores at baseline as well as different rates of cognitive change over the 10-year follow up. The MetS*time*sex interaction suggested similar 10-year cognitive change in men and women (p=0.68), thus all analyses were carried out on the combined sample. In addition to terms included in basic models described above, models adjusted for covariates included terms for the interaction of each covariate with time, representing their effect on 10-year cognitive change. These models yielded an estimate of mean 10-year change in cognitive z-scores and the associated 95% confidence intervals in the two groups (with and without MetS). Finally, cross sectional and longitudinal associations of each MetS component in relation to the global cognition scores were separately examined.

In subsidiary analyses, cross sectional and longitudinal associations between MetS and cognition were examined in a subsample of participants with data on *APOE* genotype. In addition, these analyses were repeated adjusting for occupational position as a measure of late life socioeconomic position (SEP) that may be more relevant to MetS than education, which is a measure of early life SEP.

III.1.1.3 Results

At phase 5, 5865 participants had data for MetS; 10.9% of the population had MetS. Non white participants (n=412), and those with missing data for covariates (n=299) were excluded. A total of 4668 participants with cognitive measures at phase 5 were included in cross sectional analyses.

Longitudinal analyses consisted of 5083 individuals with at least one out of three cognitive measures over 10 years; 3547 (69.8%) had data at all 3 phases, 1194 (23.5%) at 2 phases, and 340 (6.7%) at one phase. Compared with excluded individuals, those included in these analyses were more likely to be men (70.9% vs 62.9%, $p<0.001$), younger (55.6 vs 56.5 years, $p< 0.001$), and to have a university degree (30% vs 24.6%, $p<0.001$). They were also more likely to have MetS (15.4 % vs 10.9, $p<0.001$).

The characteristics of the 5083 participants included in the longitudinal analyses are presented in Table 2. Characteristics of those with (n=517) and without MetS (n=4566) are also compared. Thirty eight percent of participants (n=1933) did not have any of the MetS criteria. Among those with MetS, 72.1% (n=373) met 3, 24.2% (n=125) met 4, and 3.7% (n=19) met 5 of the MetS criteria. The most common criterion met was high blood pressure (89.5%), followed by high triglycerides (84.9%) and low HDL cholesterol (65%). Most individuals with MetS had a combination of high blood pressure-high triglycerides-low HDL cholesterol (n=230; 44%), followed by high blood pressure-high triglycerides-large waist circumference (n=211; 40.8%).

Mean cognitive z-scores in the two groups at baseline are presented in Figure 5. At baseline, cognitive scores in all tests were significantly lower for those with MetS compared to those without MetS (all p values <0.001). Baseline associations between MetS and cognitive scores are presented in Table 3. MetS was associated with lower cognitive scores in all tests except phonemic fluency, in age and sex adjusted models. Those with MetS had -0.16 SD lower score in global cognition than those without MetS (p=0.0004). After adjustment for other sociodemographic, health and life style factors, associations remained for memory (β=-0.10; 95% CI -0.19, - 0.01, p=0.02), vocabulary (β=-0.08; 95% CI -0.16, - 0.02, p=0.03), and global cognition (β=-0.09; 95% CI -0.17, - 0.04, p=0.03).

Table 4 presents estimates of 10-year change in cognitive scores for the two groups (with and without MetS). These results show similar 10-year change in cognitive scores in the two groups; there was no evidence of more rapid cognitive decline in those with MetS compared with those without MetS. Adjustment for covariates did not result in great changes in the estimates. None of the covariates except age were associated with 10-year cognitive change.

Among components of MetS, only high systolic blood pressure was associated with lower global cognitive scores at baseline (β=-0.10; 95% CI -0.15, -0.05, *p<0.0001*) in multivariable adjusted models (Table 5). In longitudinal analyses (Table 6), there was some indication of an

association of hyperglycemia with faster cognitive decline (β =-0.07; 95% CI -0.13, 0.001, *p= 0.05*)

The subsidiary analyses on the subsample of study participants with *APOE* genotype data (n=3961 for cross sectional, n=4344 for longitudinal analyses), revealed no interaction of MetS and *APOE ε4* with cognitive scores at baseline (*p* interaction=0.53) or with 10-year cognitive change (*p* interaction =0.27). That is, cognitive scores at baseline as well as 10-year cognitive change among those with MetS who were *APOE ε4* carriers were no different to non-carriers. Independently, *APOE* genotype was not associated with cognitive scores at baseline but was strongly associated with 10-year cognitive change (*p*=0.004). But adjusting for *APOE* genotype in cross sectional and longitudinal analyses did not greatly change the results. In addition, adjusting for occupational position instead of education did not result in considerable changes in the observed associations reported above.

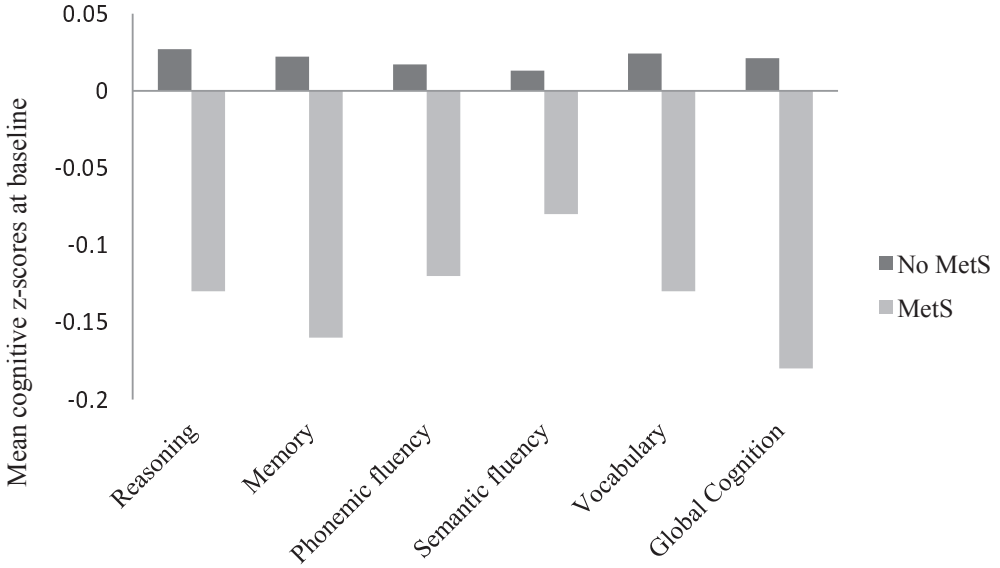

Figure 5. Mean cognitive z-scores at baseline by MetS status

Table 2. Characteristics of the study sample at baseline

	Total Sample (n=5083)	No MetS (n=4566)	MetS (n=517)	*p*
High blood pressure	40.8	35.3	89.5	*<0.0001*
High waist	14.1	8.6	63.1	*<0.0001*
High triglycerides	24.4	17.5	84.9	*<0.0001*
Low HDL cholesterol	18.6	13.4	65.0	*<0.0001*
High glycemia	5.9	3.3	29.0	*<0.0001*
Covariates				
Age, years, mean (SD)	55.6 (5.8)	55.5 (5.6)	56.4 (5.9)	*0.001*
Men	70.8	70.9	70.4	*0.79*
Marital status, married/cohabiting	76.3	76.9	71.5	*0.006*
Education				*0.008*
Lower primary/secondary	43.4	42.7	49.3	
A levels	26.4	26.5	25.5	
University	30.1	30.6	25.1	
Occupational position				*0.0004*
High	47.2	47.8	41.2	
Intermediate	42.4	42.2	43.9	
Low	10.4	9.9	14.9	
History of coronary heart disease	5.5	4.7	13.5	*<0.0001*
Depressive symptoms	11.6	11.3	13.7	*<0.0001*
Alcohol intake				*0.008*
None	12.6	12.2	16.6	
Moderate	61.5	62.1	56.8	
Heavy	25.8	25.7	26.5	
Physical activity				*<0.0001*
Low	26.9	25.7	37.7	
Moderate	16.7	16.7	17.2	
High	56.3	57.6	45.1	

Values are percentages unless otherwise indicated.

Metabolic syndrome (MetS) was defined by the National Cholesterol Education Program-Adult Treatment Panel III criteria: systolic blood pressure >130 mm Hg or diastolic blood pressure >85 mm, or medication; waist circumference >88 cm in women or >102 cm in men; triglycerides ≥ 150 mg/dL; HDL cholesterol <50 mg/dL in women or <40 mg/dL in men; fasting glycemia ≥ 126 mg/dL or nonfasting glycemia ≥200 mg/dL or antidiabetic medication.

Table 3. Associations of MetS with cognitive scores at baseline, N=4668

	Unadjusted		*Age-and sex- adjusted*		*Multivariable adjusted* [a]	
			β (95% CI) *p*			
Reasoning	-0.20 (-0.29, -0.10)	*<0.0001*	-0.13 (-0.21, -0.04)	*0.004*	-0.06 (-0.13, 0.02)	*0.15*
Memory	-0.18 (-0.27, -0.08)	*0.0002*	-0.15 (-0.23, -0.05)	*0.001*	-0.10 (-0.19, -0.01)	*0.02*
Semantic fluency	-0.14 (-0.23, -0.04)	*0.004*	-0.10 (-0.19, -0.009)	*0.03*	-0.04 (-0.13, 0.04)	*0.32*
Phonemic fluency	-0.10 (-0.19, -0.006)	*0.03*	-0.07 (-0.16, 0.02)	*0.14*	-0.02 (-0.10, 0.07)	*0.70*
Vocabulary	-0.15 (-0.25, -0.06)	*0.001*	-0.14 (-0.23, -0.05)	*0.001*	-0.08 (-0.16, -0.02)	*0.03*
Global cognition	-0.16 (-0.25, -0.07)	*0.0008*	-0.16 (-0.25, -0.07)	*0.0004*	-0.09 (-0.17, -0.04)	*0.03*

Cognitive scores are expressed as z-scores.
[a] Adjusted for age, sex, marital status, education, history of coronary heart disease, depressive symptoms, alcohol intake, and physical activity.

Table 4. 10-year change in cognitive scores as a function of MetS status, N=5083

	Unadjusted			*Age-and sex- adjusted*			*Multivariable adjusted* [a]		
	No MetS	MetS	*p*	No MetS	MetS	*p*	No MetS	MetS	*p*
Reasoning	-0.34 (-0.36, -0.32)	-0.35 (-0.41, -0.29)	*0.80*	-0.34 (-0.42, -0.28)	-0.35 (-0.41, -0.31)	*0.75*	-0.39 (-0.44, -0.34)	-0.39 (-0.45, -0.32)	*0.89*
Memory	-0.26 (-0.29, -0.23)	-0.29 (-0.38, -0.19)	*0.63*	-0.34 (-0.43, -0.26)	-0.36 (-0.48, -0.23)	*0.71*	-0.26 (-0.35, -0.17)	-0.30 (-0.41, -0.17)	*0.50*
Semantic fluency	-0.33 (-0.36, -0.31)	-0.33 (-0.41, -0.25)	*0.82*	-0.39 (-0.49, -0.29)	-0.40 (-0.47, -0.33)	*0.72*	-0.33 (-0.41, -0.26)	-0.33 (-0.43, -0.24)	*0.98*
Phonemic fluency	-0.37 (-0.39, -0.34)	-0.38 (-0.45, -0.31)	*0.68*	-0.42 (-0.49, -0.35)	-0.43 (-0.53, -0.34)	*0.71*	-0.45 (-0.52, -0.38)	-0.46 (-0.56, -0.37)	*0.76*
Vocabulary	0.02 (0.009, 0.01)	-0.01 (-0.05, 0.04)	*0.19*	-0.02 (-0.07, 0.02)	-0.05 (-0.11, 0.01)	*0.26*	0.002 (-0.04, 0.05)	-0.02 (-0.08, 0.04)	*0.31*
Global cognition	-0.37 (-0.38, -0.35)	-0.39 (-0.43, -0.33)	*0.44*	-0.43 (-0.48, -0.38)	-0.44 (-0.51, -0.37)	*0.72*	-0.40 (-0.45, -0.31)	-0.41(-0.48, -0.35)	*0.55*

Cognitive scores are expressed as z-scores. Estimates for 10-year cognitive change are derived from linear mixed effects models using three cognitive assessments.
[a] Adjusted for age, sex, marital status, education, history of coronary heart disease, depressive symptoms, alcohol intake, and physical activity.

Table 5. Association of components of MetS with global cognitive scores at baseline (phase 5), N=4668

	Unadjusted	*Age-and sex-adjusted*	*Multivariable adjusted* [a]
		β (95% CI) *p*	
High blood pressure	-0.22 (-0.28, -0.16) *<0.0001*	-0.13 (-0.19, -0.08) *<0.0001*	-0.10 (-0.15, -0.05) *<0.0001*
High waist	-0.13 (-0.21, -0.16) *0.001*	-0.08 (-0.16, -0.004) *0.03*	-0.03 (-0.10, 0.04) *0.38*
High triglycerides	-0.06 (-0.13, 0.004) *0.07*	-0.10 (-0.16, -0.03) *0.002*	0.04 (-0.09, 0.02) *0.20*
Low HDL cholesterol	-0.11 (-0.18, -0.04) *0.002*	-0.07 (-0.14, 0.001) *0.05*	-0.01 (-0.07, 0.05) *0.74*
High glycemia	-0.09 (-0.21, 0.03) *0.13*	-0.04 (-0.15, 0.07) *0.49*	-0.08 (-0.18, 0.02) *0.12*

All components are dichotomous (0 for absence and 1 for presence). Categories are based on National Cholesterol Education Program-Adult Treatment Panel III criteria (NCEP-ATP III): high blood pressure: >130 mm Hg systolic or >85 mm Hg diastolic blood pressure, or use of hypertensive medication; high waist circumference: women >88 cm and men >102 cm; high triglycerides: ≥ 150 mg/dL; low HDL cholesterol: <40 mg/dL for men and <50 mg/dL for women; high glycemia: fasting glucose ≥110 mg/dL or non-fasting glucose ≥200 mg/dL, or antidiabetic medication.

[a] Adjusted for age, sex, marital status, education, history of coronary heart disease, depressive symptoms, alcohol intake, and physical activity.

Table 6. Association of components of MetS with 10-year cognitive change in global cognitive scores, N=5083

	Unadjusted	*Age-and sex-adjusted*	*Multivariable adjusted* [a]
		β (95% CI) *p*	
High blood pressure	-0.03 (-0.06, 0.0007) *0.04*	-0.0008 (-0.03, 0.03) *0.95*	-0.0008 (-0.03, 0.03) *0.96*
High waist	-0.02 (-0.07, 0.01) *0.25*	-0.03 (-0.07, 0.02) *0.20*	-0.03 (-0.07, 0.01) *0.17*
High triglycerides	-0.009 (-0.03, 0.03) *0.96*	-0.01 (-0.02, 0.04) *0.49*	-0.01 (-0.05, 0.02) *0.50*
Low HDL cholesterol	-0.008 (-0.04, 0.03) *0.70*	-0.006 (-0.04, 0.04) *0.97*	-0.007 (-0.03, 0.03) *0.95*
High glycemia	-0.09 (-0.16, -0.02) *0.01*	-0.06 (-0.13, 0.005) *0.06*	-0.07 (-0.13, 0.001) *0.05*

All components are dichotomous (0 for absence and 1 for presence). Categories are based on National Cholesterol Education Program-Adult Treatment Panel III criteria (NCEP-ATP III): high blood pressure: >130 mm Hg systolic or >85 mm Hg diastolic blood pressure, or use of hypertensive medication; high waist circumference: women >88 cm and men >102 cm; high triglycerides: ≥ 150 mg/dL; low HDL cholesterol: <40 mg/dL for men and <50 mg/dL for women; high glycemia: fasting glucose ≥110 mg/dL or non-fasting glucose ≥200 mg/dL, or antidiabetic medication.

[a] Adjusted for age, sex, marital status, education, history of coronary heart disease, depressive symptoms, alcohol intake, and physical activity.

III.1.1.4 Discussion

The association between MetS and risk of cognitive impairment and dementia remains unclear. Most studies support a link between MetS and cognitive impairment in the elderly. However, studies of MetS and cognition in midlife are rare; none have examined both cross sectional and longitudinal associations of MetS and cognitive outcomes in the same population. In the present study that explores these associations, MetS was associated with lower cognitive scores at baseline but it was not related to faster 10-year cognitive decline; cognitive change was similar among those with and without MetS. Among components of the MetS, only hyperglycemia was associated with faster global cognitive decline over ten years.

Several components of the MetS have been individually related to cognitive outcomes; hypertension, hyperlipidemia, diabetes and abdominal obesity have been associated with midlife cognitive deficits and late life dementia (Kivipelto et al., 2001a; Kivipelto et al., 2001b; Knopman et al., 2001; Pappolla et al., 2003; Solomon et al., 2009; Whitmer et al., 2005b; Xu et al., 2011). Consistent with the role of CVD risk factor clustering in affecting cardiovascular and cognitive outcomes, MetS as a multidimensional entity that includes several CVD risk factors may be a better measure of cardiovascular and metabolic risk for predicting cognitive outcomes. Although there are a few studies that have not confirmed an association between MetS and cognitive deficits such as MCI (Roberts et al., 2010; Solfrizzi et al., 2011) or have reported an increased risk of progression to dementia only among those with MCI (Solfrizzi et al., 2011), the evidence for the link between MetS and increased risk of cognitive impairment and dementia in elderly populations is fairly consistent (Dik et al., 2007; Ho et al., 2008; Komulainen et al., 2007; Panza et al., 2010; Raffaitin et al., 2011; Yaffe et al., 2004; Yaffe et al., 2007; Yaffe, 2007). The few studies that examined the association of MetS with specific cognitive domains among older adults have linked MetS with deficits in memory, visuospatial abilities, processing speed and executive function (Bokura et al., 2010; Cavalieri et al., 2010; Komulainen et al., 2007; Raffaitin et al., 2011; Schuur et al., 2010; Segura et al., 2009), although each component of MetS was not associated in the same way with cognitive decline. Despite the challenge in uncoupling the independent and interactive effects of MetS on cognition, as MetS is etiologically heterogeneous with high degrees of comorbidity, a cumulative influence of MetS on late life cognitive outcomes has been reported (Dik et al., 2007; Yaffe, 2007). These findings have led some to propose a

metabolic-cognitive syndrome (MCS) in patients with MetS plus cognitive impairment of degenerative or vascular origin (Frisardi et al., 2010).

However, the link between MetS and cognitive outcomes at midlife is far less conclusive. In fact most studies (none with longitudinal analyses) that examined these associations in non-elderly populations (younger than 60 years of age) did not find a clear association between MetS and cognitive outcomes (Akbaraly et al., 2010; Haley et al., 2010; Tournoy et al., 2010). A prospective analysis of the Whitehall II study found that only persistent MetS was associated with lower cognitive function in late midlife (Akbaraly et al., 2010). A study of 13 individuals with MetS and 25 healthy adults aged between 40 and 60 years, found an association of MetS with peripheral metabolic dysfunction (higher myoinositol/creatine and glutamate/creatine ratios) in occipitoparietal grey matter, but there were no differences in global cognitive function, memory, language, and psychomotor performance between the two groups. These findings suggest that even in young cognitively intact adults, subclinical alterations in cerebral metabolism and cerebrovascular reactivity may represent early cerebral damage resulting from peripheral metabolic disturbances (Haley et al., 2010). But these biological changes may not translate to lowered cognition detectable by neuropsychological tests. Similarly, another cross sectional study involving 3369 men (mean age=59 years), found no association between MetS and cognitive performance on various cognitive tests including memory, executive function and processing speed. But of the individual components of MetS, hyperglycemia was associated with poorer performance in all cognitive tests (Tournoy et al., 2010).

Taken together, these results and our findings of lack of evidence for longitudinal associations of MetS at midlife with 10-year cognitive decline suggest that among middle aged individuals MetS may not be a strong predictor of cognitive decline. The contrasting cross sectional and longitudinal associations of MetS with cognition observed in the present study may in part explain the reported associations between MetS and cognitive deficits based on cross sectional and prospective studies. Although, these inconsistencies may also be due to differences in study populations; higher prevalence of CVD risk factors and MetS, around 30% in the elderly (Denys et al., 2009) may give rise to stronger associations between MetS and cognitive deficits reported in older populations. It should be noted that lack of evidence of an association between MetS and more rapid cognitive decline, as observed in the present study, does not exclude the possibility of an association of MetS with late life dementia.

In non-elderly populations in particular, the definition of MetS has important limitations that may affect its predictive value. These include requiring 3 out of 5 cardio-metabolic abnormalities and use of dichotomous risk factor categories. For example, one study that found no differences in cognitive outcomes between the MetS and no MetS groups, when the whole study population was compared using actual number of MetS criteria met, lowered cognitive performance was observed with each additional MetS criteria (Gatto et al., 2008). Although in the present analysis evidence of such graded association with number of MetS criteria and cognition was not found, among middle aged individuals who have generally fewer and lower levels of risk factors, this definition may not adequately capture the continuity of risk and distinguish individuals with borderline risk factors. In the present study 10.9% of participants had MetS compared to almost 40% in studies based on older populations (Yaffe et al., 2004). The higher degree of cardiovascular comorbidity among older adults is also reflected in the higher proportion of individuals with MetS who have more than 3 cardio-metabolic abnormalities; 44% for 70-79 year olds (Yaffe et al., 2004) compared to 28% in the present study.

In addition, the most commonly accepted definition of MetS would not recognize an individual with only hyperglycemia (or diabetes) and abdominal obesity to be at higher risk of cardiovascular disease or cognitive deficits even though both of these risk factors are independently associated with increased risk of cardiovascular disease and adverse cognitive outcomes (Akomolafe et al., 2006; Luchsinger, 2010; Ott et al., 1999a; Schnaider et al., 2004; Strachan et al., 2008; Whitmer et al., 2005a; Whitmer et al., 2005b; Xu et al., 2011). Indeed, several studies have identified hyperglycemia as the main contributor to cognitive deficits in individuals with MetS (Bokura et al., 2010; Dik et al., 2007; Roberts et al., 2010; Tournoy et al., 2010; Yaffe, 2007). In the present study too, hyperglycemia was the only component of MetS with some evidence of an association with 10-year cognitive decline. Hyperglycemia and insulin resistance play an important role in the etiology of MetS (Yaffe, 2007). Yet in our study sample almost half of participants with hyperglycemia did not have MetS and thus would not be considered high risk according to this MetS definition. This is a major shortcoming because prediabetes and impaired glucose metabolism have been consistently linked with increased risk of major manifestations of cardiovascular disease (Tabak et al., 2012). Fasting hyperglycemia, post-load glucose and HbA1c are all robust predictors of vascular mortality (Barr et al., 2007; Brunner et al., 2006; Sarwar et al., 2010a). Moreover these associations have been shown to be

independent of co-occurring CVD risk factors such as blood pressure and triglycerides (Sarwar et al., 2010b; Seshasai et al., 2011). Further, there is compelling evidence for a causal relationship between alterations in glycemic control and subsequent brain ischemic and atrophic changes (Knopman et al., 2011).

In addition to the role of vascular mechanisms involved in the pathophysiology of MetS and its effect on cerebral integrity and cognition (e.g. increased silent brain infarctions and periventricular white matter hyperintensivities), elevated inflammation, an important feature of MetS has emerged as a key player in these associations. Although it is unclear whether inflammation leads to MetS or vice versa, those with MetS who have higher inflammation levels are at higher risk of cognitive impairment (Dik et al., 2007; Yaffe et al., 2004; Yaffe et al., 2007). A recent study offers compelling evidence for the role of inflammation in the association of MetS and cognitive deficits (Reijmer et al., 2011a). In this study that examined whether the relation between the MetS and cognitive dysfunction is mediated by measures of atherosclerosis or clinically manifest cardiovascular disease, found that although both MetS and markers of atherosclerosis were both associated with reduced cognitive function, atherosclerosis did not modulate the relation between the MetS and cognition. Therefore shared etiological factors such as inflammation may drive the association between MetS and cognition. This study also found that hyperglycemia slightly modulated the association with cognition (Reijmer et al., 2011a).

The relation between MetS and cognition is undoubtedly complex. This analysis suggests that MetS as a construct may not be useful in predicting cognitive decline in this middle aged population and that hyperglycemia seems to be especially important in affecting cognitive outcomes.

III.1.2 Framingham General Cardiovascular Risk Profile

III.1.2.1 Background and Rationale

The Framingham General Cardiovascular Disease Risk Profile is one of the latest risk functions developed by the investigators of the Framingham Heart Study (D'Agostino, Sr. et al., 2008). Recognizing the shared risk factors and treatments for coronary heart disease (CHD) and stroke, the risk function combines the two outcomes to predict first onset CVD (fatal or non fatal CHD event or any stroke).

Although this risk score is not yet widely validated, similar Framingham risk functions such as the Framingham CHD or stroke risk scores have been examined in numerous populations in relation to prediction of cardiovascular and cerebrovascular events, as well as subclinical features of cardiovascular disease (Brindle et al., 2006). The Framingham CVD risk score has been correlated with carotid artery intima-media thickness (Touboul et al., 2007), an early marker of atherosclerosis that is associated with increased risk of CHD and stroke (O'Leary et al., 1999; Polak et al., 2011). Similarly, the Framingham Stroke Risk Profile has been shown to predict onset and progression of coronary artery calcium, a subclinical measure of atherosclerosis (DeFilippis et al., 2011). However, less attention has been given to whether these risk scores predict cognitive outcomes.

A number of studies have examined Framingham risk scores in relation to cognitive outcomes. One study examining the association of Framingham CHD risk score with 10-year cognitive decline in community dwelling adults (mean age 65 years) reported that this risk profile was associated with the rate of cognitive decline in women but not men; women with very low CHD risk maintained higher level of cognitive function compared to women with higher CHD risk. These differences in the rates of cognitive decline in tests of semantic fluency and long term recall were evident early in the follow up and persisted to the end of the 10-year follow up. Among men, despite higher CHD risk, the pattern of cognitive decline did not differ by CHD risk profile (Laughlin et al., 2011). Other studies have used the Framingham Stroke Risk Profile to examine cognitive outcomes including incident cognitive impairment (Unverzagt et al., 2011) and worse performance on various cognitive tests including abstract reasoning (Elias et al., 2004a), although these studies are hampered by limitations such as cross sectional designs (Elias et al., 2004a; Llewellyn et al., 2008; Seshadri et al., 2004) or short term follow-ups (Unverzagt et al., 2011). However, given the advantages of these risk functions over the individual risk factors in

measuring cumulative CVD risk burden, these studies are a step in the right direction and provide important initial evidence for the utility of cardiovascular risk scores to predict cognitive outcomes.

The Framingham General Cardiovascular Disease Risk Profile has not previously been examined in relation to cognitive outcomes. The Framingham Stroke Risk Profile, used in previous studies, is developed to predict stroke and does not cover the full range of cardiovascular disease such as myocardial infarction and angina that are more common in the general population. The objective of this analysis is to examine this risk score and its association with cognitive performance and 10-year cognitive change among middle-aged individuals.

III.1.2.2 Methods

All Whitehall II participants free of cardiovascular disease at phase 5, and for whom Framingham CVD risk could be calculated and who had at least one cognitive measure over 3 assessments were eligible for these analyses. A total of 319 participants with a history of CHD or stroke at phase 5 were excluded. CHD was defined as non-fatal myocardial infarction and definite angina. Diagnosis of myocardial infarction was based on clinical examinations and corroborated with medical records using MONICA criteria (Tunstall-Pedoe et al., 1994). History of angina was based on participant reports of symptoms with corroboration in medical records or abnormalities on ECG or coronary angiogram. History of stroke or transient ischemic attack was based on participant self-reports.

Statistical analysis

Due to the interaction between CVD risk and sex at baseline, all analyses are stratified by sex, but all analyses were also carried out in the combined sample of men and women since these interactions were much weaker in longitudinal analyses and not present for all cognitive tests. Linear regression analyses were carried out to assess cross sectional associations between 10% increment in CVD risk and cognitive scores at baseline (phase 5). Basic unadjusted models were examined first; adjustment for covariates was then performed in three steps. First, models were adjusted for age. Then a second model adjusted for age, ethnicity, marital status and education and finally in a third model, health and life style factors (depressive symptoms, alcohol intake, and physical activity) were added. In longitudinal analyses linear mixed effects models were used to examine the association of 10% increments in CVD risk with 10-year cognitive change.

Adjustment for covariates was done similar to the cross sectional analyses. Finally, cross sectional and longitudinal associations of CVD risk factor components of the risk score with cognition were also examined.

III.1.2.3 Results

Cross sectional analyses involve 4450 participants (after excluding those with history of CVD: n=327 or missing covariates: n=201); longitudinal analyses were carried out on 4839 individuals. Compared with these participants, individuals excluded from the analyses had higher CVD risk (12.0% vs 9.1%, $p<0.001$). They were also older (56.5 vs 55.0 years, $p<0.001$), less likely to be men (62.9% vs 72.0%, $p<0.001$) and to have a university degree (26% vs 29.5%, $p<0.001$). The characteristics of the study sample at baseline are presented in Table 7. Men had a higher 10-year CVD risk than women (12.2% vs 4.0%, $p<0.001$). At baseline men had higher cognitive scores in tests of reasoning, semantic fluency and vocabulary than women. With respect to 10-year cognitive change, men and women differed in tests of semantic fluency and vocabulary where men showed steeper decline (Table 8).

Associations of 10% increment in CVD risk and cognitive scores at baseline appear in Table 9. In cross sectional analyses adjusted for age, 10% increment in CVD risk was associated with lower cognitive scores including global cognitive score at baseline, in both men and women (all p values ≤ 0.02), and in the combined sample where 10% higher CVD risk was associated with -0.11 SD lower global cognitive score (95% CI= -0.15, -0.07, $p<0.0001$) at baseline. Although adjusting for all other covariates resulted in an attenuation of the associations between CVD risk and cognitive scores, 10% higher CVD risk was associated with lower cognitive scores including the global cognitive score in both men (β=-0.05; 95% CI=-0.09, -0.01, $p=0.01$) and women (β=-0.10; 95% CI=-0.18, -0.03, $p=0.008$). In the combined sample 10% increment in CVD risk was associated with -0.04 (95% CI=-0.08, -0.006) SD lower global cognitive score ($p=0.02$).

The associations of 10% increment in CVD risk with 10-year cognitive change are presented in Table 10. In age-adjusted models 10% increment in CVD risk was associated with faster cognitive decline in reasoning, vocabulary and global cognition in men; in women there was some evidence of an association of higher CVD risk with decline in phonemic fluency. In the combined sample, 10% increment in CVD risk was associated with faster cognitive decline in all tests except reasoning and semantic fluency. When adjusted for all demographic, health and life

style factors, 10% increment in CVD risk was associated with more rapid decline in global cognitive scores in men (β= -0.03; 95% CI=-0.05, 0.0005, *p*=0.05), but not in women (β= -0.009; 95% CI=-0.06, 0.04, *p*=0.75). In the combined sample, 10% increment in CVD risk was associated with faster cognitive decline in all tests except reasoning. Ten percent increment in CVD risk was associated with -0.03 SD (95% CI=-0.04, -0.006, p=0.01) faster decline in global cognitive scores.

Analyses examining the association of CVD risk factor components of the Framingham CVD risk score (systolic blood pressure, total cholesterol, HDL cholesterol, diabetes, and cigarette smoking) with cognition were carried out on the combined sample of men and women. In cross sectional analyses (Table 11), adjusted for age, systolic blood pressure (β= -0.05; 95% CI=-0.07, -0.02, *p*=<0.0001), diabetes (β= -0.25; 95% CI=-0.41, -0.09, *p*=0.001), and smoking (β= -0.28; 95% CI=-0.38, -0.18, *p*<0.0001) were associated with lower cognitive scores at baseline (phase 5). When adjusted for all demographic, health and life style factors, systolic blood pressure (β= -0.03; 95% CI=-0.05, -0.01, *p*=0.01), HDL cholesterol (β= -0.02; 95% CI=-0.04, 0.004, *p*=0.05), and smoking (β= -0.17; 95% CI=-0.25, -0.08, *p*<0.0001) were associated with lower cognitive scores at baseline. For the association of diabetes with cognition at baseline, there was a strong interaction with ethnicity; 2.8% of participants of white ethnicity vs 10.7% of non white participants had diabetes. The association between diabetes and cognitive scores at baseline was stronger among non whites (β= -0.25; 95% CI=-0.61, 0.10, *p*=0.09) than white participants (β= 0.004; 95% CI=-0.15, 0.16, *p*=0.95). Therefore the pooled estimate showing no associations between diabetes and baseline cognitive scores is due to this interaction. Similar interactions with ethnicity were not found for other components of the Framingham CVD risk score.

In longitudinal analyses (Table 12), systolic blood pressure, total cholesterol and diabetes were associated with faster 10-year cognitive decline in basic models. These associations remained only for total cholesterol (β=-0.002; 95% CI=-0.03, -0.00516, *p*=0.01), and diabetes (β= -0.09; 95% CI=-0.18, 0.0002, *p*=0.05) when adjusted for demographic, health and life style variables. Covariates were associated with cognition only at baseline (intercept) and did not greatly affect rate of cognitive decline except for systolic blood pressure where there was a strong longitudinal effect of age in the association of systolic blood pressure and rate of cognitive decline. For diabetes, unlike cross sectional effects, ethnicity did not greatly affect 10-year cognitive decline.

Table 7. Characteristics of the study sample at baseline

	Men (n=3202)	Women (n=1248)	*p*
Framingham general cardiovascular risk profile, mean (SD)	12.0 (7.3)	4.0 (2.7)	*<0.001*
Components			
Age (years), mean (SD)	55.2 (5.9)	55.0 (5.3)	*0.19*
HDL cholesterol (mg/dL), mean (SD)	53.3 (13.1)	65.0 (16.3)	*<0.001*
Total cholesterol (mg/dL), mean (SD)	226.5 (38.1)	232.9 (40.3)	*0.006*
Untreated systolic blood pressure (mm Hg), mean (SD)	122.0 (15.0)	118.9 (16.1)	*<0.001*
Treated systolic blood pressure (mm Hg), mean (SD)	131.6 (15.2)	129.9 (15.5)	*0.19*
Current smoker	7.7	10.2	*<0.001*
History of diabetes	3.7	3.8	*0.49*
Covariates			
Marital status			
Married/cohabiting	83.4	60.1	*<0.001*
Single/widowed/divorced	15.9	39.6	
Ethnicity			
White	94.2	87.8	*<0.001*
Non-white	5.5	12.5	
Education			
Lower primary/secondary	36.4	52.2	*<0.001*
A levels	27.1	23.8	
University	34.2	23.0	
Depressive symptoms	10.5	13.5	*0.01*
Alcohol intake			*<0.001*
None	10.02	25.5	
Moderate	61.6	58.5	
Heavy	28.0	15.2	
Physical activity			*<0.001*
Low	22.3	42.4	
Moderate	16.9	18.0	
High	61.7	38.2	

Values are percentages unless otherwise indicated.

Table 8. Cognitive characteristics of the study sample

	Men (n=3202)	Women (n=1248)	*p*
Cognitive test raw scores at baseline (Phase 5)			
Reasoning (AH4-I, range, 0-65)	49.9 (9.0)	42.3 (11.2)	*<0.001*
Memory (range, 0-20)	6.8 (2.2)	7.8 (2.3)	*0.21*
Semantic fluency (range, 0-35)	16.5 (3.4)	16.1 (4.3)	*<0.001*
Phonemic fluency (range, 0-35)	17.2 (4.1)	16.6 (4.2)	*0.36*
Vocabulary (Mill Hill, range, 0-33)	25.3 (3.5)	23.0 (5.0)	*<0.001*
10-year cognitive change [a]			
Reasoning (AH4-I, range, 0-65)	-3.9 (6.6)	-3.6 (6.2)	*0.39*
Memory (range, 0-20)	-0.7 (2.1)	-0.5 (3.1)	*0.22*
Semantic fluency (range, 0-35)	-1.5 (3.3)	-1.2 (3.5)	*0.02*
Phonemic fluency (range, 0-35)	-1.9 (3.8)	-1.5 (4.2)	*0.87*
Vocabulary (Mill Hill, range, 0-33)	-0.02 (2.2)	0.2 (2.5)	*0.006*

[a] 10-year cognitive change is estimated using three cognitive assessments.

Table 9. Associations of 10% increment in CVD risk and cognitive scores at baseline

	Unadjusted			*+ age*			*+ demographic factors* [a]			*+ health and life style factors* [b]		
Cognitive test	β	(95% CI)	*p*	β	(95% CI)	*p*	β	(95% CI)	*p*	β	(95% CI)	*p*
MEN (n=3202)												
Reasoning	-0.15	(-0.18, -0.11)	*<0.0001*	-0.08	(-0.13, -0.04)	*0.0004*	-0.03	(-0.07, 0.01)	*0.16*	-0.02	(-0.07, 0.02)	*0.25*
Memory	-0.19	(-0.23, -0.16)	*<0.0001*	-0.06	(-0.11, -0.02)	*0.007*	-0.05	(-0.09, 0.001)	*0.05*	-0.04	(-0.09, 0.06)	*0.09*
Semantic fluency	-0.18	(-0.22, -0.14)	*<0.0001*	-0.07	(-0.12, -0.03)	*0.001*	-0.04	(-0.08, 0.005)	*0.08*	-0.04	(-0.08, 0.08)	*0.10*
Phonemic fluency	-0.17	(-0.21, -0.13)	*<0.0001*	-0.07	(-0.11, -0.02)	*0.004*	-0.04	(-0.08, 0.006)	*0.09*	-0.03	(-0.08, 0.01)	*0.14*
Vocabulary	-0.04	(-0.07, 0.003)	*0.07*	-0.11	(-0.16, -0.06)	*<0.0001*	-0.05	(-0.09, -0.01)	*0.01*	-0.06	(-0.10, -0.01)	*0.007*
Global cognition	-0.20	(-0.24, -0.16)	*<0.0001*	-0.10	(-0.16, -0.07)	*<0.0001*	-0.06	(-0.10, -0.02)	*0.007*	-0.05	(-0.09, -0.01)	*0.01*
WOMEN (n=1248)												
Reasoning	-0.45	(-0.54, -0.37)	*<0.0001*	-0.24	(-0.33, -0.14)	*<0.0001*	-0.11	(-0.19, -0.03)	*0.008*	-0.09	(-0.17, -0.02)	*0.01*
Memory	-0.35	(-0.44, -0.26)	*<0.0001*	-0.23	(-0.33, -0.13)	*<0.0001*	-0.17	(-0.27, -0.07)	*0.0009*	-0.16	(-0.26, -0.06)	*0.001*
Semantic fluency	-0.39	(-0.47, -0.30)	*<0.0001*	-0.15	(-0.25, -0.05)	*0.002*	-0.04	(-0.13, 0.04)	*0.30*	-0.04	(-0.12, 0.04)	*0.39*
Phonemic fluency	-0.29	(-0.38, -0.21)	*<0.0001*	-0.11	(-0.21, -0.01)	*0.02*	-0.04	(-0.13, 0.06)	*0.44*	-0.02	(-0.11, 0.07)	*0.60*
Vocabulary	-0.34	(-0.43, -0.26)	*<0.0001*	-0.24	(-0.34, -0.14)	*<0.0001*	-0.09	(-0.17, -0.009)	*0.03*	-0.07	(-0.15, 0.004)	*0.06*
Global cognition	-0.47	(-0.56, -0.39)	*<0.0001*	-0.26	(-0.35, -0.16)	*<0.0001*	-0.12	(-0.19, -0.04)	*0.004*	-0.10	(-0.18, -0.03)	*0.008*
COMBINED (n=4450) [c]												
Reasoning	-0.19	(-0.23, -0.15)	*<0.0001*	-0.08	(-0.13, -0.05)	*<0.0001*	-0.02	(-0.06, 0.01)	*0.22*	-0.01	(-0.05, 0.02)	*0.39*
Memory	-0.21	(-0.25, -0.18)	*<0.0001*	-0.09	(-0.13, -0.05)	*<0.0001*	-0.07	(-0.11, -0.02)	*0.002*	-0.06	(-0.10, -0.01)	*0.004*
Semantic fluency	-0.21	(-0.25, -0.18)	*<0.0001*	-0.07	(-0.11, -0.02)	*0.0009*	-0.02	(-0.06, 0.01)	*0.24*	-0.02	(-0.06, 0.01)	*0.32*
Phonemic fluency	-0.19	(-0.23, -0.16)	*<0.0001*	-0.07	(-0.11, -0.02)	*0.002*	-0.03	(-0.07, 0.009)	*0.13*	-0.03	(-0.06, 0.01)	*0.22*
Vocabulary	-0.09	(-0.13, -0.06)	*<0.0001*	-0.10	(-0.14, -0.06)	*<0.0001*	-0.03	(-0.07, 0.004)	*0.08*	-0.03	(-0.06, 0.005)	*0.10*
Global cognition	-0.25	(-0.28, -0.21)	*<0.0001*	-0.11	(-0.15, -0.07)	*<0.0001*	-0.05	(-0.08, -0.01)	*0.009*	-0.04	(-0.08, -0.006)	*0.02*

Cognitive scores are standardized.
[a] Demographic factors include: ethnicity, marital status, and education.
[b] Health and life style factors include: depressive symptoms, alcohol intake, and physical activity.
[c] Adjusted for sex.

Table 10. Associations of 10% increment in CVD risk and 10-year change in cognitive scores

	Unadjusted			*+ age*			*+ demographic factors* [a]			*+ health and life style factors* [b]		
Cognitive test	β	(95% CI)	*p*	β	(95% CI)	*p*	β	(95% CI)	*p*	β	(95% CI)	*p*
MEN												
Reasoning	-0.11	(-0.13, -0.08)	*<0.0001*	-0.03	(-0.06, -0.0007)	*0.04*	-0.03	(-0.06, -0.001)	*0.03*	-0.03	(-0.06, -0.004)	*0.03*
Memory	-0.01	(-0.05, 0.03)	*0.64*	0.04	(-0.003, 0.10)	*0.06*	0.04	(-0.07, 0.09)	*0.08*	0.04	(-0.006, 0.09)	*0.08*
Semantic fluency	-0.06	(-0.09, -0.02)	*0.0008*	-0.03	(-0.07, 0.009)	*0.12*	-0.03	(-0.07, 0.004)	*0.07*	-0.04	(-0.08, -0.0009)	*0.04*
Phonemic fluency	-0.03	(-0.06, 0.0005)	*0.05*	-0.04	(-0.08, 0.001)	*0.05*	-0.04	(-0.08, -0.01)	*0.04*	-0.04	(-0.08, 0.002)	*0.06*
Vocabulary	-0.05	(-0.07, -0.03)	*<0.0001*	-0.03	-0.05, -0.007)	*0.01*	-0.03	(-0.05, -0.006)	*0.01*	-0.03	(-0.05, -0.004)	*0.02*
Global cognition	-0.07	(-0.09, -0.05)	*<0.0001*	-0.03	(-0.06, -0.003)	*0.03*	-0.03	(-0.05, 0.0002)	*0.05*	-0.03	(-0.05, 0.0005)	*0.05*
WOMEN												
Reasoning	-0.06	(-0.1, -0.005)	*0.03*	0.04	(-0.01, 0.10)	*0.17*	0.04	(-0.01, 0.10)	*0.11*	0.04	(-0.01, 0.11)	*0.13*
Memory	-0.03	(-0.12, 0.07)	*0.59*	0.06	(-0.05, 0.18)	*0.25*	0.05	(-0.06, 0.16)	*0.36*	0.05	(-0.06, 0.16)	*0.37*
Semantic fluency	-0.03	(-0.09, 0.04)	*0.46*	-0.01	(-0.09, 0.07)	*0.78*	-0.03	(-0.11, 0.05)	*0.51*	-0.03	(-0.11, 0.06)	*0.52*
Phonemic fluency	-0.10	(-0.18, -0.03)	*0.006*	-0.08	(-0.17, 0.004)	*0.06*	-0.08	(-0.17, 0.001)	*0.05*	-0.09	(-0.18, -0.002)	*0.04*
Vocabulary	-0.05	(-0.09, -0.008)	*0.01*	-0.03	(-0.08, 0.01)	*0.18*	-0.03	(-0.08, 0.01)	*0.13*	-0.04	(-0.08, 0.01)	*0.15*
Global cognition	-0.06	(-0.1, -0.01)	*0.01*	-0.01	(-0.06, 0.008)	*0.35*	-0.01	(-0.06, 0.04)	*0.78*	-0.01	(-0.06, 0.04)	*0.75*
COMBINED [c]												
Reasoning	-0.09	(-0.11, -0.06)	*<0.0001*	-0.01	(-0.04, 0.009)	*0.23*	-0.01	(-0.03, 0.01)	*0.24*	-0.01	(-0.04, 0.008)	*0.19*
Memory	-0.01	(-0.05, 0.03)	*0.63*	0.05	(0.008, 0.10)	*0.01*	0.05	(0.003, 0.09)	*0.03*	0.05	(0.002, 0.09)	*0.04*
Semantic fluency	-0.05	(-0.08, -0.02)	*0.001*	-0.03	(-0.06, 0.006)	*0.11*	-0.04	(-0.07, -0.0007)	*0.04*	-0.04	(-0.07, -0.001)	*0.04*
Phonemic fluency	-0.04	(-0.07, -0.01)	*0.006*	-0.04	(-0.07, -0.004)	*0.02*	-0.04	(-0.08, -0.007)	*0.01*	-0.04	(-0.08, -0.007)	*0.01*
Vocabulary	-0.05	(-0.07, -0.03)	*<0.0001*	-0.03	(-0.05, -0.01)	*0.004*	-0.03	(-0.05, -0.01)	*0.004*	-0.03	(-0.05, -0.009)	*0.005*
Global cognition	-0.06	(-0.08, -0.04)	*<0.0001*	-0.03	(-0.05, -0.0009)	*0.04*	-0.02	(-0.04, 0.002)	*0.08*	-0.03	(-0.04, -0.006)	*0.01*

Cognitive scores are standardized. Estimates for 10-year cognitive change are derived from linear mixed effects models using three cognitive assessments.

[a] Demographic factors include: ethnicity, marital status, and education.

[b] Health and life style factors include: depressive symptoms, alcohol intake, and physical activity.

[c] Adjusted for sex.

Table 11. Associations of CVD risk factor components of the Framingham General Cardiovascular Disease Risk Profile and cognitive scores at baseline, N=4450

Cognitive test	**SBP**	**Total cholesterol**	**HDL cholesterol**	**Diabetes**	**Smoking**
			β (95% CI) *p*		
Unadjusted					
Reasoning	-0.07 (-0.10, -0.05) *<0.0001*	-0.02 (-0.04, 0.01) *0.25*	0.02 (0.0009, 0.04) *0.04*	-0.33 (-0.49, -0.16) *<0.0001*	-0.27 (-0.37, -0.16) *<0.0001*
Memory	-0.07 (-0.10, -0.05) *<0.0001*	-0.01 (-0.04, 0.01) *0.33*	-0.04 (-0.06, -0.02) *0.0002*	-0.20 (-0.36, -0.04) *0.01*	-0.13 (-0.23, -0.03) *0.01*
Semantic fluency	-0.07 (-0.10, -0.05) *<0.0001*	-0.02 (-0.05, 0.009) *0.17*	-0.01 (-0.04, 0.006) *0.16*	-0.20 (-0.36, -0.03) *0.01*	-0.12 (-0.22, -0.01) *0.02*
Phonemic fluency	-0.06 (-0.09, -0.04) *<0.0001*	-0.004 (-0.03, 0.03) *0.80*	-0.02 (-0.04, 0.001) *0.07*	-0.12 (-0.28, 0.03) *0.13*	-0.10 (-0.20, 0.0001) *0.05*
Vocabulary	-0.04 (-0.07, -0.02) *<0.0001*	-0.002 (-0.03, 0.02) *0.90*	-0.005 (-0.03, 0.02) *0.63*	-0.27 (-0.43, -0.11) *0.0009*	-0.28 (-0.38, -0.17) *<0.0001*
Global cognition	-0.09 (-0.11, -0.06) *<0.0001*	-0.02 (-0.04, 0.01) *0.29*	-0.01 (-0.04, 0.005) *0.14*	-0.30 (-0.47, -0.14) *0.0002*	-0.24 (-0.34, -0.14) *<0.0001*
Age adjusted					
Reasoning	-0.04 (-0.06, -0.01) *0.001*	-0.01 (-0.04, 0.02) *0.42*	0.02 (-0.0005, 0.04) *0.05*	-0.28 (-0.44, -0.12) *0.0005*	-0.30 (-0.40, -0.20) *<0.0001*
Memory	-0.03 (-0.06, -0.01) *0.002*	-0.01 (-0.04, 0.01) *0.23*	-0.05 (-0.07, -0.02) *<0.0001*	-0.16 (-0.31, 0.001) *0.05*	-0.16 (-0.26, -0.06) *0.001*
Semantic fluency	-0.03 (-0.05, -0.09) *<0.001*	-0.01 (-0.05, 0.02) *0.34*	-0.02 (-0.04, 0.004) *0.10*	-0.14 (-0.31, 0.01) *0.06*	-0.15 (-0.25, -0.05) *0.002*
Phonemic fluency	-0.03 (-0.06, -0.006) *0.01*	-0.03 (-0.02, 0.05) *0.07*	-0.02 (-0.04, -0.0006) *0.04*	-0.07 (-0.23, 0.08) *0.33*	-0.13 (-0.23, -0.03) *0.008*
Vocabulary	-0.04 (-0.06, -0.01) *0.001*	0.005 (-0.02, 0.03) *0.73*	-0.006 (-0.03, 0.02) *0.60*	-0.26 (-0.42, -0.10) *0.001*	-0.28 (-0.39, -0.18) *<0.0001*
Global cognition	-0.05 (-0.07, -0.02) *<0.0001*	-0.02 (-0.06, 0.02) *0.16*	-0.02 (-0.04, 0.002) *0.08*	-0.25 (-0.41, -0.09) *0.001*	-0.28 (-0.38, -0.18) *<0.0001*
Multivariable adjusted [a]					
Reasoning	-0.03 (-0.05, -0.005) *0.01*	-0.001 (-0.02, 0.02) *0.87*	0.0004 (-0.01, 0.02) *0.96*	-0.01 (-0.14, 0.11) 0.84 [b]	-0.17 (-0.25, -0.09) *<0.0001*
Memory	-0.03 (-0.05, -0.003) *0.02*	0.008 (-0.02, 0.03) *0.57*	-0.03 (-0.05, -0.007) *0.009*	-0.05 (-0.20, 0.10) 0.51 [b]	-0.13 (-0.22, -0.03) *0.009*
Semantic fluency	-0.02 (-0.04, 0.02) *0.08*	-0.001 (-0.02, 0.02) *0.91*	-0.007 (-0.03, 0.01) *0.52*	0.03 (-0.11, 0.18) 0.64 [b]	-0.08 (-0.17, 0.009) *0.07*
Phonemic fluency	-0.02 (-0.04, 0.003) *0.09*	0.01 (-0.01, 0.04) *0.37*	-0.006 (-0.03, 0.01) *0.57*	0.05 (-0.09, 0.20) 0.47 [b]	-0.07 (-0.16, 0.03) *0.16*
Vocabulary	-0.02 (-0.04, -0.005) *0.01*	-0.01 (-0.03, 0.01) *0.44*	-0.03 (-0.04, -0.008) *0.005*	0.003 (-0.12, 0.13) 0.95 [b]	-0.16 (-0.24, -0.07) *0.0002*
Global cognition	-0.03 (-0.05, -0.01) *0.001*	0.002 (-0.02, 0.02) *0.85*	-0.02 (-0.04, 0.004) *0.05*	0.01 (-0.12, 0.13) 0.95 [b]	-0.17 (-0.25, -0.08) *<0.0001*

Cognitive scores are standardized.
Components are based on categories of the risk score: Systolic blood pressure (SBP) (mmHg): (1) <120, (2) 120-129, (3) 130-139, (4) 140-159, (5) ≥160; total cholesterol (mg/dL): (1) <160, (2) 160-199, (3) 200-239, (4) 240-279, (5) ≥280; HDL cholesterol (mg/dL): (1) ≥60, (2) 50-59, (3) 45-49, (4) 35-44, (5) <35; diabetes: (1) no, (2) yes; smoking: (1) no, (2) yes.
[a] Adjusted for age, sex, ethnicity, marital status, education, depressive symptoms, alcohol intake, and physical activity.
[b] An interaction with ethnicity is present. Estimates of multivariable adjusted models (adjusted for ethnicity) may not be accurate.

Table 12. Associations of CVD risk factor components of the Framingham General Cardiovascular Disease Risk Profile and 10-year cognitive change, N=4839

Cognitive test	**SBP**	**Total cholesterol**	**HDL cholesterol**	**Diabetes**	**Smoking**
			β (95% CI) *p*		
Unadjusted					
Reasoning	-0.01 (-0.03, -0.001) *0.03*	-0.02 (-0.01, -0.004) *0.01*	-0.0005 (-0.01, 0.01) *0.93*	-0.02 (-0.04, -0.0009) *0.04*	-0.03 (-0.09, 0.02) *0.24*
Memory	0.007 (-0.02, 0.03) *0.55*	-0.01 (-0.04, 0.01) *0.41*	0.01 (-0.01, 0.03) *0.26*	-0.07 (-0.24, 0.10) *0.44*	0.06 (-0.04, 0.17) *0.23*
Semantic fluency	-0.01 (-0.03, 0.003) *0.11*	-0.01 (-0.04, 0.007) *0.16*	-0.007 (-0.02, 0.01) *0.44*	-0.01 (-0.03, 0.003) *0.11*	-0.03 (-0.11, 0.05) *0.46*
Phonemic fluency	-0.01 (-0.03, 0.004) *0.12*	-0.02 (-0.04, -0.0005) *0.04*	0.003 (-0.01, 0.02) *0.71*	-0.02 (-0.16, 0.11) *0.71*	-0.04 (-0.13, 0.04) *0.29*
Vocabulary	-0.01 (-0.02, -0.002) *0.01*	-0.008 (-0.02, 0.006) *0.24*	-0.005 (-0.01, 0.006) *0.37*	-0.02 (-0.05, 0.0005) *0.05*	-0.005 (-0.06, 0.04) *0.83*
Global cognition	-0.01 (-0.03, -0.002) *0.02*	-0.02 (-0.04, -0.007) *0.004*	-0.00004 (-0.01, 0.01) *0.99*	-0.01 (-0.02, -0.002) *0.02*	-0.01 (-0.06, 0.04) *0.67*
Age adjusted					
Reasoning	0.004 (-0.009, 0.01) 0.54	-0.02 (-0.03, -0.003) *0.01*	-0.001 (-0.1, 0.01) *0.82*	-0.06 (-0.15, 0.03) *0.23*	-0.05 (-0.11, 0.003) *0.06*
Memory	0.01 (-0.007, 0.04) 0.15	-0.01 (-0.04, 0.01) *0.46*	0.01 (-0.01, 0.03) *0.27*	-0.05 (-0.22, 0.12) *0.57*	0.04 (-0.06, 0.15) *0.38*
Semantic fluency	-0.01 (-0.03, 0.009) 0.30	-0.01 (-0.04, 0.007) *0.18*	-0.007 (-0.02, 0.01) *0.42*	-0.002 (-0.13, 0.13) *0.97*	-0.04 (-0.12, 0.04) *0.34*
Phonemic fluency	-0.01 (-0.03, 0.006) 0.18	-0.02 (-0.04, -0.0008) *0.04*	0.003 (-0.01, 0.02) *0.70*	-0.02 (-0.16, 0.11) *0.74*	-0.05 (-0.13, 0.03) *0.22*
Vocabulary	-0.008 (-0.02, 0.004) 0.18	-0.08 (-0.02, 0.006) *0.25*	-0.005 (-0.02, 0.005) *0.34*	-0.07 (-0.16, 0.01) *0.08*	-0.01 (-0.06, 0.03) *0.61*
Global cognition	-0.003 (-0.01, 0.01) 0.70	-0.02 (-0.04, -0.006) *0.005*	-0.0005 (-0.01, 0.01) *0.93*	-0.06 (-0.15, 0.02) *0.15*	-0.03 (-0.08, 0.02) *0.34*
Multivariable adjusted [a]					
Reasoning	0.003 (-0.01, 0.02) 0.64	-0.01 (-0.03, -0.002) *0.02*	-0.006 (-0.01, 0.006) *0.34*	-0.06 (-0.15, 0.03) *0.19*	-0.05 (-0.10, 0.006) *0.08*
Memory	0.02 (-0.009, 0.04) 0.20	-0.009 (-0.04, 0.02) *0.55*	0.01 (-0.008, 0.04) *0.18*	-0.08 (-0.25, 0.09) *0.37*	0.03 (-0.07, 0.14) *0.54*
Semantic fluency	-0.01 (-0.03, 0.008) 0.23	-0.01 (-0.04, 0.009) *0.23*	-0.006 (-0.02, 0.01) *0.51*	-0.04 (-0.17, 0.09) *0.52*	-0.05 (-0.14, 0.02) *0.17*
Phonemic fluency	-0.01 (-0.03, 0.006) 0.16	-0.02 (-0.04, 0.0005) *0.05*	0.006 (-0.01, 0.02) *0.54*	-0.04 (-0.17, 0.09) *0.57*	-0.06 (-0.15, 0.01) *0.13*
Vocabulary	-0.008 (-0.02, 0.004) 0.19	-0.007 (-0.02, 0.007) *0.31*	-0.006 (-0.01, 0.01) *0.92*	-0.08 (-0.17, 0.0009) *0.05*	-0.01 (-0.06, 0.03) *0.63*
Global cognition	-0.004 (-0.01, 0.009) 0.56	-0.002 (-0.03, -0.005) *0.01*	-0.0007 (-0.01, 0.01) *0.91*	-0.09 (-0.18, 0.0002) *0.05*	-0.04 (-0.09, 0.01) *0.18*

Cognitive scores are standardized.
Estimates for 10-year cognitive change are derived from linear mixed effects models using three cognitive assessments.
Components are based on categories of the risk score. Systolic blood pressure (SBP) (mmHg): (1) <120, (2) 120-129, (3) 130-139, (4) 140-159, (5) ≥160; total cholesterol (mg/dL): (1) <160, (2) 160-199, (3) 200-239, (4) 240-279, (5) ≥280; HDL cholesterol (mg/dL): (1) ≥60, (2) 50-59, (3) 45-49, (4) 35-44, (5) <35; diabetes: (1) no, (2) yes; smoking: (1) no, (2) yes.
[a] Adjusted for age, sex, ethnicity, marital status, education, depressive symptoms, alcohol intake, and physical activity.

III.1.3 Framingham Stroke Risk Profile

III.1.3.1 Background and Rationale

Since its development over two decades ago, The Framingham Stroke Risk Profile (FSRP) performance in predicting incident stroke has been evaluated in different populations (Bineau et al., 2009; Choi et al., 2009; Touboul et al., 2005; Voko et al., 2004). In addition to incident stroke, the FSRP has been shown to be associated with subclinical features of cardiovascular disease; in the Multi-Ethnic Study of Atherosclerosis (MESA), the FSRP predicted onset and progression of coronary artery calcium, a subclinical measure of atherosclerosis (DeFilippis et al., 2011).

With accumulating evidence for the role of stroke and stroke risk factors in relation to cognition, a number of studies have examined the association of stroke risk with various cognitive outcomes. One study examining the association between stroke risk and cognition in normal aging and Alzheimer's disease with and without depression, found that 10-year stroke risk predicted Alzheimer's disease in both depressed and non-depressed individuals. In addition, stroke risk was associated with poorer performance on memory and processing speed, but not on measures of attention, language, and executive functioning (Bangen et al., 2010).

A number of studies have examined the association between stroke risk and cognitive aging. In the earliest of such studies involving 235 older men, 10-year stroke risk was associated with decline in verbal fluency after 3 years; no association between stroke risk and decline in immediate or delayed verbal recall, and visual spatial function was observed (Brady et al., 2001). A number of studies based on the Framingham Offspring Study have followed. One reported an inverse association between stroke risk and cognitive performance in multiple cognitive domains including visual-spatial memory, attention, organization, scanning, and abstract reasoning (Elias et al., 2004a). Other studies in which neuropsychological tests were supplemented with quantitative MRI measures, demonstrated the association of stroke risk with age-associated brain atrophy. Higher stroke risk was associated with lower total cerebral brain volume ratio (TCBVr); lower TCBVr was associated with poorer performance on cognitive tests of attention, executive function, and visuospatial function. Among components of the FSRP, hypertension, diabetes, smoking, and previous CVD were independently and inversely associated with TCBVr (Seshadri et al., 2004). In addition, the FSRP and its components measured on average 7.5 years before

MRI were associated with white matter hyperintensity volume (WMHV) (Jeerakathil et al., 2004).

In the English Longitudinal Study of Ageing (ELSA), among 7377 adults 50 years and older, higher stroke risk was associated with poor global cognitive function, immediate and delayed verbal memory, semantic verbal fluency and processing speed (Llewellyn et al., 2008). Finally, among 23,752 participants of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, followed for an average of 4.1 years, stroke risk was related to rate of incident cognitive impairment (Unverzagt et al., 2011). Of the FSRP components, elevated blood pressure and left ventricular hypertrophy predicted clinically significant cognitive dysfunction (Unverzagt et al., 2011). However, limitations of these studies include their cross sectional design (Elias et al., 2004a; Llewellyn et al., 2008), a small select population (Brady et al., 2001), and short follow up and use of a single-item measure of cognitive performance (Unverzagt et al., 2011).

The objective of the current analysis is to examine the association between stroke risk (FSRP) and longitudinal change in cognitive performance starting in midlife, using three cognitive assessments over 10 years.

III.1.3.2 Methods

All Whitehall II participants free of stroke at baseline and for whom stroke risk could be calculated were included in this analysis. Forty eight individuals with prevalent stroke at baseline were excluded. Diagnosis of stroke or transient ischemic attack was based on participant self report. Risk score components (age, systolic blood pressure, use of antihypertensive mediation, diabetes mellitus, cigarette smoking, prior cardiovascular events, atrial fibrillation, left ventricular hypertrophy) were drawn from questionnaire and clinical examination data at phase 5 (baseline of this study) measured according to standard protocols described earlier.

Statistical analyses

Stroke risk was analyzed both in its continuous and categorical forms. As there was some suggestion of non-linearity in the association of stroke risk and cognitive scores at baseline, and 10-year cognitive change, stroke risk was categorized into quartiles with the first quartile representing lowest risk and the fourth quartile representing highest risk. In its continuous form, stroke risk was examined after a log transformation to correct the distribution's slight departure

from normality. The stroke risk × sex × time interaction did not suggest differences in10-year cognitive change between men and women; the analyses are therefore not stratified by sex.

Mean cognitive test scores in each stroke risk quartile were compared and cross sectional associations between stroke risk and cognitive scores at baseline were examined using linear regression. Association of stroke risk (as a continuous variable) and cognitive scores at baseline were first examined in unadjusted models, followed by models adjusted for demographic variables (age centered at the mean, sex, ethnicity, and education), and finally in models further adjusted for health related variables (depressive symptoms, physical activity, and alcohol intake).

Estimates of 10-year change in cognitive scores were obtained using linear mixed effects models. Adjustment for covariates were carried out similar to the cross sectional analyses. In these models, in addition to fixed effects terms for each covariate, their interactions with time were also included. In continuous form, representing a broader range of stroke risk, the effect of 1 unit increase in stroke risk and change in cognitive scores over 10 years (z-sores) was modeled. In its categorical form, 10-year cognitive change was estimated for each quartile and the lowest quartile of stroke risk was used as the referent category to tests differences in cognitive change in the other three quartiles.

In sensitivity analyses, the effect of interim stroke events on the association of stroke risk and 10-year cognitive change was examined by either excluding those with incident stroke during follow up, or adjusting for this in the analyses. In addition, we tested the effect of *APOE* genotype by repeating the analyses on a subset of participants with these data (n=4936).

III.1.3.3 Results

Cross sectional analyses are based on 5372 individuals with cognitive data at baseline and longitudinal analyses are based on 5810 participants with at least one out of three cognitive assessments; individuals with a history of stroke (n=48) and those missing data for covariates (n=260) were excluded.

Compared to individuals who were included in the longitudinal analyses, those who were not included were older (57.5 years vs. 55.6 years at phase 5, $p<0.001$), less likely to be men (65.1 vs 71%, $p<0.01$), or have a university degree (15% vs. 28%, $p<0.001$). Seventy three percent of participants had cognitive measures at all three phases and 20.2% at two phases. Compared to participants with data at one or two phases, those with complete cognitive data were primarily men (72% vs 67%, $p<0.01$), were younger (55.2 years vs. 56.7 years at phase 5,

p<0.01), and more likely to have a university education (29.8% vs 24.9%, p<0.01). They also had a lower stroke risk (4.3% vs 5.1%, p<0.001).Characteristics of the study sample (analytical sample of longitudinal analyses) are presented in Table 13. Mean 10-year stroke risk (%) in the entire sample was 4.5 (SD=3.5); mean stroke risk in the lowest risk quartile was 2.4 and in the highest quartile, 9.3. There was a marked negative trend in cognitive scores at baseline across the stroke risk quartiles; mean cognitive z-scores in all tests were lower in the highest stroke risk quartile compared with the lowest quartile (*p* for trend <0.001 in all tests except vocabulary where *p*=0.07) (Figure 6).

Cross sectional associations between stroke risk (quartiles) and cognitive scores at baseline (Table 14), indicate an inverse association between stroke risk and cognitive scores in all five cognitive tests as well as global cognitive score. For example higher stroke risk quartile, corresponding to an average 2% increase in stroke risk was associated with -0.04 SD (95% CI=-0.06, -0.02, *p* <0.0001) lower global cognitive score when adjusted for demographic factors. These associations remained after adjusting for demographic and health related factors. Similar associations were observed in analyses with stroke risk as a continuous variable (Table 15).

Longitudinal associations of stroke risk (quartiles) and 10-year change in cognitive scores are presented in Table 16. When adjusted for demographic variables, those in the highest stroke risk quartile had higher cognitive decline in phonemic and semantic fluency, vocabulary and global cognitive score, compared with individuals in the referent lowest quartile of stroke risk. Those in the middle two quartiles (2 and 3) had a similar rate of decline compared to the referent lowest risk quartile. Similar associations were observed when estimates were adjusted for demographic and health related factors. For example, compared with -0.21 SD (95% CI=-0.24, -0.19) decline in global cognitive score over 10 years, for those in the lowest stroke risk quartile, the corresponding decline in the highest risk quartile was -0.25 SD (95% CI=-0.28, -0.21, *p*=0.02). Again, these associations were evident only when comparing the highest stroke risk quartile (stroke risk ≥6%) with the lowest quartile (stroke risk <4%). The association of stroke risk in continuous form and 10-year cognitive change yielded similar results; higher stroke risk was associated with more rapid decline in phonemic and semantic fluency, vocabulary, and global cognitive score (Table 17).

Associations of individual CVD risk factor components of the FSRP with 10-year cognitive change are presented in Table 18. After adjusting for demographic and health related

factors, only diabetes was associated independently with faster decline in global cognitive score (β=-0.06; 95% CI=-0.01, -0.003, *p*=0.03). There was also some evidence of an association of left ventricular hypertrophy with faster decline in global cognition (β=-0.04; 95% CI=-0.08, -0.0004, *p*=0.05).

Results of sensitivity analyses accounting for interim stroke events did not affect the association between stroke risk and cognitive scores at baseline, or 10-year cognitive change. In addition, there was no interaction between stroke risk and *APOE* genotype in relation to 10-year cognitive change and adjusting for *APOE* genotype did not considerably affect the results.

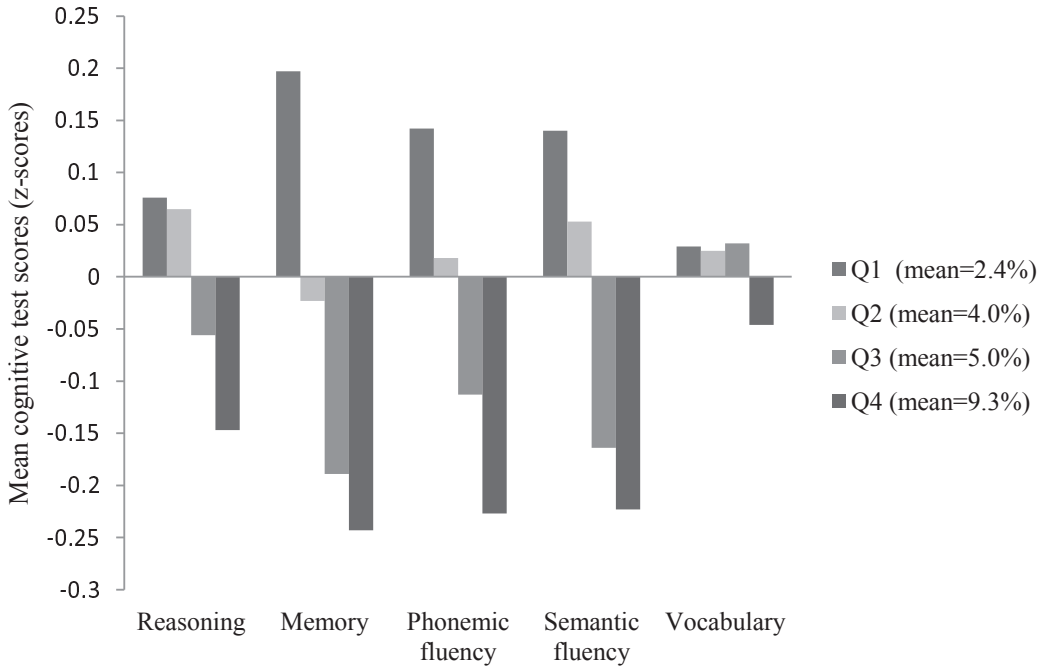

Figure 6. Mean cognitive z-scores at baseline by stroke risk quartile

Table 13. Characteristics of the study sample at baseline, N=5810

		Stroke risk quartile				
	All	1	2	3	4	*p*
Mean Framingham Stroke Risk	4.5	2.4	4.0	5.0	9.3	*<0.001*
FSRP components						
Age, y, mean (SD)	55.6 (6.0)	52.6 (4.5)	55.7 (5.6)	58.2 (5.8)	60.4 (5.5)	*<0.001*
Men	71.5	54.7	81.4	88.2	84.2	*<0.001*
Systolic blood pressure, mmHg, mean (SD)	123.0 (16.4)	113.4 (11.7)	124.5 (12.9)	129.2 (13.6)	138.1 (11.2)	*<0.001*
Antihypertensive medications	12.6	3.3	9.4	15.1	34.7	*<0.001*
Diabetes,	3.9	1.4	3.4	3.9	9.7	*<0.001*
Current smoker	9.7	3.8	10.7	14.3	15.2	*<0.001*
History of CVD	5.7	0.2	2.2	5.8	21.5	*<0.001*
Atrial fibrillation	0.5	0.09	0.2	0.5	1.2	*<0.001*
Left ventricular hypertrophy	5.0	0.8	2.8	5.4	11.1	*<0.001*
Covariates						
Education						
Lower primary/secondary	43.9	39.9	43.6	46.9	50.9	
A levels	26.2	26.5	27.6	26.3	24.4	
University	29.8	33.5	29.3	26.7	24.6	*<0.001*
White ethnicity	92.4	93.5	94.3	92.0	88.3	*<0.001*
Depressive symptoms	12.3					
Alcohol use						
None	14.9	15.8	13.9	12.4	16.1	
Moderate	60.6	62.2	59.0	58.1	60.7	
Heavy	24.4	21.9	27.1	29.5	23.2	*<0.001*
Physical activity						
Low	29.9	33.1	27.4	25.3	28.6	
Moderate	16.8	18.8	15.1	17.0	13.8	
High	53.3	47.9	57.5	57.7	57.5	*<0.001*

Values are percentages unless otherwise indicated.

Table 14. Association of stroke risk quartile with cognitive scores at baseline, N=5372

Cognitive tests	β (95% CI)	*p*
Unadjusted		
Reasoning	-0.07 (-0.09, -0.05)	*<0.0001*
Memory	-0.15 (-0.18, -0.13)	*<0.0001*
Phonemic fluency	-0.12 (-0.15, -0.10)	*<0.0001*
Semantic fluency	-0.13 (-0.15, -0.10)	*<0.0001*
Vocabulary	-0.02 (-0.04, 0.002)	*0.07*
Global cognition	-0.10 (-0.12, -0.08)	*<0.0001*
Adjusted for demographics [a]		
Reasoning	-0.03 (-0.06, -0.01)	*0.004*
Memory	-0.05 (-0.08, -0.03)	*0.0001*
Phonemic fluency	-0.04 (-0.06, -0.01)	*0.007*
Semantic fluency	-0.03 (-0.06, -0.005)	*0.01*
Vocabulary	-0.04 (-0.06, -0.02)	*0.0006*
Global cognition	-0.04 (-0.06, -0.02)	*<0.0001*
Adjusted for demographics and health related factors [b]		
Reasoning	-0.03 (-0.06, -0.01)	*0.003*
Memory	-0.05 (-0.08, -0.02)	*0.0001*
Phonemic fluency	-0.04 (-0.06, -0.01)	*0.005*
Semantic fluency	-0.03 (-0.06, -0.006)	*0.01*
Vocabulary	-0.04 (-0.06, -0.02)	*0.0002*
Global Cognition	-0.04 (-0.05, -0.02)	*<0.0001*

[a] Models adjusted for demographics include age centered at the mean, sex, ethnicity and education.
[b] Health related factors include depressive symptoms, physical activity, and alcohol consumption.

Table 15. Association of stroke risk (as continuous variable) and cognitive scores at baseline, N=5372

Cognitive tests	β (95% CI)	*p*
Unadjusted		
Reasoning	-0.07 (-0.11, -0.02)	*0.003*
Memory	-0.27 (-0.32, -0.23)	*<0.0001*
Phonemic fluency	-0.21 (-0.26, -0.17)	*<0.0001*
Semantic fluency	-0.22 (-0.26, -0.17)	*<0.0001*
Vocabulary	0.01 (-0.03, 0.05)	*0.56*
Global cognition	-0.15 (-0.18, -0.12)	*<0.0001*
Adjusted for demographics [a]		
Reasoning	-0.13 (-0.17, -0.08)	*<0.0001*
Memory	-0.09 (-0.15, -0.04)	*0.001*
Phonemic fluency	-0.09 (-0.15, -0.03)	*0.002*
Semantic fluency	-0.08 (-0.14, -0.03)	*0.003*
Vocabulary	-0.14 (-0.18, -0.09)	*<0.0001*
Global cognition		
Adjusted for demographics and health related factors [b]		
Reasoning	-0.13 (-0.17, -0.08)	*<0.0001*
Memory	-0.09 (-0.15, -0.03)	*0.002*
Phonemic fluency	-0.09 (-0.15, -0.03)	*0.002*
Semantic fluency	-0.08 (-0.14, -0.03)	*0.003*
Vocabulary	-0.15 (-0.19, -0.09)	*<0.0001*
Global Cognition	-0.11 (-0.14, -0.07)	*<0.0001*

FSRP scores were analyzed after a logarithmic transformation to normalize the distribution.

[a] Models adjusted for demographics include age centered at the mean, sex, ethnicity, and education.

[b] Health related factors include depressive symptoms, physical activity, and alcohol consumption.

Table 16. 10-year cognitive change by stroke risk quartile, N=5810

Cognitive tests	Stroke risk quartile			
	1 (mean=2.4%)	2 (mean=4.0%)	3 (mean=5.0%)	4 (mean=9.3%)
	10-year cognitive change (95% CI)			
Unadjusted				
Reasoning	-0.27 (-0.29, -0.24)	-0.31 (-0.34, -0.28) *	-0.38 (-0.42, -0.34) ***	-0.41 (-0.44, -0.37) ***
Memory	-0.24 (-0.28, -0.20)	-0.24 (-0.30, -0.18)	-0.33 (-0.39, -0.26)	-0.26 (-0.32, -0.19)
Phonemic fluency	-0.27 (-0.29, -0.24)	-0.34 (-0.39, -0.30) **	-0.34 (-0.39, -0.28) *	-0.38 (-0.43, -0.33) **
Semantic fluency	-0.27 (-0.29, -0.24)	-0.34 (-0.39, -0.29)	-0.40 (-0.45, -0.34) *	-0.41 (-0.46, -0.36) **
Vocabulary	0.05 (0.03, 0.06)	0.03 (0.008, 0.06)	-0.002 (-0.04, 0.03) **	-0.05 (-0.08, -0.02) ***
Global cognition	-0.21 (-0.23, -0.20)	-0.24 (-0.26, -0.22) *	-0.29 (-0.32, -0.26) ***	-0.31 (-0.33, -0.28) ***
Adjusted for demographics [a]				
Reasoning	-0.31 (-0.34, -0.28)	-0.30 (-0.34, -0.26)	-0.33 (-0.38, -0.29)	-0.33 (-0.37, -0.29)
Memory	-0.23 (-0.29, -0.17)	-0.18 (-0.26, -0.10)	-0.23 (-0.32, -0.14)	-0.20 (-0.24, -0.08)
Phonemic fluency	-0.32 (-0.37, -0.27)	-0.34 (-0.40, -0.28)	-0.39 (-0.46, -0.32)	-0.41 (-0.48, -0.34) *
Semantic fluency	-0.22 (-0.27, -0.17)	-0.26 (-0.33, -0.22)	-0.26 (-0.33, -0.19)	-0.30 (-0.36, -0.24) *
Vocabulary	0.05 (0.02, 0.08)	0.06 (0.02, 0.09)	0.03 (-0.004, 0.08)	-0.008 (-0.04, 0.03) **
Global cognition	-0.21 (-0.23, -0.18)	-0.21 (-0.23, -0.18)	-0.23 (-0.26, -0.21)	-0.24 (-0.27, -0.21) *
Adjusted for demographics and health related factors [b]				
Reasoning	-0.33 (-0.36, -0.29)	-0.32 (-0.36, -0.28)	-0.35 (-0.40, -0.30)	-0.35 (-0.40, -0.30)
Memory	-0.25 (-0.32, -0.18)	-0.20 (-0.28, -0.12)	-0.25 (-0.34, -0.16)	-0.18 (-0.27, -0.009)
Phonemic fluency	-0.33 (-0.39, -0.27)	-0.34 (-0.41, -0.28)	-0.39 (-0.47, -0.32)	-0.42 (-0.48, -0.13) *
Semantic fluency	-0.21 (-0.27, -0.16)	-0.27 (-0.33, -0.20)	-0.25 (-0.32, -0.18)	-0.29 (-0.36, -0.22) *
Vocabulary	0.04 (0.01, 0.08)	0.05 (0.01, 0.09)	0.03 (0.01, 0.08)	-0.01 (-0.05, 0.03) **
Global Cognition	-0.21 (-0.24, -0.19)	-0.16 (-0.24, -0.18)	-0.24 (-0.27, -0.20)	-0.25 (-0.28, -0.21) *

Difference in mean cognitive change compared to referent quartile 1, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

[a] Models adjusted for demographics include age centered at the mean, sex, ethnicity, and education.

[b] Health related factors include depressive symptoms, physical activity, and alcohol consumption.

Table 17. Association of stroke risk (as a continuous variable) and 10-year cognitive change, N=5810

Cognitive tests	β (95% CI)	*p*
Unadjusted		
Reasoning	-0.07 (-0.09, -0.05)	*0.001*
Memory	-0.05 (-0.09, -0.003)	*0.03*
Phonemic fluency	-0.06 (-0.09, -0.02)	*0.002*
Semantic fluency	-0.08 (-0.11, -0.04)	*<0.0001*
Vocabulary	-0.06 (-0.08, -0.04)	*<0.0001*
Global cognition	-0.06 (-0.08, -0.05)	*<0.0001*
Adjusted for demographics [a]		
Reasoning	-0.007(-0.03, 0.03)	*0.96*
Memory	0.01 (-0.05, 0.07)	*0.73*
Phonemic fluency	-0.06 (-0.01, -0.02)	*0.009*
Semantic fluency	-0.07 (-0.01, -0.02)	*0.005*
Vocabulary	-0.04 (-0.07, -0.008)	*0.01*
Global cognition	-0.03 (-0.05, -0.005)	*0.02*
Adjusted for demographics and health related factors [b]		
Reasoning	-0.003 (-0.04, 0.03)	*0.85*
Memory	0.009 (-0.05, 0.07)	*0.77*
Phonemic fluency	-0.06 (-0.01, -0.02)	*0.01*
Semantic fluency	-0.07 (-0.01, -0.02)	*0.004*
Vocabulary	-0.04 (-0.07, -0.007)	*0.01*
Global Cognition	-0.03 (-0.05, -0.006)	*0.01*

FSRP scores were analyzed after a logarithmic transformation to normalize the distribution.

[a] Models adjusted for demographics include age centered at the mean, sex, ethnicity, and education.

[b] Health related factors include depressive symptoms, physical activity, and alcohol consumption.

Table 18. Association of CVD risk factor components of the Framingham Stroke Risk Profile and 10-year change in global cognitive scores, N=5810

	Unadjusted			Adjusted for demographics a			Adjusted for demographic and health related factors b		
Risk factor	β	95 % CI	*p*	β	95 % CI	*p*	β	95 % CI	*p*
SBP	-0.02	(-0.05, -0.01)	*0.01*	-0.01	(-0.04, 0.02)	*0.39*	-0.01	(-0.04, 0.02)	*0.41*
Diabetes	-0.07	(-0.11, -0.01)	*0.02*	-0.04	(-0.10, 0.003)	*0.05*	-0.06	(-0.10, -0.003)	*0.03*
Smoking	-0.03	(-0.08, 0.009)	*0.16*	-0.03	(-0.07, 0.003)	*0.07*	-0.03	(-0.07, 0.003)	*0.08*
Prior CVD	-0.01	(-0.09, 0.05)	*0.64*	0.002	(-0.04, 0.05)	*0.93*	0.001	(-0.04, 0.05)	*0.94*
AF	-0.05	(-0.18, 0.10)	*0.45*	-0.05	(-0.22, 0.12)	*0.53*	-0.07	(-0.20, 0.11)	*0.54*
LVH	-0.05	(-0.13, -0.01)	*0.03*	-0.04	(-0.08, 0.003)	*0.08*	-0.04	(-0.08, -0.0004)	*0.05*

Components are based on categories of the risk score. MEN: age (years): (1) <57, (2) 57-59, (3) 60-62, (4) 63-65, (5) 66-68, (6) 69-72; untreated systolic blood pressure (SBP) (mmHg): (1) 97-105, (2) 106-115, (3) 116-125, (4) 126-135, (5) 136-145, (6) 146-155, (7) 156-165, (8) 166-145, (9) 176-185, (10) 186-195, (11) 196-205; treated SBP (mmHg): (1) 97-105, (2) 106-112, (3) 113-117, (4) 118-123, (5) 124-129, (6) 130-135, (7) 136-142, (8) 143-150, (9) 151-161, (10) 162-176, (11) 177-205; diabetes: (1) no, (2) yes; smoking: (1) no, (2) yes; prior cardiovascular disease (CVD): (1) no, (2) yes; atrial fibrillation (AF): (1) no, (2) yes; left ventricular hypertrophy (LVH): (1) no, (2) yes. WOMEN: age (years): (1) <57, (2) 57-59, (3) 60-62, (4) 63-64, (5) 65-67, (6) 68-70; untreated SBP (mmHg): (1) 95-106, (2) 107-118, (3) 119-130, (4) 131-143, (5) 144-155, (6) 156-167, (7) 168-180, (8) 181-192, (9) 193-204, (10) 205-216; treated SBP (mmHg): (1) 95-106, (2) 107-113, (3) 114-119, (4) 120-125, (5) 126-131, (6) 132-139, (7) 140-148, (8) 149-160, (9) 161-204, (10) 205-216; diabetes: (1) no, (2) yes; smoking: (1) no, (2) yes; prior CVD: (1) no, (2) yes; AF: (1) no, (2) yes; LVH: (1) no, (2) yes.

[a] Models adjusted for demographics include age centered at the mean, sex, ethnicity, and education.

[b] Health related factors include depressive symptoms, physical activity, and alcohol consumption.

III.1.3.4 Discussion

The association of the Framingham General Cardiovascular Disease Risk Profile and the Framingham Stroke Risk Profile, in relation to cognitive outcomes were examined in the preceding sections. In cross sectional analyses, higher CVD risk was associated with lower scores in memory and global cognition. Observed effects were larger in women compared with men; in women, 10% increment in CVD risk was associated with lower scores in reasoning, memory, vocabulary and global cognition; in men CVD risk was associated with lower vocabulary and global cognitive scores. Higher stroke risk was associated with poorer scores in all cognitive tests including global cognitive scores at baseline. In longitudinal analyses using three cognitive assessments over 10 years, CVD risk was associated with more rapid 10-year decline in all cognitive scores except reasoning; magnitude of the associations were similar in men and women. Higher stroke risk was associated with faster 10-year cognitive decline in all cognitive tests except memory and reasoning.

The differences between the two risk scores in relation to cognition are likely related to differences in the distribution of CVD and stroke risk profiles, which is expected since the two risk scores were developed to predict different outcomes. Regardless, these results demonstrate that both CVD and stroke risk are associated not only with cognitive scores at baseline but also rates of long-term cognitive decline on more than one cognitive test. The longitudinal results are particularly important as they provide a less biased estimate of the causal association between CVD /stroke risk and cognition than do cross sectional data. The relationship between CVD risk factors and cognition is subject to the influence of multiple factors, thus cross sectional studies do not provide the means to examine the direction of this association. In particular, among older adults who have more cardiovascular comorbidity as well as age related cerebral changes, these associations are further confounded. The findings of the present study indicate that even at younger ages and among cognitively intact middle aged individuals with relatively lower cardiovascular comorbidity, CVD risk factor aggregation is indicative of differential cognitive decline. These observations are consistent with the notion of clustering and conjoint influences of multiple risk factors in mediating CVD risk (De et al., 2003; Kannel et al., 2004; Yusuf et al., 2004). In relation to cognition, it is likely that mid to low risk levels on more than one component of the risk scores can lead to a threshold of risk that is detrimental to cognitive aging (Kivipelto et al., 2005; Whitmer et al., 2005b).

The Framingham General Cardiovascular Disease Risk Profile was developed relatively recently and although a number of studies have used this risk score to assess CVD risk in relation to carotid atherosclerosis (Cardenas et al., 2012), frontal lobe glucose metabolism (Kuczynski et al., 2009), and Alzheimer's disease pathologic progression (Lo et al., 2012), its association with cognitive outcomes remains unknown. Some comparison can be made however with one longitudinal study with repeat cognitive assessments that examined the Framingham Risk Score for CHD to assess 10-year cognitive decline trajectories among older men and women (mean age 65 years) (Laughlin et al., 2011). This study found that higher CHD risk was associated with a faster rate of cognitive decline in women but not men. Differences in the rate of decline were observed for global cognition and MMSE as well as individual tests of semantic fluency, long term recall, and Trail-Making Test B, a test of visuo-motor tracking, and executive function (Laughlin et al., 2011). Similarly, our longitudinal analyses revealed an association of CVD risk with 10-year decline on all cognitive tests except reasoning. However contrary to their findings, we found more apparent associations of CVD risk and cognitive decline in men. However these sex-specific associations between the two studies cannot be compared because this longitudinal study is based on an elderly population and thus is vulnerable to selective attrition. There is evidence to suggest that compared to women with cognitive impairment, men with cognitive impairment are more likely to die and since in this study more men than women died during follow up, survival bias could have prevented detection of associations with CHD risk in men (Kurland et al., 2009). In our study, differences in the distribution of CVD risk in men and women can partly explain the observed associations. Since we examined CVD risk as a continuous variable (10% increments in CVD risk), the effects seem larger for women than for men. This is in part due to the differences in CVD risk distributions in men and women. In our study women had a much lower CVD risk compared with men (4.1% vs 12%). Therefore a 10% increase in CVD risk may be a considerably larger increase in risk in women compared to men. Whereas cross sectional associations between CVD risk and cognitive scores at baseline appear to be stronger in women, effect sizes for the associations of CVD risk with 10-year cognitive change between men and women are more similar.

A number of studies have shown that increased stroke risk as measured by the FSRP is related to poorer cognitive performance cross-sectionally (Elias et al., 2004a; Llewellyn et al., 2008) and prospectively (Brady et al., 2001; Seshadri et al., 2004). Although our results cannot be

directly compared with these studies due to major differences in study populations and cognitive tests used, our results are largely consistent with these reports. Our cross sectional findings of an association of stroke risk with lower cognitive scores on all tests at baseline is similar to results of a cross sectional study of 7377 participants of the English Longitudinal Study of Aging (ELSA) that found a 10 percentage point increase in stroke risk to be associated with a large decrement in global cognitive function and poor performance in multiple tests including immediate and delayed verbal memory, semantic verbal fluency, and processing speed (Llewellyn et al., 2008). Likewise, a cross sectional analysis based on 1275 men and women from the Framingham Offspring Study, found an inverse association between stroke risk and abstract reasoning, visual-spatial memory, visual organization, concentration, and visual scanning and tracking. However, contrary to our results, this study did not find an association of stroke risk with memory (Elias et al., 2004a).

Results of our longitudinal analysis suggesting faster 10-year decline in verbal fluency, vocabulary and global cognition are also consistent with results of one longitudinal study with more than two cognitive assessments (over an average follow up of 4 years) that found increased rate of incident cognitive impairment related to higher stroke risk. However, this study used a global cognitive measure (Six-item Screener) and did not examine different cognitive domains (Unverzagt et al., 2011). Some comparisons can be made with prospective studies including a more recent analysis of the Framingham Offspring cohort that examined FSRP in relation to performance on neuropsychological tests as well as subclinical brain injury determined by quantitative brain MRI (Seshadri et al., 2004). This study reported an inverse association between stroke risk and total cerebral brain volume ratio which was in turn positively associated with performance on tests of executive function, attention and visual-spatial function but not with performance on tests of verbal memory. Like our longitudinal results, the absence of an association of stroke risk with memory was also reported in the prospective study of 235 older men that found an association between stroke risk and decline only in verbal fluency but not memory or visual-spatial function (Brady et al., 2001). A longitudinal study of CVD risk factor exposure in midlife with cognitive decline reported associations with decline in executive function and not memory (Debette et al., 2011).

A commonly used index of frontally mediated cognitive function is verbal fluency including letter fluency (S words) and category fluency (animal names) where an individual is

asked to generate as many unique words as possible within a short time period. There is a preponderance of evidence showing that performance on verbal fluency test is dependent on frontal lobe functions to a greater degree than other brain functions. This evidence comes from neuropsychological studies of individuals with frontal lobe lesions who show greater deficits on verbal fluency tests compared to those with lesions to other brain regions (Martin et al., 1990). Moreover, studies of healthy individuals have demonstrated physiological activation of the frontal lobes during these tests, although activation of other brain areas has also been observed (Mummery et al., 1996). There is also evidence that in persons with stroke related cognitive dysfunction, verbal fluency is disproportionately impaired relative to other cognitive functions (e.g. memory). Further, phonemic (letter) fluency that requires greater selection may be more sensitive to frontal lobe dysfunction than semantic (category) fluency (Lafosse et al., 1997; Robinson et al., 2012). Therefore, it appears that cognitive changes related to CVD risk may be manifested as decline in executive function and verbal fluency more than verbal memory.

Although all components of the Framingham CVD and stroke risk scores have been linked with cognitive outcomes, though to varying degrees, we found that of the components of the Framingham CVD risk score, diabetes and total cholesterol, and of components of the Framingham stroke risk score, diabetes and left ventricular hypertrophy were associated with greater 10-year cognitive decline. Previous studies of the FSRP that also examined individual risk score components have found independent associations with multiple components of the risk score (Elias et al., 2004a; Llewellyn et al., 2008; Seshadri et al., 2004). In one cross sectional study only diabetes, smoking and history of cardiovascular disease were independently associated with poorer cognitive function (Llewellyn et al., 2008). Another cross sectional study based on the Framingham Offspring cohort found that all FSRP components were inversely related to performance on at least one cognitive test; all components except systolic blood pressure were associated with poorer scores on concentration, visual scanning and tracking composite score; AF was related to the Similarities test score (abstract reasoning), and systolic blood pressure was inversely related to visual-spatial memory and organization (Elias et al., 2004a). The prospective analysis of the same cohort found independent prospective associations of hypertension, diabetes, smoking and history of CVD with lower total cerebral brain volume ratio (TCBVr) and poorer performance on cognitive tests of attention, executive function and visual-spatial function (Seshadri et al., 2004). In the only longitudinal analysis with repeat cognitive measures, LVH was

the only FSRP component independently associated with incident cognitive impairment (Unverzagt et al., 2011). However, the lack of findings for an independent association of other risk score components with cognitive decline may be due to the use of only one broad measure of cognition like MMSE that may be less sensitive than specific cognitive tests (e.g. verbal fluency and processing speed in detecting subclinical cognitive deficits and cognitive decline (Cukierman et al., 2005).

Our findings of an independent association of diabetes with 10-year cognitive decline is consistent with a large body of evidence linking diabetes with accelerated cognitive decline (Knopman et al., 2009), incident cognitive impairment (Arvanitakis et al., 2004; Crowe et al., 2010; Knopman et al., 2001), and incident dementia (Kuller et al., 2003; Luchsinger et al., 2001; Ott et al., 1999a; Schnaider et al., 2004; Schrijvers et al., 2010). In fact in the present study, of all individual CVD risk factor components of the risk scores, diabetes showed the largest effect in relation to 10-year cognitive decline. Of components of the Framingham CVD risk score, total cholesterol was associated with 10-year cognitive decline although the magnitude of the association was small. Although there are no previous studies of the Framingham CVD risk score with which to compare these results, several studies have linked high total cholesterol and low HDL cholesterol levels to cognitive decline, MCI (Kivipelto et al., 2001a) and dementia (Dufouil et al., 2005), although we did not find an association between HDL cholesterol and 10-year cognitive decline.

There was also indication of an association between LVH and faster 10-year cognitive decline. LVH is a pathologic reaction to cardiovascular disease and a marker of long term exposure to high blood pressure whereby an increase in the load the heart contracts against results in an increase in volume of heart muscles and functional degradation (Gardin et al., 1997; Verdecchia et al., 2001). A cross sectional study based on the Framingham Offspring Study cohort reported an inverse association between LVH and cognition; this relationship was attenuated when blood pressure was considered and eliminated when coronary heart disease and various cardiovascular risk factors (e.g. cholesterol, diabetes, smoking) were taken into account (Elias et al., 2007). A longitudinal study linking LVH (and FSRP) to incident cognitive impairment extends these findings by showing a longitudinal relationship between LVH and cognitive impairment independent of other demographic and cardiovascular risk factors (Unverzagt et al., 2011). This study also found that elevations in systolic blood pressure were

associated with incident cognitive impairment even in those without LVH, suggesting an early role for elevated blood pressure in the relationship of LVH and cognitive decline. In contrast to this and other studies that reported a relationship of hypertension with cognitive decline (Debette et al., 2011; Elias et al., 2004b; Knopman et al., 2001; Knopman et al., 2009), cognitive impairment and dementia (Kivipelto et al., 2001a; Kivipelto et al., 2001b; Launer et al., 2000; Reitz et al., 2007), in our study, systolic blood pressure did not show an independent association with cognitive decline over 10 years. These findings may be due to the age and systolic blood pressure distribution of our study population that consisted mainly of middle aged adults (mean age of 55 years at baseline) with over 70% having systolic blood pressure values in the low range (untreated SBP <136 mmHg and treated SBP<124 mmHg). However, in our study there was evidence of a threshold effect. Individuals in the lowest four SBP categories (men untreated SBP<136 mmHg, treated SBP<124 mmHg; women untreated SBP<144 mmHg, treated SBP<126 mmHg) had similar 10-year decline in global cognitive scores; those in the middle SBP category (men untreated SBP136 to145 mmHg, and women untreated SBP 144 to 155 mmHg) had significantly greater decline compared to the lowest SBP category (see Appendix Table A6). Therefore there may be a threshold at and above which adverse effects of elevated blood pressure in relation to cognitive decline may be more apparent.

Although direct independent associations of systolic blood pressure and cognitive decline were not apparent it is likely that systolic blood pressure would have a mediating role in the relation between LVH with cognitive decline as LVH is a marker of long term exposure to elevation blood pressure. Indeed in the current analysis, the association of LVH with 10-year cognitive decline disappeared after adjusting for systolic blood pressure and history of CVD. Clearly, these risk factors (i.e. blood pressure, heart disease, LVH) and their separate effects on cerebrovascular changes, or cognition cannot be differentiated; this very notion supports the use of a multi-risk factor model.

The mechanisms underlying the association involving CVD/stroke risk with cognitive decline have been discussed earlier. These include subclinical cerebrovascular changes including white matter abnormalities, brain atrophy, and silent brain infarction (Das et al., 2008; Seshadri et al., 2004). An accumulation of insults from multiple risk factors is likely to underlie the association of composite vascular risk with cognitive decline.

The importance of these findings is threefold. First, we found that in our relatively low-risk middle aged population there was detectable decline in cognitive performance over 10 years related to elevated CVD risk. Second, that CVD risk is associated with cognitive decline in multiple cognitive domains with possibly greater involvement of frontally mediated functions such as verbal fluency as previously speculated. Third, that both Framingham risk scores while initially developed to predict cardiovascular and cerebrovascular events, are also useful in assessing risk of cognitive decline especially at midlife where greatest benefit can be achieved from modification of CVD risk factors.

III.2 Comparison of Framingham cardiovascular risk scores with a dementia risk score for predicting cognitive outcomes

III.2.1 Background and Rationale

The Framingham General Cardiovascular Disease Risk Profile and the Framingham Stroke Risk Profile were shown to predict cognitive outcomes in multiple domains, starting in midlife as described in the preceding sections. However similar evidence for use of dementia risk scores to predict cognitive outcomes at earlier ages is lacking. Only one dementia risk score developed based on midlife risk factors exists (Kivipelto et al., 2006) and only one study has examined whether the CAIDE dementia risk score developed to assess dementia risk based on risk factors present at midlife is associated with early cognitive outcomes. This prospective study of a middle aged population found that the CAIDE dementia risk score predicted cognitive impairment after 15 years (Reijmer et al, 2011b).

In addition, given the recent interest in utilizing risk scores particularly cardiovascular risk scores to assess cognitive outcomes, and the increasing emphasis on early detection and risk modification, the question remains regarding the best screening tools and risk scores to use in clinical and research settings in non-elderly populations. There is a dearth of comparative studies of dementia risk scores mainly due to major limitations of these risk scores (e.g. unobtainable measures and low predictive accuracy). Moreover the relative utility and predictive power of cardiovascular risk scores and dementia risk scores in relation to cognitive outcomes remains unknown.

The objective of this study is to examine the association of the CAIDE dementia risk score in relation to 10-year cognitive decline and to compare this dementia risk score with two well known cardiovascular risk scores to determine which risk score performs better in predicting cognitive change over 10 years in a middle aged population. The decision regarding which score may be better suited to this purpose would have to be based on predictive value as well as availability, feasibility and ease of application of the risk score, which will be discussed in this study.

III.2.2 Methods

This study involves two sets of analyses: one to compare the dementia risk score with the Framingham Stroke Risk Profile; the other, to compare the dementia risk score with the Framingham General Cardiovascular Disease Risk Profile. The methods used are similar for both analytical samples. For simplicity and to avoid repetition, details of the methods are described for the first set of samples that compare the dementia risk score with the stroke risk score and only specific differences between the two sets of analyses will be pointed out.

Components of the CAIDE dementia risk score and the stroke risk score were drawn from questionnaire and clinical examinations data at phase 5 and risk scores were calculated according to the risk functions described in preceding sections. There are two versions of the CAIDE dementia risk score (with and without *APOE ε4* genotype status). Since in the Whitehall II study *APOE* genotype was determined in a subsample of participants, the two versions of the dementia risk score are based on different samples. Hereafter, sample 1 corresponds to the first version of the dementia risk score that does not include *APOE ε4* genotype, and sample 2 corresponds to the second version of the risk score that incorporates *APOE ε4* genotype. All analyses were performed separately on both samples.

Statistical analysis

Risk scores were assessed in two forms. First, they were categorized into three risk groups in which the numbers per group were most comparable between the two risk scores (constructing exact tertiles or quartiles was not possible due to the distribution of risk values). These were taken to represent groups of low, intermediate, and high risk individuals. Although cut off values for risk categories have been reported for the CAIDE dementia risk score, these cut off points do not correspond to the risk distribution in our study sample who have lower dementia risk compared to

the CAIDE population. Therefore in these analyses risk categories are based on the risk distribution in the analytical sample of the Whitehall II population. Dementia risk groups were categorized as low (0-6), intermediate (7-8), and high (9-15); stroke risk groups were low (1-3), intermediate (4-5), and high (≥6). CVD risk groups were low (1-7), intermediate (≥7 -13), and high (≥13). Second, we examined risk in its continuity both as a form of sensitivity analysis and to represent a wider range of risk. Risk values were log transformed (to correct slight departure from normality in FSRP distribution), and standardized (z-scores, mean=0, SD=1) to allow comparability of the two risk scores.

In cross sectional analyses linear regression was used to examine the association between the risk scores and cognitive scores at baseline. Longitudinal analyses consisted of fitting linear mixed effects models to estimate cognitive change using three cognitive measures over 10 years. Models included fixed effects for time, the main effect term for dementia/stroke risk and interactions between time and dementia/stroke risk where the main effect represents its effect at time 0 (baseline) and the interaction between the variable and time represents the effect of the variable on change in cognitive score over time. Both slope and intercept were fitted as random effects allowing them to vary between individuals.

Since the primary objective in this study was to compare the predictive performance of the two risk scores, a practical approach was taken with an interest to examining how these risk scores compare if they were to be used in primary care settings. Therefore we compared the risk scores as they are without any statistical adjustments for additional variables. The most important factors that would normally be expected to be taken into account are age and sex and co-occurring CVD risk factors that are already incorporated in the risk scores.

In order to compare estimates of the association of dementia risk and cognitive scores (10-year cognitive change in longitudinal analyses) with those of stroke risk, we used beta estimates derived from the analyses based on standardized risk scores by subtracting $\text{beta}_{\text{FSRP}}$ from $\text{beta}_{\text{CAIDE}}$. A 95% confidence interval around the differences was then calculated using a bootstrap method with 2000 resamplings. This method was used because the beta estimates for the two risk scores are unlikely to be independent since they are calculated from samples based on the same population (Whitehall II) and the fact that the risk scores share some components (e.g. systolic blood pressure). Therefore the conventional method for comparing two independent statistics

would be inappropriate. The bootstrap method enables calculation of confidence intervals around the difference between the estimates to determine if the two estimates are statistically different.

Post-hoc analyses

We supplemented the main analyses by extending the examination of the association of dementia and stroke risk scores to their constituents. Cross sectional and longitudinal analyses similar to those described above were carried out to determine whether the observed associations between stroke or dementia risk are tied to a single component of the risk scores, focusing on components not common to both risk scores.

Cross sectional analyses revealed education to be the component in the dementia risk score most strongly associated with cognitive scores. The association of education with cognitive scores at baseline was largest compared to the other components-not an unexpected finding since education is a strong predictor of cognitive outcomes. Suspecting education to have a major effect in driving the observed associations between the CAIDE dementia risk and cognitive scores, we carried out the main analyses on a modified version of the dementia risk score that did not include the education term. These analyses were only exploratory since in the absence of one or more component of a composite risk measure, coefficients of the remaining components would take different values and recalibration of the prediction model would be required.

III.2.3 Results

Comparison of CAIDE dementia risk score and the Framingham Stroke Risk Profile

Of the 7830 participants in phase 5 of the Whitehall II study, 5278 (67%) had complete data for all components of both dementia and stroke risk scores; 4418 (56%) also had data for *APOE* genotype. Forty four individuals with a history of stroke or TIA at baseline were excluded. Of the remaining participants, 4812 individuals in sample 1 and 4057 in sample 2 had cognitive data at phase 5 and were included in the cross sectional analyses; 5157 individuals in sample 1 and 4374 in sample 2 had at least one out of three cognitive measures over the 10 year follow up and were included in the longitudinal analyses. Approximately 74% of individuals in sample 1 and 84% in sample 2 had cognitive data at all three phases.

Characteristics of the study sample at baseline are presented in Table 19 for sample 1 (appendix Table A2 for sample 2). Mean age of participants at baseline was 55.6 years (SD=5.9)

in sample 1, and 55.4 years (SD=5.9) in sample 2; approximately 70% of participants in both samples were men. Compared to individuals not included in the analyses, the analytical samples consisted of younger and more educated adults: in sample 1 mean age was 55.6 years vs. 57.5 years at phase 5 (p<0.001); 29.5% vs. 24.7% had a university degree (p<0.001). The correlation between FSRP and dementia risk score were 0.35 and 0.33 for versions 1 and 2 respectively (p<0.05). For dementia and stroke risk groups, there was no substantial overlap between the two risk groups, such that high dementia risk and high stroke risk groups consist of the same individuals. In the high risk group, 41% of sample 1 and 46% of sample 2 were overlapping between the two risk scores.

In cross sectional analyses both dementia and stroke risk were inversely associated with cognitive scores at baseline in all tests except stroke risk that was not associated with vocabulary. In sample 1 (Table 20), 1 unit increase in dementia risk was associated with -0.22 SD (95% CI= -0.24, -0.20) lower global cognitive score; the equivalent for stroke risk was -0.09 SD (95 % CI = -0.11, -0.07). This difference of -0.13 (95% CI= -0.16, -0.11) was statistically significant (as indicated by bootstrap calculated confidence intervals around the difference) pointing to stronger cross-sectional associations between dementia risk and cognitive scores in all tests except memory. In sample 2 (Table A3), 1 unit increase in dementia risk was associated with -0.26 SD (95% CI= -0.29, -0.23) lower global cognitive score; the equivalent for stroke risk was -0.08 SD (95 % CI = -0.10, -0.06). Again, confidence intervals around the differences in the estimates indicate statistically stronger associations between dementia risk and cognitive scores at baseline, compared to stroke risk, in all tests except memory.

In longitudinal analyses estimating 10-year change in cognitive scores as a function of dementia and stroke risk, both by risk group, and continuous standardized risk, higher stroke risk was associated with faster cognitive decline in all cognitive tests except memory, whereas higher dementia risk was not associated with faster cognitive decline in memory, phonemic and semantic fluency. Confidence intervals indicated statistically different associations for semantic fluency and global cognition. In sample 1 (Table 21), for semantic fluency (difference in betas=0.04; 95 % CI = 0.02, 0.06) and global cognition (difference in betas=0.02; 95 % CI = 0.01, 0.04) there was evidence of faster cognitive decline as a function of stroke risk compared to dementia risk. Similarly, in sample 2 (Table A4), there was evidence of faster cognitive decline as a function of stroke risk compared to dementia risk in semantic fluency (difference in

betas=0.05; 95 % CI = 0.03, 0.07) and global cognitive score (difference in betas=0.02; 95 % CI = 0.01, 0.04).

Of the components of CAIDE dementia risk score in sample 1 (Table 22), all risk factors were associated with global cognitive score at baseline (all *p* values <0.001) except total cholesterol (*p*=0.31). The magnitude of the effect was strongest for education (β=-0.46; 95% CI=-0.49, -0.43). All FSRP components except atrial fibrillation and left ventricular hypertrophy were associated with global cognitive score at baseline; the observed effect was largest for diabetes (β=-0.34; 95% CI=-0.44, -0.23) (Table 23). In sample 2, all risk factors of the dementia risk score were associated with global cognitive score at baseline (all *p* values <0.001) except total cholesterol (*p*=0.75) and *APOE ε4* genotype (*p*=0.26). Again, the magnitude of effects was strongest for education (β=-0.46; 95% CI=-0.50, -0.44) (Table A5). Similar to sample 1, all FSRP components except atrial fibrillation and left ventricular hypertrophy were inversely associated with global cognitive score at baseline (all *p* values <0.001) with similar large effects observed for diabetes (β=-0.34; 95% CI=-0.47, -0.22) (Table A6).

In longitudinal analyses (Table 24, sample 1), among components of dementia risk score, age (β=-0.06; 95% CI=-0.08, -0.05), sex (β=-0.03; 95% CI=-0.009, -0.05), systolic blood pressure (β=-0.04; 95% CI=-0.08, -0.01), and total cholesterol (β=-0.04; 95% CI=-0.06, -0.01) were independently associated with faster 10-year cognitive decline; education, BMI, and physical activity were not associated with cognitive decline. Of components of FSRP (Table 25, sample 1), age (β=-0.04; 95% CI=-0.05, -0.03), sex (β=-0.03; 95% CI=-0.009, -0.05), systolic blood pressure (β=-0.009; 95% CI=-0.01, -0.003), diabetes (β=-0.06; 95% CI=-0.12, -0.006), and left ventricular hypertrophy (β=-0.05; 95% CI=-0.10, -0.008) were independently associated with faster10-year cognitive decline; no associations were observed for smoking, prior CVD and atrial fibrillation with 10-year cognitive decline.

In sample 2 (Table A7), of components of the dementia risk score, age (β=-0.07; 95% CI=-0.09, -0.05), sex (β=-0.03; 95% CI=-0.06, -0.006), systolic blood pressure (β=-0.05; 95% CI=-0.09, -0.02), total cholesterol (β=-0.03; 95% CI=-0.06, -0.008) and *APOE ε4* genotype (β=-0.05; 95% CI=-0.07, -0.02) were independently associated with faster 10-year cognitive decline; education, BMI, and physical activity were not associated with 10-year cognitive decline. Of components of the FSRP, age (β=-0.05; 95% CI=-0.06, -0.04), sex (β=-0.03; 95% CI=-0.06, -0.006), systolic blood pressure (β=-0.01; 95% CI=-0.02, -0.004), and left ventricular hypertrophy

(β=-0.06; 95% CI=-0.11, -0.01) were associated with faster 10-year cognitive decline. There was some evidence of an association for diabetes (β=-0.06; 95% CI=-0.12, 0.004, *p*=0.05) and smoking (β=-0.04; 95% CI=-0.08, 0.001, *p*=0.05) with faster 10 year cognitive decline but no associations were evident for prior CVD and atrial fibrillation with 10-year cognitive decline (Table A8).

Comparison of CAIDE dementia risk score and Framingham General Cardiovascular Disease Risk Profile

Cross sectional analyses involve 4066 and 3436 participants in sample 1and 2 respectively, who were free of cardiovascular disease (stroke, TIA, or CHD) at baseline and who had data for all components of both risk scores and had cognitive measures at phase 5. Longitudinal analyses are based on 4374 participants in sample 1 and 3718 in sample 2, with at least one cognitive measure over 10 years. Characteristics of the study sample at baseline are presented in Table 26 for sample 1 (Table A9 for sample 2). The correlation between CVD risk and dementia risk was 0.48 in sample 1 and 0.45 in sample 2. In sample 1, 61.5% of individuals in high dementia risk group also fell into the high cardiovascular risk group; 51% were in both low dementia and low CVD risk groups. In sample 2, the overlap was 61.5% for the high risk and 48.8% for the low risk groups.

In cross sectional analyses, both dementia and CVD risk were inversely associated with cognitive scores at baseline, except CVD risk that was not associated with vocabulary in sample 1 (Table 27) and reasoning in sample 2 (Table A10). Cross sectional associations between dementia risk and cognitive scores were stronger compared with CVD risk. For example in sample 1, 1 unit increase in dementia risk was associated with -0.29 SD (95% CI=-0.33, -0.27) lower global cognitive scores, whereas 1 unit increase in cardiovascular risk was associated with -0.13 SD (95% CI=-0.16, -0.10) lower global cognitive scores. Confidence intervals around the differences in estimates based on the two risk scores point to stronger associations between dementia risk and baseline cognitive scores in all tests except memory in both sample 1 and 2.

In longitudinal analyses and in both samples, higher dementia risk was associated with faster decline in reasoning, vocabulary and global cognitive scores over 10 years; CVD risk was associated with faster decline in all cognitive tests, and global cognitive score (sample 1, Table 28; sample 2, Table A11). Confidence intervals around the differences in the estimates based on

the two risk scores suggested statistically different associations for semantic fluency and global cognitive score. For example in sample 1, there was evidence of faster decline as a function of CVD risk compared with dementia risk, in semantic fluency (difference in betas=0.05; 95 % CI=0.02, 0.08) and global cognition (difference in betas=0.03; 95 % CI=0.01, 0.05).

Of components of the Framingham CVD Risk Profile, all risk factors except total cholesterol and HDL cholesterol were inversely associated with global cognitive score at baseline (sample 1,Table 29; sample 2, Table A12). In longitudinal analyses based on sample 1 (Table 30), of CVD risk factor components of the risk score, higher systolic blood pressure (β=-0.03; 95% CI=-0.05, -0.007, *p*=0.003), and total cholesterol (β=-0.02; 95% CI=-0.04, -0.006) were associated with more rapid decline in global cognitive scores over 10 years. There was also evidence of an association of diabetes with 10-year cognitive decline (β=-0.08; 95% CI=-0.17, 0.003, *p*=0.06). Compared to other components, the effect size for the association of diabetes with 10-year cognitive decline was largest. Results based on sample 2 pointed to similar associations (Table A13).

Subsidiary analyses

In exploratory analysis where the education term was removed from the dementia risk score, both cross sectional and longitudinal associations between dementia risk and cognition were attenuated. For example in sample 1, beta estimate for the association of modified dementia risk score with global cognitive score at baseline was -0.10 (95% CI=-0.12, -0.08), compared with -0.22 for the original risk score with education as a component. These results no longer showed evidence of stronger cross sectional associations with the dementia risk, compared to stroke risk for phonemic and semantic fluency and global cognition. However tests of reasoning and vocabulary retained stronger associations with dementia risk compared to stroke risk (Table A14). Similarly in sample 2, the association of dementia risk and cognitive scores at baseline attenuated with the modified dementia risk score; beta estimate for the association of modified dementia risk score with global cognitive score at baseline was -0.10 (95% CI=-0.13, -0.08), compared with -0.26 for the original risk score. Here too, there was no longer evidence of stronger cross sectional associations between dementia risk and cognition, compared to stroke risk, for phonemic and global cognitive scores (Table A15).

The associations between modified dementia risk score and 10-year cognitive change did not greatly change and the estimates remained similar to those obtained for the unmodified dementia risk score. However, in both samples, the associations of modified dementia score and 10-year change in global cognitive score were no longer different to the stroke risk as indicated by confidence intervals around the difference of estimates of the associations obtained for the two risk scores (Tables A16 and A17).

Table 19. Characteristics of the study sample at baseline, Sample 1, N=5157

	CAIDE Dementia risk score				
	All N=5157	Low (0-6) N=2306	Intermediate (7-8) N=1651	High (9-15) N=1200	*p*
Components					
Age, y, mean (SD)	55.6 (5.9)	53.0 (5.4)	56.9 (5.6)	58.7 (5.4)	*<0.001*
Men	70.8	70.0	73.0	66.9	*<0.001*
Education <10 years	11.4	0.9	13.0	32.0	*<0.001*
Systolic blood pressure > 140 mm Hg	14.6	2.3	11.9	42.0	*<0.001*
BMI >30 kg/m2	13.8	43	12.6	33.8	*<0.001*
Total cholesterol > 6.5 mmol/L	26.4	7.4	28.3	60.4	*<0.001*
Physical activity, inactive	58.7	46.2	64.4	75.0	*<0.001*
	Framingham Stroke Risk Profile				
	All N=5157	Low (1-3) N=2289	Intermediate (4-5) N=1836	High (≥6) N=1032	*p*
Components					
Age, y, mean (SD)	55.6 (5.9)	52.6 (4.5)	56.7 (5.8)	60.4 (5.4)	*<0.001*
Men	70.8	53.4	84.9	84.5	*<0.001*
Systolic blood pressure, mean (SD)	122.9 (16.4)	113.3 (11.7)	126.2 (13.4)	138.3 (16.3)	*<0.001*
Antihypertensive medication use	12.7	3.7	11.5	34.7	*<0.001*
Diabetes	4.1	1.6	4.0	9.7	*<0.001*
Current smoker	9.8	3.9	14.0	15.4	*<0.001*
History of heart disease	5.6	0.3	3.7	21.0	*<0.001*
Atrial fibrillation	1.8	0	0.2	1.8	*<0.001*
Left ventricular hypertrophy	6.0	0.2	1.8	6.3	*<0.001*

Values are percentages unless otherwise indicated.

Table 20. Associations of CAIDE dementia and Framingham stroke risk with cognitive scores at baseline, Sample 1, N=4814

Cognitive test	Risk groups				Standardized risk	
	Low	Intermediate	High			
		Mean (SD)		*p*	β (95% CI)	Δ (95% CI) [a]
Reasoning						
CAIDE	0.27 (0.87)	-0.08 (0.98)	-0.42 (1.08)	*<0.0001*	-0.26 (-0.28, -0.22)***	
FSRP	0.06 (0.96)	0.006 (0.98)	-0.15 (1.08)	*<0.0001*	-0.04 (-0.06, -0.008)**	-0.22 (-0.25, -0.18)
Memory						
CAIDE	0.19 (1.00)	-0.11 (0.96)	-0.21 (0.98)	*<0.0001*	-0.19 (-0.21, -0.16)***	
FSRP	0.19 (1.02)	-0.09 (0.96)	-0.27 (0.92)	*<0.0001*	-0.16 (-0.19, -0.13)***	-0.03 (-0.05, 0.009) ns
Phonemic fluency						
CAIDE	0.21 (0.97)	-0.06 (0.99)	-0.33 (0.96)	*<0.0001*	-0.21 (-0.24, -0.18)***	
FSRP	0.15 (1.01)	-0.04 (0.98)	-0.25 (0.95)	*<0.0001*	-0.14 (-0.17, -0.11)***	-0.07 (-0.11, -0.04)
Semantic fluency						
CAIDE	0.24 (0.45)	-0.09 (0.98)	-0.36 (0.98)	*<0.0001*	-0.25 (-0.28, -0.22)***	
FSRP	0.13 (0.99)	-0.04 (0.98)	-0.22 (0.98)	*<0.0001*	-0.13 (-0.16, -0.10)***	-0.12 (-0.15, -0.09)
Vocabulary						
CAIDE	0.23 (0.87)	-0.07 (1.00)	-0.36 (1.09)	*<0.0001*	-0.21 (-0.24, -0.18)***	
FSRP	0.01 (1.00)	0.01 (0.97)	-0.05 (1.04)	*0.16*	0.02 (-0.007, 0.04)	-0.23 (-0.27, -0.19)
Global cognition						
CAIDE	0.23 (0·95)	-0.08 (0.98)	-0.33 (1.0)	*<0.0001*	-0.22 (-0.24, -0.20)***	
FSRP	0.11 (0.92)	-0.03 (0.97)	-0.19 (0.99)	*<0.0001*	-0.09 (-0.11, -0.07)***	-0.13 (-0.16, -0.11)

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

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

[a] Difference in beta coefficients: $\beta_{CAIDE} - \beta_{FSRP}$; bootstrapped 95% confidence intervals.

Table 21. Associations of CAIDE dementia and Framingham stroke risk with 10-year cognitive change, Sample 1, N=5157

Cognitive test	Risk groups				Standardized risk	
	Low	Intermediate	High			
	10-year cognitive change (95% CI)			*p trend*	β (95% CI)	Δ (95% CI) [a]
Reasoning						
CAIDE	-0.28 (-0.30, -0.26)	-0.35 (-0.38, -0.32)	-0.37 (-0.40, -0.33)	*<0.0001*	-0.05 (-0.06, -0.04)***	
FSRP	-0.27 (-0.29, -0.24)	-0.34 (-0.36, -0.31)	-0.42 (-0.45, -0.38)	*0.0001*	-0.05 (-0.06, -0.03)***	0.00 (-0.02, 0.02) ns
Memory						
CAIDE	-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)	
FSRP	-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						
CAIDE	-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)	
FSRP	-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						
CAIDE	-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)	
FSRP	-0.26 (-0.29, -0.22)	-0.33 (-0.37, -0.29)	-0.40 (-0.44, -0.34)	*<0.0001*	-0.05 (-0.08, -0.03)***	0.04 (0.02, 0.06)
Vocabulary						
CAIDE	0.05 (0.03, 0.07)	0.006 (-0.02, 0.03)	-0.03 (-0.06, -0.002)	*<0.0001*	-0.03 (-0.04, -0.01)***	
FSRP	0.04 (0.03, 0.07)	0.02 (-0.001, 0.04)	-0.05 (-0.08, -0.02)	*<0.0001*	-0.04 (-0.05, -0.02)***	0.01 (-0.004, 0.03) ns
Global cognition						
CAIDE	-0.22 (-0.24, -0.21)	-0.27 (-0.29, -0.25)	-0.27 (-0.29, -0.24)	*0.0003*	-0.02 (-0.03, -0.01)***	
FSRP	-0.21 (-0.23, -0.19)	-0.26 (-0.28, -0.24)	-0.31 (-0.34, -0.29)	*<0.0001*	-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 beta coefficients: $\beta_{CAIDE} - \beta_{FSRP}$; bootstrapped 95% confidence intervals.

Table 22. Associations of CAIDE dementia risk score components with cognitive scores at baseline, Sample 1, N=4814

	Age	Sex	Education	SBP	Total cholesterol	BMI	Physical activity
				β (95% CI) *p*			
Reasoning	-0.28 (-0.32, -0.23) *<0.0001*	0.61 (0.55, 0.67) *<0.0001*	-0.61 (-0.64, -0.57) *<0.0001*	-0.25 (-0.33, -0.17) *<0.0001*	-0.07 (-0.14, -0.07) *0.03*	-0.13 (-0.22, -0.05) *0.001*	-0.23 (-0.29, -0.18) *<0.0001*
Memory	-0.30 (-0.35, -0.25) *<0.0001*	-0.02 (-0.08, 0.04) *0.46*	-0.25 (-0.29, -0.21) *<0.0001*	-0.16 (-0.24, -0.08) *0.0001*	-0.02 (-0.09, 0.04) *0.46*	-0.06 (-0.14, 0.02) *0.13*	-0.14 (-0.20, -0.08) *<0.0001*
Phonemic fluency	-0.27 (-0.32, -0.23) *<0.0001*	0.07 (0.007, 0.13) *0.03*	-0.40 (-0.44, -0.36) *<0.0001*	-0.23 (-0.31, -0.15) *<0.0001*	0.05 (-0.01, 0.11) *0.13*	-0.07 (-0.15, 0.01) *0.09*	-0.21 (-0.27, -0.15) *<0.0001*
Semantic fluency	-0.35 (-0.40, -0.30) *<0.0001*	0.18 (0.19, 0.24) *<0.0001*	-0.45 (-0.49, -0.41) *<0.0001*	-0.19 (-0.27, -0.11) *<0.0001*	-0.02 (-0.08, 0.04) *0.50*	-0.06 (-0.14, 0.02) *0.15*	-0.23 (-0.29, -0.17) *<0.0001*
Vocabulary	-0.07 (-0.11, -0.02) *0.006*	0.57 (0.51, 0.63) *<0.0001*	-0.60 (0.63, -0.56) *<0.0001*	-0.09 (-0.17, -0.008) *0.03*	-0.05 (-0.12, 0.01) *0.11*	-0.24 (-0.32, -0.16) *<0.0001*	-0.26 (-0.32, -0.20) *<0.0001*
Global cognition	-0.25 (-0.29, -0.22) *<0.0001*	0.28 (0.24, 0.32) *<0.0001*	-0.46 (-0.49, -0.43) *<0.0001*	-0.18 (-0.24, -0.12) *<0.0001*	-0.02 (-0.07, 0.02) *0.31*	-0.11 (-0.17, -0.05) *0.0002*	-0.21 (-0.26, -0.17) *<0.0001*

Components are based on categories of the risk score. Age (years): (1) <47, (2) 47-53, (3) >53; sex: (1) women, (2) men; education (years): (1) ≥10, (2) 7-9, (3) 0-6; systolic blood pressure (SBP) (mmHg): (1) ≤ 140, (2) ≥140; total cholesterol (mmol/L): (1) ≤6.5, (2) ≥6.5; body mass index (BMI) (kg/m^2): (1) ≤30, (2) > 30; physical activity: (1) Active, (2) inactive.

Table 23. Associations of Framingham Stroke Risk score components with cognitive scores at baseline, Sample 1, N=4814

	Age	Sex	SBP	Diabetes	Smoking	Prior CVD	AF	LVH
	β (95% CI) *p*							
Reasoning	-0.16 (-0.18, -0.14) *<0.0001*	0.61 (0.55, 0.67) *<0.0001*	-0.08 (-0.09, -0.06) *<0.0001*	-0.51 (-0.65, -0.37) *<0.0001*	-0.25 (-0.35, -0.16) *<0.0001*	-0.25 (-0.37, -0.13) *<0.0001*	0.06 (-0.38, 0.49) *0.79*	0.007 (-0.11, 0.12) *0.90*
Memory	-0.17 (-0.19, -0.14) *<0.0001*	-0.02 (-0.08, 0.04) *0.46*	-0.06 (-0.07, -0.04) *<0.0001*	-0.21 (-0.35, -0.06) *0.005*	-0.14 (-0.23, -0.04) *0.005*	-0.24 (-0.37, -0.12) *<0.0001*	-0.08 (-0.52, 0.36) *0.71*	-0.07 (-0.19, 0.04) *0.22*
Phonemic fluency	-0.16 (-0.18, -0.14) *<0.0001*	0.07 (0.007, 0.13) *0.03*	-0.06 (-0.08, -0.04) *<0.0001*	-0.25 (-0.39, -0.11) *0.005*	-0.16 (-0.26, -0.07) *0.0007*	-0.21 (-0.33, -0.09) *0.0008*	-0.14 (-0.57, 0.30) *0.53*	-0.006 (-0.12, 0.11) *0.92*
Semantic fluency	-0.17 (-0.19, -0.15) *<0.0001*	0.18 (0.19, 0.24) *<0.0001*	-0.07 (-0.08, -0.05) *<0.0001*	-0.32 (-0.46, -0.18) *<0.0001*	-0.14 (-0.23, -0.04) *0.005*	-0.28 (-0.40, -0.16) *<0.0001*	-0.03 (-0.47, 0.41) *0.89*	-0.007 (-0.13, 0.11) *0.91*
Vocabulary	-0.04 (-0.07, -0.02) *<0.0001*	0.57 (0.51, 0.63) *<0.0001*	-0.06 (-0.08, -0.04) *<0.0001*	-0.39 (-0.53, -0.25) *<0.0001*	-0.28 (-0.38, -0.18) *<0.0001*	-0.17 (-0.29, -0.04) *0.007*	0.06 (-0.22, 0.11) *0.18*	0.01 (-0.11, 0.13) *0.85*
Global cognition	-0.14 (-0.16, -0.12) *<0.0001*	0.28 (0.24, 0.32) *<0.0001*	-0.06 (-0.08, -0.05) *<0.0001*	-0.34 (-0.44, -0.23) *<0.0001*	-0.19 (-0.26, -0.12) *<0.0001*	-0.23 (-0.32, -0.14) *<0.0001*	-0.02 (-0.30, 0.34) *0.89*	-0.01 (-0.10, 0.07) *0.76*

Components are based on categories of the risk score. MEN: age (years): (1) <57, (2) 57-59, (3) 60-62, (4) 63-65, (5) 66-68, (6) 69-72; untreated systolic blood pressure (SBP) (mmHg): (1) 97-105, (2) 106-115, (3) 116-125, (4) 126-135, (5) 136-145, (6) 146-155, (7) 156-165, (8) 166-145, (9) 176-185, (10) 186-195, (11) 196-205; treated SBP (mmHg): (1) 97-105, (2) 106-112, (3) 113-117, (4) 118-123, (5) 124-129, (6) 130-135, (7) 136-142, (8) 143-150, (9) 151-161, (10) 162-176, (11) 177-205; diabetes: (1) no, (2) yes; smoking: (1) no, (2) yes; prior cardiovascular disease (CVD): (1) no, (2) yes; atrial fibrillation (AF): (1) no, (2) yes; left ventricular hypertrophy (LVH): (1) no, (2) yes. WOMEN: age (years): (1) <57, (2) 57-59, (3) 60-62, (4) 63-64, (5) 65-67, (6) 68-70; untreated SBP (mmHg): (1) 95-106, (2) 107-118, (3) 119-130, (4) 131-143, (5) 144-155, (6) 156-167, (7) 168-180, (8) 181-192, (9) 193-204, (10) 205-216; treated SBP (mmHg): (1) 95-106, (2) 107-113, (3) 114-119, (4) 120-125, (5) 126-131, (6) 132-139, (7) 140-148, (8) 149-160, (9) 161-204, (10) 205-216; diabetes: (1) no, (2) yes; smoking: (1) no, (2) yes; prior CVD: (1) no, (2) yes; AF: (1) no, (2) yes; LVH: (1) no, (2) yes.

Table 24. Associations of CAIDE dementia risk score components with 10-year cognitive change, Sample 1, N=5157

	Age	**Sex**	**Education**	**SBP**	**Total cholesterol**	**BMI**	**Physical activity**
				β (95% CI) *p*			
Reasoning	-0.13 (-0.15, -0.14) *<0.0001*	0.01 (-0.05, 0.02) 0.51	-0.03 (-0.05, -0.01) *0.02*	-0.06 (-0.11, -0.02) *0.01*	-0.01 (-0.05, 0.02) *0.51*	-0.03 (-0.07, 0.02) *0.21*	-0.01 (-0.04, 0.02) *0.64*
Memory	-0.06 (-0.1, -0.01) *0.01*	-0.06 (-0.12, 0.01) 0.08	-0.004 (-0.04, 0.04) *0.86*	-0.04 (-0.13, 0.04) *0.28*	-0.03 (-0.09, 0.04) *0.39*	*0.03 (-0.05, 0.11)* *0.41*	*0.05 (-0.009, 0.11)* *0.10*
Phonemic fluency	-0.04 (-0.07, 0.001) *0.06*	-0.02 (-0.03, 0.07) 0.53	-0.03 (-0.06, -0.01) *0.06*	-0.05 (-0.11, 0.02) *0.13*	-0.09 (-0.13, -0.04) *0.01*	-0.02 (-0.09, 0.04) *0.44*	-0.02 (-0.04, 0.06) *0.37*
Semantic fluency	-0.03 (-0.07, 0.004) *0.08*	-0.07 (-0.12, -0.02) 0.003	-0.03 (-0.05, -0.01) *0.05*	-0.03 (-0.09, 0.03) *0.33*	-0.05 (-0.12, -0.001) *0.04*	0.008 (-0.06, 0.07) *0.80*	-0.02 (-0.05, 0.07) *0.34*
Vocabulary	-0.05 (-0.07, -0.02) *<0.001*	-0.04 (-0.07, -0.01) 0.009	-0.02 (-0.04, -0.001) *0.03*	-0.06 (-0.09, -0.02) *0.003*	-0.008 (-0.04, 0.02) *0.61*	-0.01 (-0.05, 0.02) *0.46*	-0.01 (-0.03, 0.02) *0.67*
Global cognition	-0.06 (-0.08, -0.05) *<0.0001*	-0.03 (-0.05, -0.01) 0.007	-0.005 (-0.02, 0.01) *0.56*	-0.04 (-0.08, -0.01) *0.006*	-0.04 (-0.06, -0.01) *0.003*	-0.002 (-0.03, 0.03) *0.91*	-0.001 (-0.03, 0.01) *0.50*

Components are based on categories of the risk score. Age (years): (1) <47, (2) 47-53, (3) >53; sex: (1) women, (2) men; education (years): (1) ≥10, (2) 7-9, (3) 0-6; systolic blood pressure (SBP) (mmHg): (1) ≤ 140, (2) ≥140; total cholesterol (mmol/L): (1) ≤6.5, (2) ≥6.5; body mass index (BMI) (kg/m^2): (1) ≤30, (2) > 30; physical activity: (1) Active, (2) inactive.

Table 25. Associations of Framingham Stroke Risk Profile components with 10-year cognitive change, Sample 1, N=5157

	Age	Sex	SBP	Diabetes	Smoking	Prior CVD	AF	LVH
	β (95% CI) *p*							
Reasoning	-0.08 (-0.09, -0.06) *<0.0001*	0.01 (-0.05, 0.02) 0.51	-0.02 (-0.03, -0.01) *<0.0001*	-0.06 (-0.14, 0.02) *0.16*	-0.05 (-0.10, 0.01) *0.08*	-0.02 (-0.09, 0.04) *0.49*	0.05 (-0.18, 0.16) 0.61	-0.01 (-0.08, 0.05) *0.64*
Memory	-0.04 (-0.06, -0.01) *0.002*	-0.06 (-0.09, 0.01) 0.08	0.005 (-0.01, 0.02) 0.51	-0.12 (-0.27, 0.03) *0.12*	-0.02 (-0.12, 0.08) *0.68*	-0.03 (-0.15, 0.09) *0.65*	-0.01 (-0.10, 0.09) 0.41	-0.02 (-0.14, 0.10) *0.77*
Phonemic fluency	-0.02 (-0.04, -0.001) *0.03*	-0.02 (-0.03, 0.07) 0.53	-0.01 (-0.03, -0.001) *0.03*	-0.08 (-0.14, 0.10) *0.76*	-0.02 (-0.09, 0.06) *0.65*	-0.09 (-0.18, 0.01) *0.07*	-0.03 (-0.11, 0.09) 0.22	-0.08 (-0.18, 0.01) *0.08*
Semantic fluency	-0.04 (-0.06, -0.02) *<0.0001*	-0.07 (-0.02, -0.12) 0.003	-0.01 (-0.02, 0.004) *0.20*	-0.04 (-0.16, 0.08) *0.53*	-0.05 (-0.13, 0.02) *0.16*	-0.04 (-0.13, 0.06) *0.44*	-0.07 (-0.18, 0.25) 0.40	-0.08 (-0.17, 0.01) *0.09*
Vocabulary	-0.03 (-0.04, -0.02) *<0.0001*	-0.04 (-0.09, -0.02) 0.009	-0.008 (-0.02, -0.001) *0.03*	-0.06 (-0.13, 0.01) *0.11*	-0.02 (-0.07, 0.03) *0.40*	-0.04 (-0.10, 0.02) *0.15*	-0.08 (-0.22, 0.08) 0.18	-0.06 (-0.11, -0.001) *0.04*
Global cognition	-0.04 (-0.05, -0.03) *<0.0001*	-0.03 (-0.009, -0.05) 0.007	-0.009 (-0.01, -0.003) *0.004*	-0.06 (-0.12, -0.01) *0.03*	-0.03 (-0.07, 0.01) *0.11*	-0.03 (-0.08, 0.02) *0.21*	-0.04 (-0.10, 0.18) *0.38*	-0.05 (-0.10, -0.01) *0.02*

Components are based on categories of the risk score. MEN: age (years): (1) <57, (2) 57-59, (3) 60-62, (4) 63-65, (5) 66-68, (6) 69-72; untreated systolic blood pressure (SBP) (mmHg): (1) 97-105, (2) 106-115, (3) 116-125, (4) 126-135, (5) 136-145, (6) 146-155, (7) 156-165, (8) 166-145, (9) 176-185, (10) 186-195, (11) 196-205; treated SBP (mmHg): (1) 97-105, (2) 106-112, (3) 113-117, (4) 118-123, (5) 124-129, (6) 130-135, (7) 136-142, (8) 143-150, (9) 151-161, (10) 162-176, (11) 177-205; diabetes: (1) no, (2) yes; smoking: (1) no, (2) yes; prior cardiovascular disease (CVD): (1) no, (2) yes; atrial fibrillation (AF): (1) no, (2) yes; left ventricular hypertrophy (LVH): (1) no, (2) yes. WOMEN: age (years): (1) <57, (2) 57-59, (3) 60-62, (4) 63-64, (5) 65-67, (6) 68-70; untreated SBP (mmHg): (1) 95-106, (2) 107-118, (3) 119-130, (4) 131-143, (5) 144-155, (6) 156-167, (7) 168-180, (8) 181-192, (9) 193-204, (10) 205-216; treated SBP (mmHg): (1) 95-106, (2) 107-113, (3) 114-119, (4) 120-125, (5) 126-131, (6) 132-139, (7) 140-148, (8) 149-160, (9) 161-204, (10) 205-216; diabetes: (1) no, (2) yes; smoking: (1) no, (2) yes; prior CVD: (1) no, (2) yes; AF: (1) no, (2) yes; LVH: (1) no, (2) yes.

Table 26. Characteristics of the study sample at baseline, Sample 1, N= 4374

	CAIDE dementia risk score				
	All N=4374	Low (0-6) N=1970	Intermediate (7-8) N=1404	High (9-15) N=1000	*p*
Components					
Age, y, mean (SD)	55.2 (5.1)	52.8 (4.9)	56.1 (5.1)	57.9 (5.1)	*<0.001*
Men	72.3	70.1	72.3	67.5	*<0.001*
Education <10 years	12.4	1.1	13.4	33.4	*<0.001*
Systolic blood pressure > 140 mm Hg	14.9	2.9	10.8	40.1	*<0.001*
BMI >30 kg/m2	12.8	5.1	12.4	30.5	*<0.001*
Total cholesterol > 6.5 mmol/L	25.9	6.9	25.4	59.7	*<0.001*
Physical activity, inactive	56.9	43.7	63.1	74.5	*<0.001*
	Framingham General Cardiovascular Risk Profile				
	All N=4374	Low (1-7) N=1472	Intermediate (7.5-13) N=1445	High (≥13) N=1457	*p*
Components					
Age, y, mean (SD)	55.2 (5.1)	51.9 (4.7)	55.02 (5.3)	59.4 (5.3)	*<0.001*
Men	72.3	45.5	61.8	79.0	*<0.001*
Systolic blood pressure, mean (SD)	122.5 (15.9)	112.7 (12.3)	122.9 (13.5)	134.2 (15.6)	*<0.001*
Antihypertensive medication use	11.8	3.1	7.6	22.6	*<0.001*
Diabetes	4.0	1.8	2.0	7.5	*<0.001*
Current smoker	10.1	4.5	7.7	16.3	*<0.001*
Total cholesterol (mg/dL), mean (SD)	229.7 (40.4)	214.6 (36.4)	231.1 (37.3)	243.5 (41.9)	*<0.001*
HDL cholesterol (mg/dL), mean (SD)	56.7 (15.3)	64.7 (15.5)	55.8 (13.7)	49.6 (12.5)	*<0.001*

Values are percentages unless otherwise indicated.

Table 27. Associations of CAIDE dementia and Framingham general cardiovascular disease risk with cognitive scores at baseline, Sample 1, N=4066

Cognitive test	Risk groups				Standardized risk	
	Low	Intermediate	High			
	Mean (SD)			*p*	β (95% CI)	Δ (95% CI) [a]
Reasoning						
CAIDE	0.26 (0.87)	-0.08 (0.99)	-0.41 (1.09)	*<0.0001*	-0.25 (-0.28, -0.22)***	
CVDRP	0.01 (0.98)	0.04 (0.99)	-0.06 (1.01)	*0.04*	-0.04 (-0.07, -0.006)*	-0.21 (-0.25, -0.17)
Memory						
CAIDE	0.18 (1.0)	-0.12 (0.95)	-0.19 (0.99)	*<0.0001*	-0.16 (-0.21, -0.15)***	
CVDRP	0.21 (1.0)	0.01 (0.98)	-0.22 (0.95)	*<0.0001*	-0.18 (-0.21, -0.15)***	-0.02 (-0.03, 0.03) ns
Phonemic fluency						
CAIDE	0.21 (0.96)	-0.06 (0.99)	-0.34 (0.96)	*<0.0001*	-0.21 (-0.24, -0.18)***	
CVDRP	0.14 (1.01)	0.03 (0.97)	-0.17 (0.98)	*<0.0001*	-0.15 (-0.17, -0.11)***	-0.06 (-0.10, -0.03)
Semantic fluency						
CAIDE	0.25 (0.96)	-0.10 (0.97)	-0.36 (0.98)	*<0.0001*	-0.26 (-0.29, -0.22)***	
CVDRP	0.13 (1.02)	0.04 (0.98)	-0.18 (0.98)	*<0.0001*	-0.15 (-0.18, -0.12)***	-0.11 (-0.15, -0.07)
Vocabulary						
CAIDE	0.23 (0.87)	-0.08 (1.01)	-0.35 (1.10)	*<0.0001*	-0.21 (-0.24, -0.18)***	
CVDRP	-0.05 (1.05)	0.04 (0.94)	0.01 (0.99)	*0.11*	0.02 (-0.005, 0.06)	-0.23 (-0.26, -0.20)
Global cognition						
CAIDE	0.31 (0.90)	-0.12 (0.97)	-0.45 (1.03)	*<0.0001*	-0.29 (-0.33, -0.27)***	
CVDRP	0.12 (1.03)	0.04 (0.96)	-0.17 (0.98)	*<0.0001*	-0.13 (-0.16, -0.10)***	-0.16 (-0.20, -0.13)

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

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

[a] Difference in beta coefficients: $\beta_{CAIDE} - \beta_{CVDRP}$; bootstrapped 95% confidence intervals.

Table 28. Associations of CAIDE dementia and Framingham general cardiovascular disease risk with 10-year cognitive change, Sample 1, N=4374

Cognitive test	Risk groups				Standardized risk	
	Low	Intermediate	High			
	10-year cognitive change (95% CI)			*p trend*	β (95% CI)	Δ (95% CI) [a]
Reasoning						
CAIDE	-0.28 (-0.31, -0.26)	-0.35 (-0.38, -0.32)	-0.36 (-0.39, -0.33)	*<0.0001*	-0.05 (-0.06, -0.03)***	
CVDRP	-0.26 (-0.29, -0.23)	-0.31 (-0.34, -0.28)	-0.41 (-0.44, -0.38)	*<0.0001*	-0.06 (-0.08, -0.04)***	0.01 (-0.004, 0.03) ns
Memory						
CAIDE	-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)	
CVDRP	-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						
CAIDE	-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)	
CVDRP	-0.31 (-0.35, -0.27)	-0.36 (-0.40, -0.32)	-0.39 (-0.44, -0.35)	*0.008*	-0.03 (-0.06, -0.01)**	0.02 (-0.005, 0.05) ns
Semantic fluency						
CAIDE	-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)	
CVDRP	-0.31 (-0.35, -0.27)	-0.36 (-0.40, -0.32)	-0.39 (-0.44, -0.35)	*<0.0001*	-0.05 (-0.07, -0.02)***	0.05 (0.02, 0.08)
Vocabulary						
CAIDE	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)**	
CVDRP	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						
CAIDE	-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)**	
CVDRP	-0.26 (-0.28, -0.23)	-0.34 (-0.37, -0.32)	-0.40 (-0.43, -0.37)	*<0.0001*	-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 beta coefficients: $\beta_{CAIDE} - \beta_{CVDRP}$; bootstrapped 95% confidence intervals.

Table 29. Associations of Framingham General Cardiovascular Disease Risk Profile components with cognitive scores at baseline, Sample 1, N=4066

	Age	Sex	SBP	Diabetes	Smoking	Total cholesterol	HDL cholesterol
				β (95% CI) *p*			
Reasoning	-0.16 (-0.19, -0.14) *<0.0001*	0.65 (0.58, 0.71) *<0.0001*	-0.07 (-0.09, -0.04) *<0.0001*	-0.42 (-0.58, -0.26) *<0.0001*	-0.24 (-0.34, -0.13) *<0.0001*	-0.03 (-0.06, 0.005) *0.10*	0.02 (0.0004, 0.04) *0.04*
Memory	-0.18 (-0.20, -0.16) *<0.0001*	-0.02 (-0.07, 0.06) *0.94*	-0.08 (-0.10, -0.05) *<0.0001*	-0.21 (-0.37, -0.05) *0.009*	-0.12 (-0.22, -0.02) *0.02*	-0.01 (-0.04, 0.02) *0.50*	-0.04 (-0.06, -0.01) *0.0006*
Phonemic fluency	-0.18 (-0.20, -0.15) *<0.0001*	0.08 (0.01, 0.14) *0.01*	-0.07 (-0.10, -0.05) *<0.0001*	-0.16 (-0.33, -0.007) *0.04*	-0.11 (-0.22, -0.009) *0.03*	-0.01 (-0.02, 0.04) *0.50*	-0.02 (-0.05, 0.0008) *0.05*
Semantic fluency	-0.20 (-0.22, -0.17) *<0.0001*	0.19 (0.12, 0.26) *<0.0001*	-0.07 (-0.10, -0.05) *<0.0001*	-0.25 (-0.41, -0.09) *0.002*	-0.11 (-0.22, -0.009) *0.03*	-0.01 (-0.05, 0.01) *0.35*	-0.01 (-0.04, 0.008) *0.19*
Vocabulary	-0.04 (-0.07, -0.02) *0.0005*	0.61 (0.54, 0.67) *<0.0001*	-0.04 (-0.06, -0.01) *0.003*	-0.29 (-0.45, -0.13) *0.0003*	-0.26 (-0.37, -0.16) *<0.0001*	-0.003 (-0.03, 0.02) *0.86*	-0.00004 (-0.02, 0.24) *0.99*
Global cognition	-0.15 (-0.17, -0.13) *<0.0001*	0.30 (0.25, 0.35) *<0.0001*	-0.07 (-0.08, -0.05) *<0.0001*	-0.27 (-0.39, -0.15) *<0.0001*	-0.17 (-0.24, -0.09) *<0.0001*	-0.009 (-0.03, 0.01) *0.45*	-0.01 (-0.03, 0.006) *0.21*

Components are based on categories of the risk score. Age (years): (1) 30-34, (2) 35-39, (3) 40-44, (4) 45-49, (5) 50-54, (6) 55-59, (7) 60-64, (8) 65-69, (9) 70-74, (10) ≥75; systolic blood pressure (SBP) (mmHg): (1) <120, (2) 120-129, (3) 130-139, (4) 140-159, (5) ≥160; diabetes: (1) no, (2) yes; smoking: (1) no, (2) yes; total cholesterol (mg/dL): (1) <160, (2) 160-199, (3) 200-239, (4) 240-279, (5) ≥280; HDL cholesterol (mg/dL): (1) ≥60, (2) 50-59, (3) 45-49, (4) 35-44, (5) <35.

Table 30. Associations of Framingham General Cardiovascular Disease Risk Profile components with 10-year cognitive change, Sample 1, N= 4374

	Age	Sex	SBP	Diabetes	Smoking	Total cholesterol	HDL cholesterol
				β (95% CI) *p*			
Reasoning	-0.08 (-0.09, -0.07) *<0.0001*	0.01 (-0.03, 0.04) *0.55*	-0.02 (-0.03, -0.004) *0.01*	-0.05 (-0.01, 0.04) *0.28*	-0.04 (-0.1, 0.01) *0.18*	-0.01 (-0.03, 0.003) *0.11*	-0.005 (-0.01, 0.01) *0.45*
Memory	-0.04 (-0.06, -0.01) *0.006*	-0.06 (-0.1, 0.01) *0.08*	-0.0002 (-0.02, 0.02) *0.99*	-0.09 (-0.3, 0.07) *0.26*	0.03 (-0.08, 0.13) *0.61*	-0.01 (-0.04, 0.02) *0.50*	0.008 (-0.02, 0.03) *0.53*
Phonemic fluency	-0.001 (-0.03, 0.01) *0.33*	-0.02 (-0.07, 0.03) *0.47*	-0.02 (-0.04, 0.002) *0.07*	-0.03 (-0.2, 0.10) *0.70*	-0.03 (-0.12, 0.05) *0.43*	-0.03 (-0.06, -0.005) *0.01*	-0.0007 (-0.2, 0.01) *0.94*
Semantic fluency	-0.03 (-0.05, -0.01) *0.001*	-0.08 (-0.1, -0.03) *0.003*	-0.02 (-0.04, -0.00) *0.04*	0.002 (-0.13, 0.13) *0.97*	-0.04 (-0.12, 0.04) *0.34*	-0.02 (-0.04, 0.01) *0.18*	-0.08 (-0.03, 0.01) *0.41*
Vocabulary	-0.03 (-0.04, -0.02) *<0.0001*	-0.05 (-0.08, -0.01) *0.002*	-0.01 (-0.03, -0.002) *0.02*	-0.09 (-0.17, -0.007) *0.03*	-0.004 (-0.05, 0.04) *0.86*	-0.01 (-0.03, 0.004) *0.14*	-0.004 (-0.01, 0.01) *0.44*
Global cognition	-0.05 (-0.07, -0.04) *<0.0001*	-0.05 (-0.09, -0.02) *0.002*	-0.03 (-0.05, -0.007) *0.003*	-0.08 (-0.17, 0.003) *0.06*	-0.02 (-0.08, 0.04) *0.48*	-0.02 (-0.04, -0.01) *0.006*	-0.004 (-0.02, 0.01) *0.50*

Components are based on categories of the risk score. Age (years): (1) 30-34, (2) 35-39, (3) 40-44, (4) 45-49, (5) 50-54, (6) 55-59, (7) 60-64, (8) 65-69, (9) 70-74, (10) ≥75; systolic blood pressure (SBP) (mmHg): (1) <120, (2) 120-129, (3) 130-139, (4) 140-159, (5) ≥160; diabetes: (1) no, (2) yes; smoking: (1) no, (2) yes; total cholesterol (mg/dL): (1) <160, (2) 160-199, (3) 200-239, (4) 240-279, (5) ≥280; HDL cholesterol (mg/dL): (1) ≥60, (2) 50-59, (3) 45-49, (4) 35-44, (5) <35.

III.2.4 Discussion

The aim of this analysis was to compare two well-known vascular risk scores; the Framingham stroke and general cardiovascular risk scores, with the CAIDE dementia risk score that uses midlife risk factors to predict risk of late-life dementia. Our results showed the dementia risk score to have a stronger cross-sectional association than the vascular risk scores with all measures of cognitive function except memory. Longitudinal analyses using three cognitive assessments over ten years showed all three risk scores to be associated with 10-year decline in multiple cognitive tests but the two Framingham risk scores were better predictors of cognitive decline than the dementia risk score.

Since the development of the first risk models for cardiovascular disease, much work has been undertaken to develop additional risk scores or to refine and validate existing ones in different populations. Subsequently there have been many comparative studies of risk models for cardiovascular disease, stroke, and diabetes. However, such studies are rare for risk models for dementia and cognitive impairment and no attempts have so far been made to compare risk scores in predicting cognitive decline in midlife. This represents an important gap in the literature as early identification of individuals at risk of dementia will become crucial for targeting preventive interventions. The CAIDE dementia risk score is yet to be validated in other populations. With the exception of one study that found that the CAIDE dementia risk score predicted cognitive impairment after 15 years (Reijmer et al., 2011b), this dementia risk score has not been previously examined in relation to cognitive outcomes. In this comparative study, although it was not possible to test the relative discrimination and calibration of the risk scores (e.g. sensitivity, specificity, area under the ROC curve) since the outcome did not consist of a categorical event, we adopted an alternative method (i.e. bootstrapped confidence intervals) to compare the risk scores. Overall our results show that all three risk scores predict 10-year cognitive decline although the Framingham risk score showed relatively stronger associations with 10-year decline.

Comparison of these findings with other studies examining the dementia or Framingham risk scores is not possible as none of these reports have compared the two risk scores in the same population. However, the differences between the dementia and Framingham risk scores may be related to several factors. Foremost is that these risk scores were developed to predict different outcomes, thus differences in the development and validation processes are important. The populations used to develop the risk scores are also different. For example the development of the

dementia risk score was based on a relatively homogeneous CAIDE population. The extent to which this risk score predicts dementia in other populations will also help determine its utility as a prediction tool.

In addition, the composition of the risk scores is quite different, although all three risk scores are composed of risk factors relevant to cognitive outcomes. Of note is education in the dementia risk score. Education, a marker of cognitive reserve, is associated with cognitive performance and risk of dementia (Evans et al., 1997; Lindsay et al., 2002; Ott et al., 1999b; Stern et al., 1994) but it appears increasingly that it is not associated with rate of cognitive decline (Karlamangla et al., 2009; Ngandu et al., 2007; Singh-Manoux et al., 2011). In the present study, of all components of the CAIDE dementia risk score, education had the strongest association with cognitive scores at baseline even though it was not associated with 10-year cognitive decline. When education was removed from the dementia risk score, cross sectional associations were substantially attenuated, making them no different to the associations observed with stroke risk. These findings are not surprising because the dementia risk score was developed to detect clinically diagnosable dementia and it is possible that inclusion of education in the risk score has a major influence in driving the prediction of dementia. In contrast, cardiovascular risk scores are composed of mainly CVD risk factors and may be more sensitive to detecting sub-clinical cognitive decline of mainly vascular origin (e.g. verbal fluency). Cardiovascular disease risk factors in midlife have been consistently linked to structural brain aging, cerebral pathology (e.g. brain atrophy and white matter hyperintensities), as well as deficits and decline in various cognitive domains including processing speed and executive function through distinct and shared mechanisms described earlier (Das et al., 2008; Debette et al., 2011; Gorelick et al., 2011; Knopman et al., 2011; Seshadri et al., 2004; Unverzagt et al., 2011). Our findings in the present study, of an independent association of several components of the risk scores with cognitive decline suggest a cumulative effect of these risk factors on cognition. Of these, diabetes, a component of the two Framingham scores (and not the CAIDE dementia risk score) appears to have the strongest independent association with 10-year cognitive decline. Therefore it is likely that the inclusion of this and other important vascular risk factors distinguishes the two Framingham risk scores from the dementia risk score.

Differences in scoring and representation of risk factors in the Framingham and dementia risk scores are also notable; CVD risk factors as scored by the Framingham risk algorithms

represent a wider range of categories. For example, age is represented by ten categories in the Framingham scores, but only three in the CAIDE dementia risk score. Thus the majority of our study participants who are middle aged would be in the top category of age (>53 years) of the dementia risk score. Similarly, systolic blood pressure has five categories in the Framingham CVD risk score (<120, 120-129, 130-139, 140-159, ≥160 mm Hg) but only two categories (≤140 and >140 mm Hg) in the dementia risk score. This wider range of risk factor categories in the Framingham risk scores likely captures the continuous nature of risk better and distinguishes 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.

With regard to practical utility, formal assessment of the relative performance of risk prediction models for population screening is often carried out through decision analytic measures to determine the net benefit achieved by making decisions based on the model in order to quantify relative clinical usefulness of the prediction model. However, this application necessitates availability of treatments and makes assumptions on treatment guidelines. For cognitive impairment and dementia, there are currently no effective treatments 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.

In addition, 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 (Stephan et al., 2010). Although the CAIDE dementia risk score addresses many constraints of previous dementia risk scores by including easily measurable risk factors at midlife to estimate risk of late life dementia it remains unused and has not been validated in other populations. Regardless of these limitations, its use is currently not advocated, perhaps because its integration in primary care settings may not be realistic or practical at this time. First, despite the fact that 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. In the absence of evidence for real benefit of screening, clinician uptake of any risk score is unlikely to be high.

In contrast, the Framingham risk scores have been repeatedly validated (for CVD events) in several diverse populations, some very different from the Framingham population. In addition, the good performance of the Framingham primary event cardiovascular risk scores has indicated universality in cardiovascular risk across nations (Khalili et al., 2012). Framingham risk scores have been advocated 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. They have also been examined in relation to cognitive outcomes and found to predict subclinical markers of brain injury, and cognitive function (Kaffashian et al., 2011; Seshadri et al., 2004; Unverzagt et al., 2011). Given their reputation, repeated validation and evidence of utility for assessment of cognitive outcomes, the Framingham risk scores can have a dual purpose. This is especially pertinent with the shift from dementia as an outcome to earlier stages of cognitive outcomes; real benefit can be achieved by early modification of vascular risk factors to change the course of cognitive decline in the long preclinical phase of dementia during which changes occur in the brain.

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; our findings suggest that in future patients with elevated CVD risk can also be told that they may be at higher risk of poor cognitive health. This may provide an added incentive for early targeting and treatment of CVD risk factors.

CHAPTER IV: GENERAL DISCUSSION

Over the past few decades, observational and clinical epidemiology have made great contributions to the identification of risk factors for cognitive impairment and dementia and more recently the demonstration of cumulative and interactive role of vascular risk factors in affecting cognitive outcomes. But, interventional epidemiology has lagged behind and this knowledge has not been widely translated into population level interventions. Moreover, primary care providers and the public remain largely ignorant of the detrimental effects of CVD risk factors on cognitive health particularly that these risk factors exert their effect early, starting at midlife.

A major focus of this thesis was on examination of multi-risk factor estimation of CVD risk in relation to cognitive outcomes in particular long-term cognitive change. Most previous studies on CVD risk factors and cognition have examined individual risk factors separately while adjusting for concurrent risk factors. However, it is now widely accepted that such a unifactorial approach is inappropriate and may lead to wrong assumptions of confounding since CVD risk factors co-occur and their effect on cognition is cumulative (additive or synergistic) (Kivipelto et al., 2005; Luchsinger et al., 2005; Yasuno et al., 2012). This could also explain some of the inconsistencies found in the literature concerning the association of different CVD risk factors in relation to cognitive outcomes. While the debate on the relative importance and contribution of various CVD and other putative risk factors to adverse cognitive outcomes continues, that a multifactorial approach to risk estimation is required is incontestable.

In this thesis, two approaches to multifactorial risk prediction (MetS, and risk scores) were examined. MetS has been suggested as a simple clinical tool for identifying high-risk individuals predisposed to CVD or type 2 diabetes. A number of studies have demonstrated a progressive increase in the risk of CHD and type 2 diabetes, with increasing number of metabolic abnormalities, but less consistent relationships have been observed with stroke (Ford, 2004; Malik et al., 2004; Ridker et al., 2003). Some reports suggest that MetS is a far stronger predictor of type 2 diabetes and does not predict CHD as well as Framingham risk scores (Wannamethee et al., 2005). This may be partly because prediction criteria based on MetS alone do not include several well-established risk factors for cardiovascular disease and cognitive decline, such as cholesterol and smoking. In addition, criteria thresholds may be ill-defined. Indeed concerns regarding the definition and limited predictive utility of MetS for cardiovascular outcomes, has

led to recommendations that physicians should evaluate and treat all CVD risk factors regardless of whether a patient meets the criteria for diagnosis of MetS (Kahn et al., 2005). In relation to cognitive outcomes, our results showed that MetS was not a good predictor of 10-year cognitive decline in midlife.

The Framingham risk scores offer a better means of identifying high risk individuals by quantifying CVD risk based on several important demographic and CVD risk factors. In addition, the Framingham risk scores use a continuous rather than dichotomous gradient of risk for several risk factors such as blood pressure and cholesterol across their entire range; the increase in risk in the presence of more than one risk factor with elevated levels emphasizes the importance of multiple risk factors and aggregation of risk. In relation to cognitive function and 10-year cognitive decline, our results showed that elevated CVD/stroke risk as estimated by the Framingham CVD and Framingham stroke risk scores were associated with more rapid cognitive decline. Therefore these two risk scores while originally developed to predict cardiovascular events can be used to identify middle aged individuals at higher risk of faster cognitive decline. These results confirm and extend previous findings of the utility of Framingham vascular risk scores for predicting cognitive outcomes (Bangen et al., 2010; Brady et al., 2001; Elias et al., 2004a; Laughlin et al., 2011; Llewellyn et al., 2008; Seshadri et al., 2004; Unverzagt et al., 2011). In addition, studies with neuroimaging data have reported an association of Framingham CVD and stroke risk scores with subclinical markers of cerebrovascular disease including coronary artery calcification (DeFilippis et al., 2011) and carotid intima media thickness (Touboul et al., 2005), white matter abnormalities (Jeerakathil et al., 2004), brain atrophy (Seshadri et al., 2004), and silent cerebral infarctions (Das et al., 2008). Structural changes in the brain that may underlie the association of CVD risk factors and cognitive outcome are believed to reflect an effect of exposure to CVD risk factors that precedes changes in cognition (Debette et al., 2010; Debette et al., 2011). Therefore, our findings of an association of elevated CVD risk in midlife and faster decline in cognition detectable on neuropsychological tests provides further evidence for the role of vthese risk factors in affecting cognitive decline trajectories in midlife and supports the utility of vascular risk scores and CVD risk in predicting cognitive outcomes.

Despite the evidence from previous studies and the present analyses demonstrating the utility of (Framingham) vascular risk scores in predicting cognitive outcomes, the question remained as to why these risk scores instead of a dementia risk score should be used to assess

cognition in midlife. It is worth noting that comparative studies have rarely been carried out even for late life dementia risk scores that are far more numerous than dementia risk scores developed based on midlife risk factors (Stephan et al., 2010). In addition, investigation of Framingham vascular risk scores in relation to cognitive outcomes is a relatively new approach. Therefore, after examining the association of two Framingham vascular risk scores with long-term cognitive decline, we compared them with the CAIDE dementia risk score that uses midlife risk factors to predict risk of late life dementia. Although all three risk scores predicted cognitive decline, the two Framingham risk scores displayed stronger associations compared to the dementia risk score. The differences between these risk scores in their association with cognitive decline that may be mainly related to their development and validation processes are not of primary interest; rather it is the practical implications of these findings that are of importance. Many diseases including cardiovascular disease and dementia have common etiologies so it is reasonable to use a common risk score both for risk estimation and risk modification. Cardiovascular risk scores particularly the Framingham risk scores have been repeatedly validated and are often integrated into primary care. They therefore have a dual advantage over a dementia risk score both in terms of feasibility of use and potential for real benefit from CVD risk factor modification.

Other noteworthy findings of this work concern the association of individual CVD risk factors (as components of the risk scores) with cognitive function and decline. Although the aim was not to determine their relative contribution to cognitive outcomes, the findings are nonetheless important. The observation that most individual risk factors were associated with cognitive scores at baseline but few (i.e. total cholesterol, left ventricular hypertrophy, diabetes) were associated with long-term decline points to the possible causal association of these risk factors in adversely affecting cognition. However the lack of association with 10-year decline does not exclude the possibility of the role of these risk factors (e.g. systolic blood pressure, HDL cholesterol, cigarette smoking) on cognitive decline since they may still lead to subclinical brain injury and thus their effect on structural changes in the brain cannot be discounted. Since structural brain changes precede cognitive changes, it is possible that cognitive deficits could not yet be detected by neuropsychological tests in our study. For example, although left ventricular hypertrophy was associated with faster 10-year global cognitive decline, such an association was not apparent for systolic blood pressure. Since left ventricular hypertrophy is a pathologic reaction to cardiovascular disease including elevated blood pressure, it is unlikely that elevated

systolic blood pressure even in this middle aged population has no effect on cognition, rather, these effects were not reflected in diverging cognitive decline.

It is interesting to note that risk factors that were associated with faster 10-year cognitive decline were not associated with poorer cognitive scores at baseline, whereas those including blood pressure, HDL cholesterol and smoking that were associated with lower cognitive scores at baseline were not associated with 10-year cognitive decline. Although the effect of these risk factors on subclinical brain injury cannot be ruled out, these findings suggest that these risk factors including total cholesterol, left ventricular hypertrophy and diabetes in particular may have an especially detrimental effect on cognition. The wealth of epidemiological studies relating diabetes with adverse cognitive outcomes including cognitive impairment and dementia makes it a potent risk factor (Biessels et al., 2006; Biessels et al., 2008; de Bresser J. et al., 2010; Debette et al., 2011; Kivipelto et al., 2001a; Kivipelto et al., 2001b; Whitmer, 2007) and our results support this notion. Compared to some CVD risk factors such as hypertension, diabetes may be considered a syndrome with a constellation of metabolic abnormalities leading to high cardiovascular burden. Diabetes without previous CHD carries a lifetime risk of vascular death as high as that for CHD alone; some have suggested that diabetes be considered a CHD risk equivalent (Whiteley et al., 2005).

Like risk estimation, risk modification also requires a multifactorial approach. Here too, Framingham vascular risk scores offer a means of appropriate identification and targeting of risk factors. In midlife where vascular risk factor levels are relatively lower than in late life, an individual with moderate risk on several risk factors may be identified as being at sufficiently increased risk of CVD to warrant vigorous risk factor management. It is also recognized that the majority of cardiovascular events occur in individuals with average or only mildly elevated levels of risk factors, partly because this is where the largest part of the population lies (Lloyd-Jones et al., 2010). As Framingham investigators have also theoretically demonstrated, focusing on individuals with borderline but multiple risk factors would lead to a significant decrease in cardiovascular events and a substantial improvement in therapeutic efficacy (D'Agostino, Sr. et al., 2008; Wolf et al., 1991b).

Although numerous studies have indicated a beneficial effect of treating CVD risk factors in slowing cognitive decline (Deschaintre et al., 2009; Richard et al., 2012), such evidence from interventional studies and randomized controlled trials in those free of cognitive impairment is

not conclusive. In the dementia substudy of the Systolic Hypertension in Europe Trial (SYST-EUR) that aimed to determine whether antihypertensive treatment could reduce the incidence of dementia, the calcium channel blocker nitrendipine was associated with a lower incidence of stroke and dementia (Forette et al., 1998). In contrast, the HYVET-COG randomized controlled trial of prevention of hypertension found a lower incidence of dementia in the placebo group (Peters et al., 2008). Likewise, the ACCORD MIND randomized trial on the effect of intensive glucose lowering on brain structure in people with type 2 diabetes did not find a benefit of intensive glycemic lowering strategies on cognition and structural changes in the brain (Launer et al., 2011). However, participants in these trials have consisted mainly of older adults (mean age 80 year in HYVET-COG study and 62 years in ACCORD MIND trial). Therefore it is likely that irreversible structural changes in the brain related to CVD risk factors have already occurred. Although in the ACCORD MIND trial there was an indication of benefit of intensive glucose therapy on total brain volume even though no differences in cognitive function were observed. Since structural changes happen before functional changes, it is possible that over time cognitive differences between treatment groups become apparent.

In addition, most trials to date have focused principally on a single risk factor and have not investigated if treatment of several CVD risk factors may be beneficial for cognitive outcomes. A study reporting significant reductions in the incidence of dementia associated with angiotensin receptor blockers, a treatment that reduces CVD risk and complications related to diabetes, illustrates the potential of such a multifactorial approach in risk reduction in relation to cognitive outcomes (Li et al., 2010b; McFarlane, 2009). New trials including one based on the Finnish CAIDE study are underway. The Finnish Geriatric Intervention Study to prevent cognitive impairment and disability (FINGER) is an ongoing multicenter randomized controlled trial to test the effectiveness of early identification and treatment of individuals at increased risk of late life cognitive impairment through a two-year multi-domain intervention targeting several risk factors simultaneously (Solomon et al., 2012).

IV.1 Strengths

A considerable strength of the studies that form this thesis is the longitudinal analyses with repeated cognitive measurements over 10 years. The relation of CVD risk factors and cognition is complex and causal associations of CVD risk factors in affecting cognition cannot be

disentangled through cross sectional and prospective studies. These longitudinal analyses suggest that CVD risk factors are associated with long-term cognitive decline. Another significant strength is the age of the cohort of middle aged adults that allowed examination of risk factors in midlife. This is important as the effect of CVD risk factor exposure in midlife is less likely to be modified by age related concomitant disease allowing us to minimize reverse causation biases inherent in studies on cognitive aging in older adults. Finally our cognitive test battery consisting of five tests allowed cognitive assessment in different domains sensitive to cardiovascular dysfunction (e.g. executive function and verbal fluency).

IV.2 Limitations

The Whitehall II study is an occupational cohort consisting entirely of 'white color' office based employees. Therefore it may not be entirely representative of the general population potentially limiting external generalization of the results. In addition, in all the analyses presented, the analytic sample consisted of participants with a more favorable demographic and risk profile. Therefore the reported associations may underestimate true associations in the general population. This has been illustrated in analyses based on the Whitehall II study that showed the association of smoking and cognition is likely to be underestimated due to higher risk of death or dropout among smokers (Sabia et al., 2012). However this is unlikely to affect comparability of the dementia and Framingham risk scores. In addition, given our middle aged population who are expected to have relatively lower vascular risk factor levels, due to the low numbers of some of the risk factors (e.g. atrial fibrillation and left ventricular hypertrophy) it is possible that we had inadequate power to detect associations with the individual risk factors. Finally, we did not have neuroimaging data to examine subclinical markers of brain aging that may underlie the association of vascular risk factors and cognition. Since structural brain changes often precede or accompany cognitive changes, observation of these effects in our middle aged population would substantiate the evidence for the association between CVD risk and cognition.

IV.3 Implications

Given the mounting evidence for the role of multiple risk factors in cognitive impairment and cognitive decline, it is important to be able to accurately identify individuals who are at the highest risk of cognitive decline in order to effectively target treatment and prevention strategies.

Growing evidence suggests that the most beneficial effect of treatment of CVD risk factors is achieved in the preclinical stage of cognitive impairment and dementia. As they become readily available and with the switch to electronic patient record system in primary care, vascular risk scores such as the Framingham cardiovascular and stroke risk scores, offer an increasingly simple and efficient tool for risk estimation as well as guiding treatment decisions. The control of factors amenable to intervention, particularly CVD risk factors will have a two-fold benefit in not only reducing cardiovascular disease incidence but also preventing or delaying cognitive impairment. Use of vascular risk scores is already advocated in clinical practice guidelines. Future guidelines should discuss the utility of these risk scores in predicting cognitive outcomes not to estimate risk of cognitive impairment but to inform and treat those with high CVD risk adding impetus for treatment and control of CVD risk factors. Given the high prevalence of CVD risk factors in the population (including middle aged), elimination or reduction of these risk factors is likely to have a great impact in reducing future cases of cognitive impairment and dementia (Alagiakrishnan et al., 2006; Ritchie et al., 2010; Stephan et al., 2008). Recent projections suggest that risk factor reduction could potentially prevent up to 3 million cases Alzheimer's disease worldwide (Barnes et al., 2011).

IV.4 Conclusion

While the continued identification of a diverse range of novel biomarkers representing various biological pathways will advance our understanding of underlying pathological mechanisms involved in the role of CVD risk factors and cognition lead to considerable improvement in prediction of clinical and subclinical markers of vascular disease and cognitive decline (Di et al., 2012; Pikula et al., 2012), their application and implementation in clinical practice is not expected in near future before extensive piloting has been conducted (O'Bryant, 2012). Meanwhile there is great potential in preventing or delaying cognitive impairment through clinical application of already identified risk factors. The capability currently exists to favorably affect cognitive outcomes through CVD risk reduction. This lends itself to population level approaches in lowering established risk factors for cognitive impairment and dementia. Use of vascular risk scores in primary care to identify at risk individuals, and early targeting and treatment of CVDrisk factors will be pivotal to effective intervention strategies.

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APPENDECES

APPENDIX A: SUPPLEMENTARY ANALYSES

Table A1. 10-year change in global cognitive scores by systolic blood pressure categories (N=5157)

SBP, mmHg	10-year change (95% CI) [a]	*p*
1 (lowest)	-0.24 (-0.28, -0.20)	*ref*
2	-0.25 (-0.29, -0.22)	*0.32*
3	-0.25 (-0.29, -0.21)	*0.54*
4	-0.26 (-0.31, -0.22)	*0.27*
5	-0.31 (-0.36, -0.25)	*0.01*
6	-0.27 (-0.34, -0.20)	*0.41*
7	-0.27 (-0.35, -0.19)	*0.38*
8 (highest)	-0.27 (-0.34, -0.14)	*0.40*

[a] Adjusted for age and sex.
Systolic blood pressure (SBP) categories are based on categories of the Framingham Stroke Risk Profile: Men: untreated SBP (mmHg): (1) 97-105, (2) 106-115, (3) 116-125, (4) 126-135, (5) 136-145, (6) 146-155, (7) 156-165, (8) 166-145, (9) 176-185, (10) 186-195, (11) 196-205; treated SBP: (1) 97-105, (2) 106-112, (3) 113-117, (4) 118-123, (5) 124-129, (6) 130-135, (7) 136-142, (8) 143-150, (9) 151-161, (10) 162-176, (11) 177-205 (Due to small numbers in the highest four categories, they are combined); WOMEN: untreated SBP: (1) 95-106, (2) 107-118, (3) 119-130, (4) 131-143, (5) 144-155, (6) 156-167, (7) 168-180, (8) 181-192, (9) 193-204, (10) 205-216; treated SBP: (1) 95-106, (2) 107-113, (3) 114-119, (4) 120-125, (5) 126-131, (6) 132-139, (7) 140-148, (8) 149-160, (9) 161-204, (10) 205-216 (Due to small numbers in the highest two categories, they are combined).

Table A2. Characteristics of the study sample at baseline, Sample 2, N=4374

	CAIDE Dementia risk score				
	All N=4374	Low (0-7) N=1915	Intermediate (8-10) N=1546	High (11-17) N=913	*p*
Components					
Age, y, mean (SD)	55.4 (5.9)	52.6 (5.2)	56.6 (5.8)	59.5 (4.8)	*<0.001*
Men	71.8	72.8	73.5	66.8	*<0.001*
Education <10 years	12.4	0.7	11.8	33.3	*<0.001*
Systolic blood pressure > 140 mm Hg	13.7	2.8	13.8	36.5	*<0.001*
BMI >30 kg/m2	13.6	5.7	13.9	30.1	*<0.001*
Total cholesterol > 6.5 mmol/L	25.9	15.0	29.3	42.9	*<0.001*
Physical activity, inactive	57.8	47.5	60.2	75.6	*<0.001*
APOE ε4 carrier	27.2	14.5	29.6	49.8	*<0.001*
	Framingham Stroke Risk Profile				
		Low (1-3) N=1992	Intermediate (4-5) N=1566	High (≥6) N=816	*p*
Components					
Age, y, mean (SD)	55.4 (5.9)	52.5 (4.4)	56.7 (5.8)	60.4 (5.4)	*<0.001*
Men	71.8	55.1	85.8	85.7	*<0.001*
Systolic blood pressure, mean (SD)	122.5 (16.1)	113.3 (11.7)	126.2 (13.1)	137.8 (15.9)	*<0.001*
Antihypertensive medication use	11.9	3.8	10.8	33.9	*<0.001*
Diabetes	3.6	1.5	4.1	8.2	*<0.001*
Current smoker	8.9	3.3	13.3	14.1	*<0.001*
History of heart disease	5.3	0.5	3.8	23.1	*<0.001*
Atrial fibrillation	1.1	0	0.1	1.2	*<0.001*
Left ventricular hypertrophy	5.8	0.2	1.8	5.9	*<0.001*

Sample 2 is based on version 2 of the CAIDE dementia risk score that includes *APOE* genotype.
Values are percentages unless otherwise indicated.

Table A3. Associations of CAIDE dementia and Framingham stroke risk with cognitive scores at baseline, Sample 2, N=4057

Cognitive test	Risk group				Standardized risk	
	Low	Intermediate	High			
	Mean cognitive performance (SD)			*p*	β (95% CI)	Δ (95% CI) [a]
Reasoning						
CAIDE	0.27 (0.87)	-0.06 (0.97)	-0.49 (1.09)	*<0.0001*	-0.26 (-0.29, -0.23)***	
FSRP	0.06 (0.97)	-0.01 (0.99)	-0.12 (1.07)	*<0.0001*	-0.02 (-0.53, -0.008)**	-0.24 (-0.28, -0.20)
Memory						
CAIDE	0.19 (1.00)	-0.07 (0.96)	-0.30 (0.97)	*<0.0001*	-0.21 (-0.24, -0.18)***	
FSRP	0.19 (1.02)	-0.10 (0.96)	-0.31 (0.89)	*<0.0001*	-0.17 (-0.20, -0.14)***	-0.04 (-0.07, 0.001) ns
Phonemic fluency						
CAIDE	0.23 (0.97)	-0.07 (0.97)	-0.36 (0.99)	*<0.0001*	-0.22 (-0.25, -0.19)***	
FSRP	0.13 (1.00)	-0.05 (0.99)	-0.24 (0.95)	*<0.0001*	-0.13 (-0.16, -0.10)***	-0.09 (-0.12, -0.04)
Semantic fluency						
CAIDE	0.27 (0.97)	-0.10 (0.95)	-0.41 (0.96)	*<0.0001*	-0.27 (-0.30, -0.24)***	
FSRP	0.11 (1.00)	-0.05 (0.99)	-0.20 (0.97)	*<0.0001*	-0.11 (-0.14, -0.08)***	-0.16 (-0.19, -0.11)
Vocabulary						
CAIDE	0.22 (0.90)	-0.06 (0.97)	-0.39 (1.11)	*<0.0001*	-0.21 (-0.24, -0.17)**	
FSRP	-0.004 (1.02)	0.009 (0.96)	-0.008 (1.00)	*0.96*	0.04 (0.01, 0.07)	-0.25 (-0.29, -0.21)
Global cognition						
CAIDE	0.24 (0.95)	-0.07 (0.97)	-0.39 (0.95)	*<0.0001*	-0.26 (-0.29, -0.23)***	
FSRP	0.10 (0.92)	-0.04 (0.98)	-0.17 (0.95)	*<0.0001*	-0.08 (-0.10, -0.06)***	-0.15 (-0.18, -0.12)

Sample 2 is based on version 2 of the CAIDE dementia risk score that includes *APOE* genotype.
ns: not significantly different at $p<0.05$.
* $p<0.05$, ** $p<0.01$, *** $p<0.001$.
[a] Difference in beta coefficients: $\beta_{CAIDE} - \beta_{FSRP}$; bootstrapped 95% confidence intervals.

Table A4. Associations of CAIDE dementia and Framingham stroke risk with 10-year cognitive change, Sample 2, N=4374

Cognitive test	Risk groups				Standardized risk	
	Low	Intermediate	High			
	10-year cognitive change (95% CI)			*p trend*	β (95% CI)	Δ (95 % CI) [a]
Reasoning						
CAIDE	-0.26 (-0.29, -0.24)	-0.35(-0.38, -0.32)	-0.42 (-0.46, -0.39)	*<0.0001*	-0.07 (-0.08, -0.05)***	
FSRP	-0.27(-0.29, -0.25)	-0.34 (-0.37, -0.32)	-0.43 (-0.47, -0.39)	*<0.0001*	-0.05 (-0.07, -0.03)***	-0.02(-0.04, 0.005) ns
Memory						
CAIDE	-0.23 (-0.28, -0.19)	-0.28 (-0.33, -0.23)	-0.29 (-0.36, -0.22)	*0.11*	-0.02 (-0.05, 0.00)	
FSRP	-0.24 (-0.28, -0.20)	-0.29 (-0.33, -0.24)	-0.26 (-0.32, -0.19)	*0.47*	-0.03 (-0.06, -0.002)*	0.01 (-0.02, 0.03) ns
Phonemic fluency						
CAIDE	-0.34 (-0.38, -0.31)	-0.37 (-0.41, -0.33)	-0.39 (-0.45, -0.34)	*0.10*	-0.02 (-0.05, 0.00)	
FSRP	-0.33 (-0.36, -0.29)	-0.36(-0.40, -0.32)	-0.44 (-0.50, -0.39)	*0.001*	-0.04 (-0.06, -0.01)**	0.02 (-0.01, 0.05) ns
Semantic fluency						
CAIDE	-0.31 (-0.34, -0.28)	-0.33 (-0.37, -0.29)	-0.33 (-0.38, -0.27)	*0.58*	-0.01 (-0.03, 0.02)	
FSRP	-0.26 (-0.30, -0.23)	-0.33 (-0.38, -0.30)	-0.42 (-0.48, -0.37)	*<0.0001*	-0.06 (-0.08, -0.04)***	0.05 (0.03, 0.07)
Vocabulary						
CAIDE	0.06 (0.04, 0.08)	0.01 (-0.01, 0.03)	-0.05 (-0.08, -0.01)	*<0.0001*	-0.03 (-0.04, -0.02)***	
FSRP	0.04 (0.03, 0.07)	0.02 (-0.002, 0.04)	-0.05 (-0.08, -0.02)	*<0.0001*	-0.04 (-0.05, -0.02)***	0.01 (-0.01, 0.03) ns
Global cognition						
CAIDE	-0.22 (-0.24, -0.20)	-0.26 (-0.28, -0.25)	-0.30 (-0.32, -0.27)	*<0.0001*	-0.03 (-0.04, -0.02)***	
FSRP	-0.21(-0.23, -0.19)	-0.26 (-0.28, -0.24)	-0.33 (-0.35, -0.30)	*<0.0001*	-0.05 (-0.06, -0.03)***	0.02 (0.01, 0.04)

Sample 2 is based on version 2 of the CAIDE dementia risk score that includes *APOE* genotype.
ns: not significantly different at $p<0.05$.
* $p<0.05$, ** $p<0.01$, *** $p<0.001$.
[a] Difference in beta coefficients: $\beta_{CAIDE} - \beta_{FSRP}$; bootstrapped 95% confidence intervals.

Table A5. Associations of CAIDE dementia risk score components with cognitive scores at baseline, Sample 2, N=4057

	Age	Sex	Education	SBP	Total cholesterol	BMI	Physical activity	*APOE*
				β (95% CI) *p*				
Reasoning	-0.25 (-0.30, -0.19) *<0.0001*	0.58 (0.51, 0.651) *<0.0001*	-0.61 (-0.65, -0.57) *<0.0001*	-0.22 (-0.31, -0.13) *<0.0001*	-0.06 (-0.13, 0.01) *0.10*	-0.14 (-0.23, -0.06) *0.001*	-0.23 (-0.29, -0.17) *<0.0001*	0.04 (-0.02, 0.11) *0.21*
Memory	-0.30 (-0.36, -0.25) *<0.0001*	-0.04 (-0.10, 0.03) *0.31*	-0.27 (-0.31, -0.22) *<0.0001*	-0.17 (-0.26, -0.08) *0.0002*	-0.02 (-0.09, 0.05) *0.51*	-0.07 (-0.16, 0.01) *0.10*	-0.16 (-0.21, -0.09) *<0.0001*	0.009 (-0.06, 0.07) *0.78*
Phonemic fluency	-0.27 (-0.32, -0.21) *<0.0001*	0.05 (-0.02, 0.11) *0.18*	-0.39 (-0.43, -0.35) *<0.0001*	-0.20 (-0.29, -0.11) *<0.0001*	0.06 (-0.008, 0.13) *0.08*	-0.06 (-0.15, 0.03) *0.18*	-0.21 (-0.28, -0.15) *<0.0001*	0.05 (-0.01, 0.12) *0.12*
Semantic fluency	-0.33 (-0.38, -0.28) *<0.0001*	0.17 (0.10, 0.24) *<0.0001*	-0.45 (-0.50, -0.41) *<0.0001*	-0.17 (-0.27, -0.08) *0.0001*	-0.01 (-0.08, 0.06) *0.75*	-0.07 (-0.16, 0.02) *0.12*	-0.24 (-0.30, -0.18) *<0.0001*	0.006 (-0.06, 0.07) *0.87*
Vocabulary	-0.01 (-0.06, 0.04) *0.61*	0.55 (0.48, 0.61) *<0.0001*	-0.60 (-0.64, -0.55) *<0.0001*	-0.04 (-0.13, 0.05) *0.38*	-0.01 (-0.08, 0.06) *0.76*	-0.27 (-0.36, -0.19) *<0.0001*	-0.26 (-0.32, -0.19) *<0.0001*	0.03 (-0.03, 0.10) *0.34*
Global cognition	-0.23 (-0.27, -0.19) *<0.0001*	0.26 (0.21, 0.31) *<0.0001*	-0.46 (-0.50, -0.44) *<0.0001*	-0.16 (-0.23, -0.09) *<0.0001*	-0.008 (-0.06, 0.04) *0.75*	-0.12 (-0.19, -0.06) *0.0002*	-0.22 (-0.27, -0.17) *<0.0001*	0.03 (-0.22, 0.08) *0.26*

Sample 2 is based on version 2 of the CAIDE dementia risk score that includes *APOE* genotype
Components are based on categories of the risk score. age (years): (1) <47, (2) 47-53, (3) >53; sex: (1) women, (2) men; education (years): (1) ≥10, (2) 7-9, (3) 0-6; systolic blood pressure (SBP) (mmHg): (1) ≤ 140, (2) ≥140; total cholesterol (mmol/L): (1) ≤6.5, (2) ≥6.5; body mass index (BMI) (kg/m^2): (1) ≤30, (2) > 30; physical activity: (1) Active, (2) inactive; *APOE* genotype: (1) *APOE ε4* carrier, (2) *APOE ε4* non-carrier.

Table A6. Associations of Framingham Stroke Risk Profile components with cognitive scores at baseline, Sample 2, N=4057

	Age	Sex	SBP	Diabetes	Smoking	Prior CVD	AF	LVH
	β (95% CI) *p*							
Reasoning	-0.14 (-0.17, -0.12) *<0.0001*	0.58 (0.51, 0.651) *<0.0001*	-0.07 (-0.09, -0.05) *<0.0001*	-0.51 (-0.68, -0.34) *<0.0001*	-0.24 (-0.35, -0.13) *<0.0001*	-0.23 (-0.36, -0.09) *0.001*	0.05 (-0.38, 0.49) *0.67*	0.03 (-0.10, 0.16) *0.64*
Memory	-0.17 (-0.19, -0.14) *<0.0001*	-0.04 (-0.10, 0.03) *0.31*	-0.06 (-0.08, -0.04) *<0.0001*	-0.23 (-0.39, -0.06) *0.007*	-0.10 (-0.21, 0.005) *0.06*	-0.31 (-0.44, -0.17) *<0.0001*	-0.10 (-0.31, 0.34) *0.55*	-0.09 (-0.22, 0.04) *0.16*
Phonemic fluency	-0.15 (-0.18, -0.13) *<0.0001*	0.05 (-0.02, 0.11) *0.18*	-0.05 (-0.07, -0.03) *<0.0001*	-0.31 (-0.47, -0.15) *0.0002*	-0.14 (-0.25, -0.03) *0.01*	-0.17 (-0.31, -0.03) *0.01*	-0.12 (-0.50, 0.29) *0.50*	-0.01 (-0.14, 0.12) *0.84*
Semantic fluency	-0.16 (-0.18, -0.13) *<0.0001*	0.17 (0.10, 0.24) *<0.0001*	-0.06 (-0.08, -0.05) *<0.0001*	-0.28 (-0.45, -0.12) *0.0008*	-0.11 (-0.22, -0.006) *0.04*	-0.25 (-0.39, -0.11) *0.0003*	-0.02 (-0.41, 0.32) *0.69*	-0.009 (-0.14, 0.12) *0.89*
Vocabulary	-0.02 (-0.04, -0.005) *0.13*	0.55 (0.48, 0.61) *<0.0001*	-0.05 (-0.07, -0.04) *<0.0001*	-0.38 (-0.55, -0.21) *<0.0001*	-0.25 (-0.35, -0.14) *<0.0001*	-0.14 (-0.28, -0.006) *0.04*	0.05 (-0.21, 0.18) *0.25*	0.06 (-0.07, 0.19) *0.37*
Global cognition	-0.13 (-0.15, -0.11) <0.0001	0.26 (0.21, 0.31) *<0.0001*	-0.06 (-0.07, -0.05) *<0.0001*	-0.34 (-0.47, -0.22) *<0.0001*	-0.17 (-0.25, -0.09) *<0.0001*	-0.22 (-0.32, -0.11) *<0.0001*	-0.01 (-0.25, 0.31) *0.74*	-0.005 (-0.10, 0.09) *0.92*

Sample 2 is based on version 2 of the CAIDE dementia risk score that includes *APOE* genotype.
Components are based on categories of the risk score. MEN: age (years): (1) <57, (2) 57-59, (3) 60-62, (4) 63-65, (5) 66-68, (6) 69-72; untreated systolic blood pressure (SBP) (mmHg): (1) 97-105, (2) 106-115, (3) 116-125, (4) 126-135, (5) 136-145, (6) 146-155, (7) 156-165, (8) 166-145, (9) 176-185, (10) 186-195, (11) 196-205; treated SBP (mmHg): (1) 97-105, (2) 106-112, (3) 113-117, (4) 118-123, (5) 124-129, (6) 130-135, (7) 136-142, (8) 143-150, (9) 151-161, (10) 162-176, (11) 177-205; diabetes: (1) no, (2) yes; smoking: (1) no, (2) yes; prior cardiovascular disease (CVD): (1) no, (2) yes; atrial fibrillation (AF): (1) no, (2) yes; left ventricular hypertrophy (LVH): (1) no, (2) yes. WOMEN: age (years): (1) <57, (2) 57-59, (3) 60-62, (4) 63-64, (5) 65-67, (6) 68-70; untreated SBP (mmHg): (1) 95-106, (2) 107-118, (3) 119-130, (4) 131-143, (5) 144-155, (6) 156-167, (7) 168-180, (8) 181-192, (9) 193-204, (10) 205-216; treated SBP (mmHg): (1) 95-106, (2) 107-113, (3) 114-119, (4) 120-125, (5) 126-131, (6) 132-139, (7) 140-148, (8) 149-160, (9) 161-204, (10) 205-216; diabetes: (1) no, (2) yes; smoking: (1) no, (2) yes; prior CVD: (1) no, (2) yes; AF: (1) no, (2) yes; LVH: (1) no, (2) yes.

Table A7. Associations of CAIDE dementia risk score components with 10-year cognitive change, Sample 2, N=4374

	Age	Sex	Education	SBP	Total cholesterol	BMI	Physical activity	*APOE*
				β (95% CI)				
				p				
Reasoning	-0.14 (-0.17, -0.11)	0.02 (-0.02, 0.05)	-0.03 (-0.06, -0.01)	-0.06 (-0.11, -0.01)	-0.006 (-0.04, 0.03)	-0.02 (-0.06, 0.03)	-0.009 (-0.04, 0.02)	-0.06 (-0.10, -0.03)
	<0.0001	*0.35*	*0.007*	*0.01*	*0.76*	*0.48*	*0.57*	*0.0006*
Memory	-0.06 (-0.12, -0.01)	-0.06 (-0.12, 0.01)	-0.002 (-0.04, 0.04)	-0.06 (-0.14, 0.03)	-0.01 (-0.08, 0.05)	0.04 (-0.05, 0.10)	0.06 (0.003, 0.12)	-0.04 (-0.10, 0.03)
	0.01	*0.09*	*0.93*	*0.22*	*0.69*	*0.39*	*0.09*	*0.26*
Phonemic fluency	-0.04 (-0.009, -0.005)	-0.005 (-0.06, 0.05)	-0.02 (-0.09, 0.06)	-0.06 (-0.13, 0.01)	-0.09 (-0.14, -0.03)	-0.04 (-0.11, 0.03)	-0.01 (-0.03, 0.06)	-0.07 (-0.12, -0.02)
	0.02	*0.85*	*0.16*	*0.09*	*0.001*	*0.29*	*0.55*	*0.01*
Semantic fluency	-0.03 (-0.07, 0.01)	-0.08 (-0.13, -0.02)	-0.03 (-0.08, 0.04)	-0.04 (-0.11, 0.02)	-0.05 (-0.11, 0.001)	0.01 (-0.06, 0.08)	-0.03 (-0.05, -0.11)	-0.01 (-0.07, 0.04)
	0.10	*0.005*	*0.16*	*0.20*	*0.05*	*0.73*	*0.42*	*0.62*
Vocabulary	-0.05 (-0.08, -0.03)	-0.04 (-0.07, -0.006)	-0.02 (-0.04, -0.001)	-0.06 (-0.10, -0.02)	-0.01 (-0.05, 0.02)	-0.006 (-0.05, 0.04)	-0.009 (-0.04, 0.02)	-0.01 (-0.04, 0.01)
	<0.0001	*0.02*	*0.03*	*0.005*	*0.43*	*0.79*	*0.55*	*0.32*
Global cognition	-0.07 (-0.09, -0.05)	-0.03 (-0.06, -0.006)	-0.003 (-0.01, 0.02)	-0.05 (-0.09, -0.02)	-0.03 (-0.06, -0.01)	-0.0005 (-0.03, 0.03)	-0.01 (-0.01, 0.04)	-0.05 (-0.07, -0.02)
	<0.0001	*0.01*	*0.69*	*0.003*	*0.01*	*0.97*	*0.25*	*<0.001*

Sample 2 is based on version 2 of the CAIDE dementia risk score that includes *APOE* genotype.
Components are based on categories of the risk score. Age (years): (1) <47, (2) 47-53, (3) >53; sex: (1) women, (2) men; education (years): (1) ≥10, (2) 7-9, (3) 0-6; systolic blood pressure (SBP) (mmHg): (1) ≤ 140, (2) ≥140; total cholesterol (mmol/L): (1) ≤6.5, (2) ≥6.5; body mass index (BMI) (kg/m^2): (1) ≤30, (2) > 30; physical activity: (1) Active, (2) inactive; *APOE* genotype: (1) *APOE ε4* carrier, (2) *APOE ε4* non-carrier.

Table A8. Associations of Framingham Stroke Risk Profile components with 10-year cognitive change, Sample 2, N=4374

	Age	Sex	SBP	Diabetes	Smoking	Prior CVD	AF	LVH
	β (95% CI) *p*							
Reasoning	-0.08 (-0.09, -0.07) *<0.0001*	0.02 (-0.02, 0.05) *0.35*	-0.02 (-0.03, -0.01) *<0.0001*	-0.05 (-0.14, 0.04) *0.24*	-0.04 (-0.09, 0.02) *0.18*	-0.02 (-0.09, 0.05) *0.54*	0.07 (-0.11, 0.16) 0.69	-0.03 (-0.09, 0.04) *0.45*
Memory	-0.04 (-0.06, -0.02) *0.0009*	-0.06 (-0.12, 0.009) *0.09*	0.003 (-0.01, 0.02) *0.77*	-0.11 (-0.28 (0.05) *0.17*	-0.05 (-0.15, 0.06) *0.38*	-0.03 (-0.10, 0.16) *0.62*	-0.01 (-0.09, 0.08) 0.50	-0.01 (-0.14, 0.11) *0.85*
Phonemic fluency	-0.02 (-0.04, -0.004) *0.02*	-0.005 (-0.06, 0.05) *0.85*	-0.02 (-0.03, -0.004) *0.01*	0.005 (-0.13, 0.14) *0.93*	-0.05 (-0.13, 0.04) *0.27*	-0.09 (-0.20, 0.01) *0.08*	-0.03 (-0.15, 0.10) 0.13	-0.07 (-0.18, 0.02) *0.12*
Semantic fluency	-0.05 (-0.07, -0.03) *<0.0001*	-0.08 (-0.13, -0.02) *0.005*	-0.009 (-0.02, 0.004) *0.15*	-0.04 (-0.16, 0.09) *0.57*	-0.06 (-0.15, 0.02) *0.15*	-0.05 (-0.16, 0.05) *0.34*	-0.06 (-0.18, 0.20) 0.35	-0.08 (-0.18, 0.01) *0.09*
Vocabulary	-0.03 (-0.04, -0.02) *<0.0001*	-0.04 (-0.007, -0.006) *0.02*	-0.008 (-0.02, -0.0006) *0.04*	-0.05 (-0.13, 0.03) *0.21*	-0.02 (-0.08, 0.03) *0.34*	-0.03 (-0.09, 0.03) *0.30*	-0.07 (-0.20, 0.11) 0.22	-0.06 (-0.12, -0.003) *0.04*
Global cognition	-0.05 (-0.06, -0.04) *<0.0001*	-0.03 (-0.06, -0.006) *0.01*	-0.01 (-0.02, -0.004) *0.001*	-0.06 (-0.12, 0.004) *0.05*	-0.04 (-0.08, 0.001) *0.05*	-0.02 (-0.07, 0.03) *0.41*	-0.06 (-0.13, 0.25) *0.55*	-0.06 (-0.11, -0.01) *0.01*

Sample 2 is based on version 2 of the CAIDE dementia risk score that includes *APOE* genotype.
Components are based on categories of the risk score. MEN: age (years): (1) <57, (2) 57-59, (3) 60-62, (4) 63-65, (5) 66-68, (6) 69-72; untreated systolic blood pressure (SBP) (mmHg): (1) 97-105, (2) 106-115, (3) 116-125, (4) 126-135, (5) 136-145, (6) 146-155, (7) 156-165, (8) 166-145, (9) 176-185, (10) 186-195, (11) 196-205; treated SBP (mmHg): (1) 97-105, (2) 106-112, (3) 113-117, (4) 118-123, (5) 124-129, (6) 130-135, (7) 136-142, (8) 143-150, (9) 151-161, (10) 162-176, (11) 177-205; diabetes: (1) no, (2) yes; smoking: (1) no, (2) yes; prior cardiovascular disease (CVD): (1) no, (2) yes; atrial fibrillation (AF): (1) no, (2) yes; left ventricular hypertrophy (LVH): (1) no, (2) yes. WOMEN: age (years): (1) <57, (2) 57-59, (3) 60-62, (4) 63-64, (5) 65-67, (6) 68-70; untreated SBP (mmHg): (1) 95-106, (2) 107-118, (3) 119-130, (4) 131-143, (5) 144-155, (6) 156-167, (7) 168-180, (8) 181-192, (9) 193-204, (10) 205-216; treated SBP (mmHg): (1) 95-106, (2) 107-113, (3) 114-119, (4) 120-125, (5) 126-131, (6) 132-139, (7) 140-148, (8) 149-160, (9) 161-204, (10) 205-216; diabetes: (1) no, (2) yes; smoking: (1) no, (2) yes; prior CVD: (1) no, (2) yes; AF: (1) no, (2) yes; LVH: (1) no, (2) yes.

Table A9. Characteristics of the study sample at baseline, Sample 2, N= 3718

	CAIDE dementia risk score				
	All N=3718	Low (0-7) N=1673	Intermediate (8-10) N=1310	High (11-17) N=765	*p*
Components					
Age, y, mean (SD)	55.0 (5.3)	50.1 (5.0)	55.6 (5.2)	58.9 (4.5)	*<0.001*
Men	71.4	70.4	73.0	66.1	*<0.001*
Education <10 years	11.2	0.9	10.7	32.9	*<0.001*
Systolic blood pressure > 140 mm Hg	13.2	2.9	12.9	37.2	*<0.001*
BMI >30 kg/m2	13.1	5.4	13.2	32.5	*<0.001*
Total cholesterol > 6.5 mmol/L	25.1	15.6	30.1	43.8	*<0.001*
Physical activity, inactive	55.8	45.0	59.2	74.2	*<0.001*
APOE ε4 carrier	26.5	14.4	30.0	48.3	*<0.001*
	Framingham General Cardiovascular Disease Risk Profile				
	All N=3718	Low (1-7) N=1249	Intermediate (7.5-13) N=1198	High (>13) N=1271	*p*
Components					
Age, y, mean (SD)	55.0 (5.3)	51.9 (4.5)	54.9 (5.3)	59.2 (5.3)	*<0.001*
Men	71.4	43.8	60.8	77.2	*<0.001*
Systolic blood pressure, mean (SD)	121.9 (15.8)	112.9 (12.2)	122.4 (13.4)	133.1 (15.2)	*<0.001*
Antihypertensive medication use	10.9	3.2	6.7	21.1	*<0.001*
Diabetes	3.2	1.6	1.8	6.7	*<0.001*
Current smoker	8.7	3.5	7.3	14.3	*<0.001*
Total cholesterol (mg/dL), mean (SD)	229.1 (40.2)	213.8 (36.6)	229.7 (37.2)	243.4 (40.9)	*<0.001*
HDL cholesterol (mg/dL), mean (SD)	56.7 (15.2)	64.8 (15.5)	55.7 (13.6)	49.8 (12.4)	*<0.001*

Sample 2 is based on version 2 of the CAIDE dementia risk score that includes *APOE* genotype.
Values are percentages unless otherwise indicated.

Table A10. Associations of CAIDE dementia and Framingham general cardiovascular risk with cognitive scores at baseline, Sample 2, N=3436

Cognitive test	Risk group				Standardized risk	
	Low	Intermediate	High			
	Mean cognitive performance (SD)			*p*	β (95% CI)	Δ (95% CI) [a]
Reasoning						
CAIDE	0.26 (0.87)	-0.06 (0.98)	-0.48 (1.09)	*<0.0001*	-0.25 (-0.28, -0.22)***	
CVDRP	0.006 (0.98)	0.01 (1.01)	-0.02 (1.00)	*0.53*	-0.02 (-0.06, 0.09)	-0.23 (-0.27, -0.19)
Memory						
CAIDE	0.18 (1.00)	-0.06 (0.96)	-0.30 (0.97)	*<0.0001*	-0.20 (-0.23, -0.16)***	
CVDRP	0.21 (1.01)	0.0008 (0.99)	-0.21 (0.94)	*<0.0001*	-0.18 (-0.21, -0.14)***	-0.02 (-0.06, 0.02) ns
Phonemic fluency						
CAIDE	0.23 (0.99)	-0.08 (0.98)	-0.37 (0.99)	*<0.0001*	-0.23 (-0.26, -0.19)***	
CVDRP	0.13 (1.04)	0.02 (0.97)	-0.15 (1.02)	*<0.0001*	-0.14 (-0.17, -0.11)***	-0.09 (-0.13, -0.05)
Semantic fluency						
CAIDE	0.27 (0.97)	-0.11 (0.96)	-0.41 (0.95)	*<0.0001*	-0.27 (-0.31, -0.24)***	
CVDRP	0.11 (1.01)	0.02 (0.98)	-0.13 (0.99)	*<0.0001*	-0.13 (-0.16, -0.09)***	-0.14 (-0.18, -0.10)
Vocabulary						
CAIDE	0.21 (0.91)	-0.06 (0.97)	-0.38 (1.10)	*<0.0001*	-0.20 (-0.23, -0.17)***	
CVDRP	-0.07 (1.08)	0.02 (0.94)	0.06 (0.96)	*0.001*	0.05 (0.01, 0.08)**	-0.25 (-0.29, -0.21)
Global cognition						
CAIDE	0.31 (0.91)	-0.10 (0.95)	-0.53 (1.00)	*<0.0007*	-0.31 (-0.34, -0.28)***	
CVDRP	0.10 (1.03)	0.02 (0.97)	-0.12 (0.97)	*<0.0001*	-0.11 (-0.15, -0.08)***	-0.20 (-0.24, -0.16)

Sample 2 is based on version 2 of the CAIDE dementia risk score that includes *APOE* genotype.
ns: not significantly different at p<0.05.
* p<0.05, ** p<0.01, *** p<0.001.
[a] Difference in beta coefficients: $\beta_{CAIDE} - \beta_{CVDRP}$; bootstrapped 95% confidence intervals.

Table A11. Associations of CAIDE dementia and Framingham general cardiovascular disease risk with 10-year cognitive change, Sample 2, N=3718

Cognitive test	Risk groups				Standardized risk	
	Low	Intermediate	High			
	10-year cognitive change (95% CI)			*p trend*	β (95% CI)	Δ (95 % CI) [a]
Reasoning						
CAIDE	-0.27 (-0.30, -0.25)	-0.35 (-0.38, -0.32)	-0.43 (-0.47, -0.39)	*<0.0001*	-0.06 (-0.08, -0.05)***	
CVDRP	-0.26 (-0.29, -0.23)	-0.32 (-0.35, -0.28)	-0.41 (-0.45, -0.38)	*<0.0001*	-0.06 (-0.08, -0.05)***	0 (-0.02, 0.02) ns
Memory						
CAIDE	-0.23 (-0.28, -0.18)	-0.30 (-0.36, -0.25)	-0.28 (-0.36, -0.21)	*0.12*	-0.03 (-0.06, 0.00)	
CVDRP	-0.20 (-0.26, -0.15)	-0.29 (-0.35, -0.24)	-0.30 (-0.35, -0.24)	*0.01*	-0.04 (-0.08, -0.01)**	0.01 (-0.03, 0.05) ns
Phonemic fluency						
CAIDE	-0.35 (-0.39, -0.32)	-0.37 (-0.41, -0.32)	-0.39 (-0.44, -0.33)	*0.38*	-0.02 (-0.04, 0.01)	
CVDRP	-0.32 (-0.37, -0.28)	-0.35 (-0.40, -0.31)	-0.41 (-0.46, -0.37)	*0.01*	-0.04 (-0.06, -0.01)**	0.02 (-0.01, 0.05) ns
Semantic fluency						
CAIDE	-0.30 (-0.35, -0.28)	-0.31 (-0.36, -0.27)	-0.31 (-0.35, -0.28)	*0.85*	0.01 (-0.02, 0.03)	
CVDRP	-0.24 (-0.29, -0.20)	-0.33 (-0.37, -0.28)	-0.37 (-0.41, -0.32)	*<0.0001*	-0.05 (-0.08, -0.02)**	0.06 (0.03, 0.09)
Vocabulary						
CAIDE	0.06 (0.04, 0.08)	0.003 (-0.02, 0.03)	-0.04 (-0.07, -0.004)	*<0.0001*	-0.03 (-0.04, -0.01)**	
CVDRP	0.06 (0.03, 0.08)	0.03 (0.01, 0.06)	-0.03 (-0.05, 0.001)	*<0.0001*	-0.04 (-0.06, -0.03)***	0.01 (-0.01, 0.03) ns
Global cognition						
CAIDE	-0.30 (-0.32, -0.27)	-0.36 (-0.39, -0.34)	-0.39 (-0.43, -0.35)	*<0.0001*	-0.04 (-0.05, -0.02)**	
CVDRP	-0.26 (-0.29, -0.23)	-0.34 (-0.37, -0.32)	-0.42 (-0.44, -0.39)	*<0.0001*	-0.07 (-0.08, -0.05)***	0.03 (0.01, 0.05)

Sample 2 is based on version 2 of the CAIDE dementia risk score that includes *APOE* genotype.
ns: not significantly different at $p<0.05$.
* $p<0.05$, ** $p<0.01$, *** $p<0.001$.
[a] Difference in beta coefficients: $\beta_{CAIDE} - \beta_{CVDRP}$; bootstrapped 95% confidence intervals.

Table A12. Associations of Framingham General Cardiovascular Disease Risk Profile components with cognitive scores at baseline, Sample 2, N=3436

	Age	Sex	SBP	Diabetes	Smoking	Total cholesterol	HDL cholesterol
				β (95% CI) *p*			
Reasoning	-0.14 (-0.17, -0.11) *<0.0001*	0.62 (0.54, 0.69) *<0.0001*	-0.05 (-0.08, -0.03) *0.0002*	-0.44 (-0.63, -0.26) <0.0001	-0.22 (-0.34, -0.09) 0.0004	-0.02 (-0.05, 0.02) 0.33	0.02 9-0.003, 0.04) 0.08
Memory	-0.18 (-0.20, -0.15) *<0.0001*	-0.02 (-0.09, 0.05) *0.61*	-0.08 (-0.11, -0.05) *<0.0001*	-0.15 (-0.33, 0.03) 0.11	-0.10 (-0.22, 0.02) 0.10	-0.003 (-0.04, 0.03) 0.85	-0.04 (-0.06, -0.01) 0.004
Phonemic fluency	-0.17 (-0.19, -0.14) *<0.0001*	0.06 (-0.01, 0.13) *0.10*	-0.06 (-0.09, -0.03) *<0.0001*	-0.22 (-0.41, -0.03) 0.02	-0.11 (-0.23, 0.01) 0.07	-0.02 (-0.05, 0.02) 0.27	-0.02 (-0.05, 0.004) 0.09
Semantic fluency	-0.18 (-0.20, -0.15) *<0.0001*	0.19 (0.11, 0.26) *<0.0001*	-0.07 (-0.09, -0.04) *<0.0001*	-0.22 (-0.40, -0.03) 0.02	-0.08 (-0.19, 0.04) 0.21	-0.003 (-0.04, 0.03) 0.85	-0.008 (-0.03, 0.01) 0.56
Vocabulary	-0.01 (-0.04, 0.01) *0.38*	0.58 (0.51, 0.65) *<0.0001*	-0.02 (-0.05, 0.006) *0.12*	-0.30 (-0.49, -0.11) 0.001	-0.22 (-0.34, -0.09) 0.0004	-0.002 (-0.05, 0.02) 0.79	-0.004 (-0.03, 0.02) 0.73
Global cognition	-0.14 (-0.15, -0.11) <0.0001	0.28 (0.23, 0.34) <0.0001	-0.06 (-0.08, -0.04) <0.0001	-0.27 (-0.40, -0.13) 0.0002	-0.15 (-0.24, -0.06) 0.001	-0.003 (-0.02, 0.02) 0.82	-0.01 (-0.03, 0.009) 0.30

Sample 2 is based on version 2 of the CAIDE dementia risk score that includes *APOE* genotype
Components are based on categories of the risk score. Age (years): (1) 30-34, (2) 35-39, (3) 40-44, (4) 45-49, (5) 50-54, (6) 55-59, (7) 60-64, (8) 65-69, (9) 70-74, (10) ≥75; systolic blood pressure (SBP) (mmHg): (1) <120, (2) 120-129, (3) 130-139, (4) 140-159, (5) ≥160; diabetes: (1) no, (2) yes; smoking: (1) no, (2) yes; total cholesterol (mg/dL): (1) <160, (2) 160-199, (3) 200-239, (4) 240-279, (5) ≥280; HDL cholesterol (mg/dL): (1) ≥60, (2) 50-59, (3) 45-49, (4) 35-44, (5) <35.

Table A13. Associations of Framingham General Cardiovascular Disease Risk Profile components with 10-year cognitive change, Sample 2, N= 3718

	Age	Sex	SBP	Diabetes	Smoking	Total cholesterol	HDL cholesterol
				β (95% CI) *p*			
Reasoning	-0.08 (-0.1, -0.07) *<0.0001*	0.02 (-0.02, 0.05) *0.42*	-0.02 (-0.03, -0.003) *0.01*	-0.04 (-0.14, 0.060 *0.43*	-0.03 (-0.10, 0.03) *0.30*	-0.01 (-0.03, 0.005) *0.16*	-0.002 (-0.01, 0.01) *0.75*
Memory	-0.05 (-0.07, -0.02) *0.0007*	-0.06 (-0.13, 0.009) *0.08*	-0.009 (-0.03, 0.02) *0.51*	-0.14 (-0.33, 0.04) *0.12*	0.01 (-0.10, 0.13) *0.79*	-0.01 (-0.04, 0.01) *0.39*	0.0003 (-0.02, 0.03) *0.97*
Phonemic fluency	-0.01 (-0.03, 0.006) *0.15*	-0.009 (-0.06, 0.04) *0.75*	-0.02 (-0.04, 0.002) *0.07*	-0.009 (-0.16, 0.14) *0.90*	-0.06 (-0.15, 0.04) *0.23*	-0.03 (-0.06, -0.003) *0.02*	-0.002 (-0.02, 0.02) *0.81*
Semantic fluency	-0.04 (-0.06, -0.01) *0.0007*	-0.08 (-0.14, -0.03) *0.004*	-0.02 (-0.04, 0.0008) *0.05*	0.01 (-0.13, 0.16) *0.85*	-0.05 (-0.15, 0.04) *0.25*	-0.02 (-0.04, 0.009) *0.21*	-0.008 (-0.03, 0.01) *0.39*
Vocabulary	-0.03 (-0.04, -0.02) *0.0001*	-0.05 (-0.08, -0.01) *0.05*	-0.02 (-0.03, -0.002) *0.02*	-0.08 (-0.17, 0.01) *0.08*	-0.008 (-0.06, 0.05) *0.77*	-0.01 (-0.02, 0.004) *0.14*	-0.003 (-0.02, 0.009) *0.61*
Global cognition	-0.06 (-0.07, -0.04) *<0.0001*	-0.05 (-0.09, -0.01) *0.004*	-0.02 (-0.04, -0.009) *0.001*	-0.09 (-0.18, 0.008) *0.07*	-0.03 (-0.09, 0.03) *0.33*	-0.02 (-0.04, -0.007) *0.006*	-0.004 (-0.02, 0.009) *0.53*

Sample 2 is based on version 2 of the CAIDE dementia risk score that includes *APOE* genotype.
Components are based on categories of the risk score. Age (years): (1) 30-34, (2) 35-39, (3) 40-44, (4) 45-49, (5) 50-54, (6) 55-59, (7) 60-64, (8) 65-69, (9) 70-74, (10) ≥75; systolic BP (mmHg): (1) <120, (2) 120-129, (3) 130-139, (4) 140-159, (5) ≥160; diabetes: (1) no, (2) yes; smoking: (1) no, (2) yes; total cholesterol (mg/dL): (1) <160, (2) 160-199, (3) 200-239, (4) 240-279, (5) ≥280; HDL cholesterol (mg/dL): (1) ≥60, (2) 50-59, (3) 45-49, (4) 35-44, (5) <35.

Table A14. Associations of modified CAIDE dementia and Framingham stroke risk with cognitive scores at baseline (Phase 5), Sample 1, N=4814

Cognitive test	Standardized risk	
	β (95% CI)	Δ (95 % CI) [a]
Reasoning		
CAIDE	-0.09 (-0.11, -0.06)***	
FSRP	-0.04 (-0.06, -0.008)**	-0.05 (-0.08, -0.02)
Memory		
CAIDE	-0.13 (-0.16, -0.10)***	
FSRP	-0.16 (-0.19, -0.13)***	0.03 (0.002, 0.06)
Phonemic fluency		
CAIDE	-0.11 (-0.14, -0.09)***	
FSRP	-0.14 (-0.17, -0.11)***	0.03 (-0.005, 0.06) ns
Semantic fluency		
CAIDE	-0.14 (-0.16, -0.11)***	
FSRP	-0.13 (-0.16, -0.10)***	-0.01 (-0.04, 0.02) ns
Vocabulary		
CAIDE	-0.03 (-0.06, -0.006)*	
FSRP	0.02 (-0.007, 0.04)	-0.05 (-0.09, -0.02)
Global cognition		
CAIDE	-0.10 (-0.12, -0.08)***	
FSRP	-0.09 (-0.11, -0.07)***	-0.01 (-0.03, 0.01) ns

CAIDE dementia risk score modified by removing education component.
ns: not significantly different at $p<0.05$.
* $p<0.05$, ** $p<0.01$, *** $p<0.001$.
[a] Difference in beta coefficients: $\beta_{CAIDE} - \beta_{FSRP}$; bootstrapped 95% confidence intervals.

Table A15. Associations of modified CAIDE dementia and Framingham stroke risk with cognitive scores at baseline (Phase 5), Sample 2, N=4057

Cognitive test	Standardized risk	
	β (95% CI)	Δ (95 % CI) [a]
Reasoning		
CAIDE	-0.09 (-0.11, -0.05)***	
FSRP	-0.02 (-0.53, -0.008)**	-0.07 (-0.09, -0.03)
Memory		
CAIDE	-0.15 (-0.18, -0.12)***	
FSRP	-0.17 (-0.20, -0.14) ***	0.02 (-0.02, 0.05) ns
Phonemic fluency		
CAIDE	-0.12 (-0.15, -0.09)***	
FSRP	-0.13 (-0.16, -0.10)***	0.01(-0.02, 0.06) ns
Semantic fluency		
CAIDE	-0.15 (-0.18, -0.12)***	
FSRP	-0.11 (-0.14, -0.08)***	-0.04 (-0.07, -0.007)
Vocabulary		
CAIDE	-0.01 (-0.04, 0.01)	
FSRP	0.04 (0.01, 0.07)*	-0.05 (-0.09, -0.02)
Global cognition		
CAIDE	-0.10 (-0.13, -0.08)***	
FSRP	-0.08 (-0.10, -0.06)***	-0.02 (-0.005, 0.06) ns

CAIDE dementia risk score modified by removing education component.
Sample 2 is based on version 2 of the CAIDE dementia risk score that includes *APOE* genotype.
ns: not significantly different at p<0.05.
* p<0.05, ** p<0.01, *** p<0.001.
[a] Difference in beta coefficients: $\beta_{CAIDE} - \beta_{FSRP}$; bootstrapped 95% confidence intervals.

Table A16. Associations of modified CAIDE dementia and Framingham stroke risk with 10-year cognitive change, Sample 1, N=5157

Cognitive test	Standardized risk	
	β (95% CI)	Δ (95 % CI) [a]
Reasoning		
CAIDE	-0.05 (-0.06, -0.03)***	
FSRP	-0.05 (-0.06, -0.03)***	0 (-0.02, 0.02) ns
Memory		
CAIDE	-0.02 (-0.50, 0.009)	
FSRP	-0.03 (-0.06, 0.0007)	0.01(-0.03, 0.05) ns
Phonemic fluency		
CAIDE	-0.03 (-0.05, -0.008)**	
FSRP	-0.03 (-0.06, -0.01)***	0 (-0.04, 0.04) ns
Semantic fluency		
CAIDE	-0.02 (-0.04, -0.002)*	
FSRP	-0.05 (-0.08, -0.03)***	0.03 (0.0001, 0.06)
Vocabulary		
CAIDE	-0.02 (-0.04, -0.01)***	
FSRP	-0.04 (-0.05, -0.02)***	0.02 (-0.02, 0.05) ns
Global cognition		
CAIDE	-0.03 (-0.04, -0.02)***	
FSRP	-0.04 (-0.05, -0.03)***	0.01(-0.02, 0.06) ns

CAIDE dementia risk score modified by removing education component.
ns: not significantly different at $p<0.05$.
* $p<0.05$, ** $p<0.01$, *** $p<0.001$.
[a] Difference in beta coefficients: $\beta_{CAIDE} - \beta_{FSRP}$; bootstrapped 95% confidence intervals.

Table A17. Associations of modified CAIDE dementia and Framingham stroke risk with 10-year cognitive change, Sample 2, N=4374

Cognitive test	Standardized risk	
	β (95% CI)	Δ (95 % CI) [a]
Reasoning		
CAIDE	-0.07 (-0.08, -0.05)***	
FSRP	-0.05 (-0.07, -0.03)***	-0.02 (-0.01, 0.05) ns
Memory		
CAIDE	-0.03 (-0.06, -0.002)*	
FSRP	-0.03 (-0.06, -0.002)*	0 (-0.03, 0.03) ns
Phonemic fluency		
CAIDE	-0.04 (-0.06, -0.02)**	
FSRP	-0.04 (-0.06, -0.01)**	0 (-0.02, 0.02) ns
Semantic fluency		
CAIDE	-0.02 (-0.04, 0.001)	
FSRP	-0.06 (-0.08, -0.04)***	0.04 (0.0002, 0.08)
Vocabulary		
CAIDE	-0.03 (-0.04, -0.01)***	
FSRP	-0.04 (-0.05, -0.02)***	0.01 (-0.02, 0.06) ns
Global cognition		
CAIDE	-0.04 (-0.05, -0.03)***	
FSRP	-0.05 (-0.06, -0.03)***	0.01(-0.03, 0.05) ns

CAIDE dementia risk score modified by removing education component.
Sample 2 is based on version 2 of the CAIDE dementia risk score that includes *APOE* genotype.
ns: not significantly different at $p<0.05$.
* $p<0.05$, ** $p<0.01$, *** $p<0.001$.
[a] Difference in beta coefficients: $\beta_{CAIDE} - \beta_{FSRP}$; bootstrapped 95% confidence intervals.

APPENDIX B: PUBLICATIONS

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BASIC SCIENCE

Predictive utility of the Framingham general cardiovascular disease risk profile for cognitive function: evidence from the Whitehall II study

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Aims Vascular risk factors are associated with cognitive impairment and dementia, although most of the research in this domain focuses on cerebrovascular factors. We examined the relationship between the recently developed Framingham general cardiovascular risk profile and cognitive function and 10-year decline in late midlife.

Methods and results Study sample comprised of 3486 men and 1341 women, mean age 55 years [standard deviation (SD)=6], from the Whitehall II study, a longitudinal British cohort study. The Framingham General Cardiovascular Risk profile, assessed between 1997 and 1999, included age, sex, HDL cholesterol, total cholesterol, systolic blood pressure, smoking status, and diabetes status. Measures of cognitive function consisted of tests of reasoning (Alice Heim 4-I), memory, phonemic and semantic fluency, and vocabulary (Mill-Hill), assessed three times (1997–1999, 2002–2004, 2007–2009) over 10 years. In cross-sectional age-adjusted models, 10% point increments in cardiovascular risk were associated with poor performance in all cognitive domains in both men and women (all *P*-values <0.001). In models adjusted for age, ethnicity, marital status, and education, 10% higher cardiovascular risk was associated with greater overall 10-year cognitive decline in men, reasoning in particular (-0.47; 95% CI: -0.81, -0.11).

Conclusion In middle-aged individuals free of cardiovascular disease, an adverse cardiovascular risk profile is associated with poor cognitive function, and decline in at least one cognitive domain in men.

Keywords Framingham General Cardiovascular Profile • Cognitive function • Cardiovascular risk scores • Cognitive decline

Introduction

The importance of vascular risk factors and disease for cognitive impairment and dementia in older adults is widely recognized.[1–3] There is growing evidence to suggest that these risk factors are also associated with deficits in cognitive function in midlife, prior to the onset of overt clinical symptoms of dementia.[4–9] Several risk algorithms have been developed to predict the risk of stroke and cardiovascular events.[10–12] Such scores improve the efficiency of risk prediction and provide a more realistic assessment of the collective importance of risk factors as well as easier interpretation of the risk of disease. They may equally help identify persons at increased risk of disease resulting from risk below the clinical threshold on individual risk factors.

The association between multiple vascular risk factors and cognition has been examined by a number of studies using the Framingham Stroke Risk Profile (FSRP).[13–16] These studies have reported an inverse association between the 10-year risk for

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stroke and performance on multiple cognitive tests. The majority of these studies have used a cross-sectional design, which provides little information about risk prediction.[14–16] In addition, the FSRP is designed for prediction of stroke and therefore does not cover the full range of potentially relevant cardiovascular diseases, such as myocardial infarction (MI), coronary insufficiency, angina, and peripheral artery disease. We used the recently developed Framingham General Cardiovascular Disease Risk Profile to examine associations with cognitive performance and then decline over a 10-year period in a large sample of middle-aged individuals.

Methods

Data were drawn from the Whitehall II study, established in 1985 to examine the socioeconomic gradient in health and disease among 10 308 civil servants (6895 men and 3413 women). Details of the cohort have been described previously.[17] Briefly, all London-based office staff aged 35–55 working in 20 civil service departments were invited to participate, of which 73% agreed. Baseline examination took place during 1985–1988 and consisted of a clinical examination and a self-administered questionnaire that included sections on demographic characteristics, medical history, and health behaviours. Clinical examination included measures of blood pressure, anthropometry, biochemical variables, subclinical makers of cardiovascular disease, and neuroendocrine function. A battery of cognitive tests was introduced to the study at Phase 5 (1997–1999), and repeated at phases 7 (2002–2004) and 9 (2007–2009). Informed consent was obtained from all participants and the University College London ethics committee approved the study.

Assessment of risk factors for the cardiovascular disease risk profile

The Framingham general cardiovascular disease (CVD) risk score is designed for use in primary care to identify individuals at high risk for CVD events that include coronary, cerebrovascular and peripheral arterial disease, and heart failure.[11] Its development was based on the prediction of 1174 CVD events over a 12-year follow-up period of 8491 participants in the Framingham Heart study. The risk score, calculated using information on age, HDL cholesterol, total cholesterol, systolic blood pressure, cigarette smoking, and diabetes provides an estimate of the risk of CVD over a 10-year period.

The risk score components in our study were drawn from questionnaire and clinical examination data at Phase 5. HDL and total cholesterol (mg/dL) were measured from blood samples collected after either an 8 h fast for participants presenting in the morning, or at least 4 h after a light fat-free breakfast for those presenting in the afternoon. Cholesterol was measured using a Cobas Fara centrifugal analyzer (Roche Diagnostics System). HDL cholesterol was measured by precipitating non-HDL cholesterol with dextran sulfate-magnesium chloride with the use of a centrifuge and measuring cholesterol in the supernatant fluid. Systolic blood pressure (mmHg) was taken as the average of two measurements in the sitting position after a 5 min rest with the Hawksley random-zero sphygmomanometer. Treated hypertension was determined according to the antihypertensive medication use. This included diuretics, beta-blockers, ACE-inhibitors, and calcium channel blockers. Participants were categorized with respect to their cigarette smoking status as current smokers or past/non-smokers. Diabetes was defined by a fasting glucose $\geq$ 7.0 mmol/L or a 2 h post-load glucose $\geq$11.1 mmol/L or reported doctor diagnosed diabetes, or use of diabetes medication.[18]

Raw scores were calculated and then converted to 10-year risk or predicted probability of incident CVD expressed as a percentage.[11] Missing data for any risk score component were replaced by data from Phase 4 (1995–1996), $n = 27$, and in the case of biological measures (HDL cholesterol, total cholesterol, and systolic blood pressure), by data from Phase 3 (1991–1993), $n = 624$. Individuals ($n = 319$) with a history of stroke or coronary heart disease (CHD) at Phase 5 were excluded. Coronary heart disease status at Phase 5 was defined as non-fatal MI and 'definite' angina. Myocardial infarction diagnosis, based on clinical examinations at Phases 1, 3, or 5 and records obtained from general practitioners and hospitals, was assessed using MONICA criteria.[19] Angina was assessed based on participant's reports of symptoms with corroboration in medical records or abnormalities on a resting electrocardiogram, an exercise electrocardiogram, or a coronary angiogram. Stroke diagnosis was self-reported and included history of stroke or a transient ischaemic attack.

Cognitive function

The cognitive test battery, administered at the clinical examinations at Phases 5, 7, and 9, described below, consists of five standard tasks chosen to provide a comprehensive assessment of cognitive function.

The Alice Heim 4-I (AH4-I) is composed of a series of 65 verbal and mathematical reasoning items of increasing difficulty.[20] It tests inductive reasoning, measuring the ability to identify patterns and infer principles and rules. The time allowed for this test was 10 min.

Short-term verbal memory was assessed with a 20-word free recall test. Participants were presented a list of 20 one or two syllable words at two second intervals and were then asked to recall in writing as many of the words in any order and had 2 min to do so.

We used two measures of *verbal fluency*: phonemic and semantic. Phonemic fluency was assessed via 'S' words and semantic fluency via 'animal' words.[21] Subjects 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*, used in its multiple-choice format, consisting of a list of 33 stimulus words ordered by increasing difficulty and six response choices.[22]

Covariates

The following covariates were included; age, marital status, ethnicity, and education. Although age is a component of the Framingham General CVD risk score, we included it as a covariate because of its established association with cognitive function.[23] Ethnicity consisted of two groups; white and non-white. Marital status included two categories; married/cohabiting and single/divorced/widowed. Education was measured as the highest level of education achieved. Categories included (i) elementary or lower secondary, (ii) higher secondary (A' levels), and (iii) first university degree or higher. We also examined the effect of occupational position at baseline in lieu of education. This variable consisted of three categories: (i) high (administrative), (ii) intermediate (professional or executive), and (iii) low (clerical or support).

Statistical methods

Descriptive analyses were carried out to examine the distribution of the CVD risk score components, all covariates, as well as cognitive function, and decline in our study population. In order to carry out cross-sectional and longitudinal analyses on the same population, we started with those who had data at Phase 5 and at least one repeat measure so that cognitive decline could be calculated (implying participation in Phase 7 or 9 of the study). Approximately 86% of the 4837

participants included in the study had cognitive data at all three phases of this study. As follow-up time varied between individuals (mean = 10.5, SD = 0.5), we first estimated the rate of change, standardizing it to represent 10-year change for each individual. The interaction term between the risk score and sex ($P < 0.001$ for all cognitive tests) led us to stratify all analyses by sex.

We first explored correlations of the 10-year CVD risk, assessed at Phase 5, with cognitive function at Phases 5 and 9 and cognitive decline over the 10-year follow-up. Subsequently, regression analysis was used to model the impact of a 10% increment in CVD risk on cognitive function at Phase 5 and 10-year cognitive decline. In these analyses, we first calculated an overall test of association using multivariate analysis of variance (MANOVA) in order to account for the correlation between the cognitive tests and control type 1 error inflation due to multiple tests. Then, linear regression was used to determine the cross-sectional association between the CVD risk, modelled to show the impact of a 10% point increment in risk, and each cognitive test separately. We first examined unadjusted models, followed by models adjusted for age only, and finally the fully adjusted models including all four covariates.

The longitudinal analyses assessed the association between 10-year CVD risk at Phase 5 and 10-year cognitive decline, calculated using data from Phases 5, 7, and 9 as described earlier. Linear regression was used to model the association between a 10% increment in CVD risk at baseline and cognitive decline. The adjustment for covariates was performed in three steps, as in the cross-sectional analysis. MANOVA analyses were also carried out to examine the association between CVD risk and overall cognitive decline. In supplementary analyses, occupational position replaced adjustment for education in order to assess the effect of a later life measure of socioeconomic circumstances. Tests of statistical significance were two sided and results were statistically significant at $P < 0.05$. All analyses were conducted using SAS software (version 9; SAS Institute, Cary, NC).

Results

Of 10 308 participants at baseline of the Whitehall II study (Phase 1, 1985–1988), 7830 (75.9%) individuals at Phase 5 (1997–1999) responded to the questionnaire or came to the clinical examination. Of these, 5146 (65.7%) had complete data on cognitive function and all covariates. After excluding 319 participants with a history of CHD or stroke at Phase 5, our final study sample consisted of 4827 individuals (3486 men and 1341 women). Compared with the sample used in this analysis, participants at Phase 5 excluded from this study had a higher mean 10-year CVD risk (12.1 vs. 9.8%, $P < 0.001$). Missing data were also influenced by age, sex, and education as individuals excluded were more likely to be women, older, and have a lower level of education (all P-values < 0.001).

The characteristics of the study population are shown in *Table 1*. Men had a considerably higher mean 10-year CVD risk than women; 1711 (49.1%) and 514 (14.7%) of men and 71 (5.3%) and 3 (0.2%) of women had a 10-year CVD risk higher than 10 and 20%, respectively. The correlation analysis (see Supplementary material online, *Table S1*) suggested robust cross-section and prospective associations between CVD risk and cognition except the association with vocabulary at Phase 5 in men. These associations were largely similar in men and women, except for the tests of reasoning and vocabulary.

Regression analysis to model the cross-sectional associations between 10% increment in Framingham CVD risk and cognitive function are presented in *Table 2*. The MANOVA analyses show significant associations between the CVD risk and overall cognitive function in the fully adjusted model in men ($P = 0.05$) and women ($P < 0.03$). The unadjusted regression estimates show a 10% higher CVD risk to be associated with 1.66 lower score on the test of reasoning (AH4-I) for men [95% confidence interval (CI) = −2.10, −1.22]. In the unadjusted models, CVD risk was inversely associated with all individual cognitive domains except the vocabulary test in men ($P = 0.30$). These associations were robust to adjustment for age (all P-values < 0.01). In the fully adjusted models, all tests except reasoning in men ($P = 0.17$) and the verbal fluency tests in women remained associated with CVD risk. Adjustment for occupational position yielded similar results to analyses adjusted for education (see Supplementary material online, *Table S2*).

Table 3 shows the results of linear regression used to model the relation between a 10% increment in CVD risk at baseline and cognitive decline over 10 years. The unadjusted MANOVA ($P < 0.001$) suggests an association between CVD risk and overall cognitive decline only in men. In unadjusted models, a 10% increment in CVD risk was associated with 1.30 points (95% CI = −1.58, −1.02) greater decline in reasoning. In unadjusted models in men, these affects were evident for all cognitive domains except memory; in fully adjusted models, the association was robust only with reasoning ($P = 0.009$). Replacing education with occupational position did not lead to significant changes in the results (see Supplementary material online, *Table S3*).

The results on cognitive decline in women prompted us to further explore this association by categorizing the risk score differently in men and women (see Supplementary material online, *Table S4*). These results, adjusted for all covariates, suggest that all cognitive domains except vocabulary decline in all CVD risk groups in men and women.

We carried out several sensitivity analyses to test the robustness of our findings. First, we examined whether use of antihypertensive medication, a component of the Framingham CVD risk algorithm, over the follow-up period, from Phase 5 to Phase 9, affected the association between CVD risk and cognitive decline. An increasing proportion of participants in the study reported to be on antihypertensive medication, 9.0% at Phase 5, 20.3% at Phase 7, 23.3% at Phase 8, and 31.3% at Phase 9. As expected, adjustment for use of antihypertensive medication over study follow-up slightly attenuated the association between CVD risk and cognitive decline in both men and women. We obtained similar results when we adjusted for use of other classes of CVD medications (nitrates, antiplatelets, and lipid lowering drugs); results not shown but available upon request.

Second, we repeated the analyses of the association between CVD risk and cognitive decline, excluding participants who had a validated CHD event over the follow-up ($n = 160$). These results were essentially the same as those reported in the main analyses.

Third, since we had imputed the Framingham CVD risk profile for participants who were missing data for one or more components of the risk score, we repeated all analyses with the sample of participants who had complete data at Phase 5

Table I Characteristics of the study population

Variables	Men (n = 3486)	Women (n = 1341)	P-value[†]
Framingham general cardiovascular disease risk profile (%)	12.0 (7.1)	4.1 (2.8)	<0.001
General cardiovascular disease risk score components			
Mean age (years)	55.1 (5.9)	55.3 (5.9)	0.24
Mean HDL (mg/dL)	53.0 (13.2)	65.0 (16.6)	<0.001
Mean total serum cholesterol (mg/dL)	227.5 (39.1)	230.9 (41.3)	0.008
Mean untreated systolic blood pressure (mmHg)	122.4 (15.5)	119.6 (16.7)	<0.001
Mean treated systolic blood pressure (mmHg)	131.6 (15.3)	129.2 (15.7)	0.12
Current smoker (%)	7.9	10.4	<0.001
History of diabetes (%)	3.8	3.4	0.52
Covariates			
Marital status (%)			
Married/cohabiting	83.9	60.2	<0.001
Single/widowed/divorced	16.1	39.7	
Ethnicity (%)			
White	94.3	87.9	<0.001
Non-white	5.6	12.1	
Education (%)			
Lower primary/secondary	37.4	53.2	<0.001
A levels	28.1	23.0	
University	34.5	23.8	
Cognitive test raw scores at Phase 5			
Reasoning (AH4-I, range, 0–65)	49.2 (9.5)	42.9 (11.6)	<0.001
Memory (range, 0–20)	6.9 (2.3)	7.1 (2.7)	0.12
Semantic fluency (range, 0–35)	16.8 (3.9)	16.2 (4.5)	<0.001
Phonemic fluency (range, 0–35)	17.1 (4.2)	16.9 (4.6)	0.31
Vocabulary (Mill Hill, range, 0–33)	25.8 (3.6)	23.6 (5.2)	<0.001
10-year cognitive decline[a]			
Reasoning (AH4-I, range, 0–65)	−3.6 (6.1)	−3.8 (6.3)	0.47
Memory (range, 0–20)	−0.6 (2.5)	−0.5 (3.2)	0.24
Semantic fluency (range, 0–35)	−1.5 (3.4)	−1.2 (3.5)	0.03
Phonemic fluency (range, 0–35)	−1.7 (3.6)	−1.7 (4.0)	0.98
Vocabulary (Mill Hill, range, 0–33)	−0.02 (2.1)	0.2 (2.3)	0.003

Values are mean (SD) where appropriate.
[a]Decline calculated using three repeat measures Phases 5 (1997–1999), 7 (2002–2004), and 9 (2007–2009) and standardized to represent 10-year decline in order to take into account variations in the follow-up.
[†]P-value for mean difference between men and women.

(n = 4221). Again, we observed similar results to those in the analyses with the imputed data.

Discussion

In this large prospective cohort study of a middle-aged population, an adverse Framingham general CVD risk profile, a validated predictor of future CVD, was associated with poor cognitive function in middle-aged men and women. When these associations were modelled using 10% increment in CVD risk, as has been previously done for stroke risk,[14,15] the effects were much larger for women than for men. This may be due to the differences in risk distribution in men and women; in our study, and perhaps in others, the mean CVD risk in women was lower, at 4.1% compared with 12% in men. In our study, cross-sectional correlation coefficients (see Supplementary material online, *Table S1*) between CVD risk and cognitive function pointed to comparable associations in men and women. Thus, a 10% increase in CVD risk is a considerably larger increase in risk in women compared with men. In regression analyses, cross-sectional associations were robust and largely persisted after adjustment for demographic variables and education. With respect to 10-year cognitive decline, there was evidence of cognitive decline in all domains except vocabulary at all levels of CVD risk. However, higher CVD risk was associated with greater decline only in reasoning in men.

Table 2 Cross-sectional association between a 10% increment in the Framingham 10-year cardiovascular disease risk and cognitive function

Cognitive domain	Unadjusted			Adjusted for age			Multiple adjusted[a]		
	β[b]	95% CI	*P*-value	β[b]	95% CI	*P*-value	β[b]	95% CI	*P*-value
Men									
MANOVA			<0.001			<0.001			0.05
Reasoning (AH 4-I)	−1.66	−2.10, −1.22	<0.001	−0.93	−1.49, −0.37	0.001	−0.34	−0.82, 0.14	0.17
Memory	−0.56	−0.66, −0.45	<0.001	−0.20	−0.33, −0.06	0.003	−0.14	−0.27, −0.01	0.04
Semantic fluency	−0.85	−1.03, −0.67	<0.001	−0.40	−0.63, −0.17	<0.001	−0.24	−0.45, −0.02	0.03
Phonemic fluency	−0.88	−1.08, −0.69	<0.001	−0.40	−0.64, −0.15	0.001	−0.25	−0.48, −0.01	0.04
Vocabulary (Mill Hill)	−0.09	−0.26, 0.08	0.30	−0.46	−0.66, −0.24	<0.001	−0.23	−0.42, −0.05	0.01
Women									
MANOVA			<0.001			<0.001			0.03
Reasoning (AH4-I)	−8.74	−10.91, −6.58	<0.001	−5.60	−7.78, −3.43	<0.001	−2.65	−4.42, −0.87	0.003
Memory	−1.41	−1.92, −0.91	<0.001	−0.92	−1.44, 0.39	<0.001	−0.58	−1.08, −0.07	0.03
Semantic fluency	−2.57	−3.43, −1.72	<0.001	−1.33	−2.19, −0.47	0.002	−0.33	−1.08, 0.42	0.38
Phonemic fluency	−2.24	−3.12, −1.36	<0.001	−1.25	−2.15, −0.35	0.006	−0.62	−1.48, 0.23	0.15
Vocabulary (Mill Hill)	−2.96	−3.94, −1.98	<0.001	−2.28	−3.29, −1.27	<0.001	−0.81	−1.60, −0.02	0.05

[a]Adjusted for age, ethnicity, marital status, education.
[b]β represents the regression coefficient showing the impact of a 10% increase in cardiovascular disease risk.

Table 3 The association between a 10% increment in the Framingham 10-year cardiovascular disease risk and cognitive decline[a]

Cognitive domain	Unadjusted			Adjusted for age			Multiple adjusted[b]		
	β[c]	95% CI	*P*-value	β[c]	95% CI	*P*-value	β[c]	95% CI	*P*-value
Men									
MANOVA			<0.001			0.04			0.04
Reasoning (AH 4-I)	−1.30	−1.58, −1.02	<0.001	−0.46	−0.81, −0.10	0.01	−0.47	−0.82, −0.11	0.009
Memory	−0.05	−0.16, 0.07	0.45	0.08	−0.06, 0.23	0.28	0.06	−0.09, 0.21	0.43
Semantic fluency	−0.27	−0.43, −0.11	<0.001	−0.13	−0.33, 0.07	0.20	−0.15	−0.35, 0.04	0.14
Phonemic fluency	−0.17	−0.34, 0.00	0.05	−0.14	−0.36, 0.07	0.19	−0.16	−0.38, 0.05	0.14
Vocabulary (Mill Hill)	−0.25	−0.35, −0.15	<0.001	−0.09	−0.22, 0.03	0.14	−0.08	−0.21, 0.04	0.17
Women									
MANOVA			0.13			0.14			0.04
Reasoning (AH4-I)	−0.06	−1.28, 1.16	0.92	1.09	−0.16, 2.34	0.08	1.17	−0.08, 2.44	0.07
Memory	−0.33	−0.94, 0.28	0.29	−0.19	−0.82, 0.44	0.55	−0.27	−0.91, 0.36	0.39
Semantic fluency	−0.56	−1.22, 0.10	0.09	−0.48	−1.16, 0.21	0.17	−0.67	−1.36, 0.02	0.06
Phonemic fluency	−0.29	−1.06, 0.48	0.46	−0.15	0.94, 0.65	0.72	−0.08	−0.89, 0.72	0.83
Vocabulary (Mill Hill)	−0.51	−0.95, −0.06	0.03	−0.39	−0.85, 0.08	0.10	−0.42	−0.89, 0.04	0.07

[a]Decline calculated using three repeat measures Phases 5 (1997–1999), 7 (2002–2004), and 9 (2007–2009) and standardized to represent 10-year decline in order to take into account variations in the follow-up.
[b]Adjusted for age, ethnicity, marital status, education.
[c]β represents the regression coefficient showing the impact of a 10% increase in cardiovascular disease risk.

Comparison with other studies

Findings from this study support results from studies that have examined the importance of multiple vascular and cardiovascular risk factors by examining the collective effect of individual risk factors in relation to cognition.[24–28] For example, Whitmer *et al.*[28] reported that the presence of multiple cardiovascular risk factors at midlife independent of age, race, sex, and education substantially increased risk of dementia in old age. Those having

simultaneously high cholesterol, hypertension, diabetes, and being smokers had more than a two-fold greater risk of dementia than those with no such risk factors. The dementia risk score developed by Kivipelto *et al.*[24] also highlights the role of multiple cardiovascular risk factors in middle age and the future risk of dementia.

Given the importance of multiple vascular risk factors in relation to cognitive function, stroke, and CHD, the more global CVD risk scores present an important opportunity to study these associations. Although most of the studies in this domain have focused on stroke risk scores, especially the FSRP,[13–16] we can draw some comparisons with these investigations. The cross-sectional associations between CVD risk and cognitive function, observed in our study, are largely consistent with results obtained in these studies. However, comparison with their findings is limited because of differences in study populations and neuropsychological tests used. In addition, whereas we found sex differences in the associations and stratified our analyses accordingly, none of these studies reported sex differences in the association between stroke risk and cognitive function. We found that after adjusting for age, sex, and education, 10-year CVD risk was associated with poorer performance in the test of memory in both men and women. However, while one study found an association with stroke risk and memory,[15] the other two did not find a similar association.[14,16]

Our results concerning the association between CVD risk and 10-year cognitive decline suggest a similar rate of decline at all levels of risk in women. In men, there is an indication of a global effect that in individual tests show greater decline in inductive reasoning in those with higher CVD risk at baseline. A previous study on older men showed the Framingham stroke risk score to predict decline in verbal fluency but not memory and visuospatial performance.[13] Knopman *et al.*[5] reported a steeper 6-year decline in processing speed and phonemic fluency in diabetics and only in processing speed for individuals with hypertension. Another study in an older cohort found an association between hypertension and cognitive decline over a 4-year period.[29] Our finding for no greater decline in memory in those with higher CVD risk is consistent with a body of literature suggesting that frontally mediated cognitive functions, such as verbal fluency, may be more vulnerable to the pathophysiological processes linked to cardiovascular risk factors than other cognitive abilities such as memory.[5,30,31]

Strengths and limitations

There are a number of limitations to our study. First, the participants of the Whitehall II study are office-based civil servants and thus are not fully representative of the British population which may limit the generalizability of our findings. Second, individuals who were included in our analysis had a more favourable demographic and CVD risk profile, suggesting that our results may be an underestimation of the relationship between CVD risk and cognitive function. In addition, since participants were tested three times over 10 years, there is a possibility of practice effects.[32] As a result, the observed decline in cognitive function may again be an underestimation of the true extent of longitudinal cognitive decline. Finally, the relatively low 10-year CVD risk for women in our study population did not allow adequate examination of the relation between CVD risk and 10-year cognitive decline in women.

Conclusions and implications

In summary, our study is the first to examine the relationship between CVD risk as determined by the Framingham general CVD risk profile, and cognitive function and 10-year decline in a large middle-aged cohort. Our results are important as they suggest that not only adverse CVD risk is robustly related to poorer cognitive function in late midlife, it is also associated with decline in at least one cognitive domain in men. To make a difference in outcomes, current thinking about cognitive ageing must shift from focusing on thresholds to a continuum of cognitive impairment.[33] Moreover, the current emphasis on risk factors especially treatable ones such as vascular risk factors must shift from late to early stages; subtle cognitive changes have been shown to be present as early as 22 years before diagnosis of Alzheimer's disease.[34] Our own analyses concerning the role of treatment with antihypertensive medications in attenuating the association between CVD risk and cognitive decline suggest that early preventive measures and treatment of CVD risk factors may indeed have a positive impact on cognitive outcomes. The Framingham CVD risk score presents a convenient way to identify individuals at an increased risk of cognitive deficits later in life. Given the ageing of populations worldwide and the link between impaired cognitive function in midlife and dementia, early targeting and treatment of cardiovascular risk factors, already important in their own right, should gain urgency for prevention of cognitive impairment in late life.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Midlife stroke risk and cognitive decline: A 10-year follow-up of the Whitehall II cohort study

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Abstract

Background: Stroke is associated with an increased risk of dementia. However, it is unclear whether risk of stroke in those free of stroke, particularly in nonelderly populations, leads to differential rates of cognitive decline. Our aim was to assess whether risk of stroke in mid life is associated with cognitive decline over 10 years of follow-up.

Methods: We studied 4153 men and 1657 women (mean age, 55.6 years at baseline) from the Whitehall II study, a longitudinal British cohort study. We used the Framingham Stroke Risk Profile (FSRP), which incorporates age, sex, systolic blood pressure, diabetes mellitus, smoking, prior cardiovascular disease, atrial fibrillation, left ventricular hypertrophy, and use of antihypertensive medication. Cognitive tests included reasoning, memory, verbal fluency, and vocabulary assessed three times over 10 years. Longitudinal associations between FSRP and its components were tested using mixed-effects models, and rates of cognitive change over 10 years were estimated.

Results: Higher stroke risk was associated with faster decline in verbal fluency, vocabulary, and global cognition. For example, for global cognition there was a greater decline in the highest FSRP quartile (−0.25 of a standard deviation; 95% confidence interval: −0.28 to −0.21) compared with the lowest risk quartile ($P = .03$). No association was observed for memory and reasoning. Of the individual components of FSRP, only diabetes mellitus was associated independently with faster cognitive decline ($\beta = -0.06$; 95% confidence interval, −0.01 to 0.003; $P = .03$).

Conclusion: Elevated stroke risk at midlife is associated with accelerated cognitive decline over 10 years. Aggregation of risk factors may be especially important in this association.

Keywords: Vascular risk factors; Cognitive decline; Framingham Stroke Risk Profile; Aging; Mid life

1. Introduction

Stroke increases the risk of dementia considerably [1–4]. In community-based studies, the prevalence of poststroke dementia in stroke survivors is about 30% and the incidence of new onset dementia after stroke increases from 7% after 1 year to 48% after 25 years [5]. Cognitive impairment is three times more common in people who have had a stroke than in those who have not [6]. Even in the absence of stroke, individuals with a high risk of stroke have substantially higher cognitive deficits [7]. Individual risk factors such as obesity, hypertension, hypercholesterolemia, and smoking that predispose to stroke have been linked to adverse structural brain changes, cognitive impairment, and dementia [8–17]. Moreover, there is evidence that vascular risk factors predispose one to both vascular dementia and Alzheimer's disease [5,18]. The clustering of risk factors may be particularly important and may increase the risk of cognitive impairment in an additive or synergistic manner, setting individuals on a trajectory of cognitive decline in advance of clinically detectable symptoms of cognitive impairment and dementia [16].

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Current practice guidelines on management and treatment of cardiovascular disease, both coronary heart disease and stroke, recommend use of multifactorial risk prediction models. These risk scores offer an effective evaluation of vascular risk particularly in younger populations, in which the prevalence of stroke is low, but risk of stroke may nevertheless be present as a result of the accumulation of low to moderate risk of multiple risk factors for stroke. Identification of associations of subclinical vascular risk with cognitive decline at the "brain at risk" stage is important and provides a great opportunity for prevention [19,20].

The Framingham risk scores are among the most widely validated and commonly used risk algorithms in clinical and research settings. However, their utility for predicting cognitive deficits in relation to vascular risk has remained relatively unexplored. The Framingham Stroke Risk Profile (FSRP) uses routinely measured risk factors to estimate 10-year risk of stroke. A number of studies have examined the relation of the FSRP in predicting cognitive deficits. The FSRP has been shown to be associated with incident cognitive impairment [21] and worse performance on various cognitive tests such as delayed verbal memory, verbal fluency [22], and abstract reasoning [7]. However, the few studies that have examined FSRP in relation to cognition are either limited by their cross-sectional design [7,22,23]; were conducted in a small, select population [24]; or had a short follow-up and used a single-item measure of cognitive status [21].

We sought to examine the association between stroke risk and longitudinal change in cognitive test scores using three repeated cognitive measures over a 10-year period in a large sample of middle-aged individuals.

2. Methods

2.1. Study population

The Whitehall II study was established in 1985 on 10,308 London-based office staff (6895 men and 3413 women). Details of the cohort and its follow-up have been described previously [25]. Briefly, all office staff aged 35 to 55 years in 20 civil service departments in London, UK, were invited to participate. In total, 73% of those invited agreed to participate in phase 1 (1985–1988), which consisted of a clinical examination and a self-administered questionnaire. Clinical examination included measures of blood pressure, anthropometry, biochemistry, neuroendocrine function, and subclinical markers of cardiovascular disease. Subsequent phases of data collection have alternated between a questionnaire-alone phase and a questionnaire accompanied by clinical examination. Cognitive testing was introduced to the full cohort during phase 5 (1997–1999) and was repeated during phase 7 (2002–2004) and phase 9 (2007–2009). All participants provided informed consent; the University College London ethics committee approved the study.

2.2. Assessment of Framingham Stroke Risk Profile

The FSRP is a clinical risk score that is used to calculate a sex-specific 10-year probability of stroke for individuals who are free of stroke at baseline. The original algorithm is based on prediction of 427 stroke events observed throughout a 10-year follow-up period for 2372 men and 3362 women in the Framingham Heart Study. The FSRP is based on the following risk factors: age, sex, systolic blood pressure, antihypertensive medication, diabetes, cigarette smoking status, history of cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy as determined by electrocardiogram [26,27]. The FSRP has been shown to predict strongly the incidence of stroke in our cohort [28].

We drew risk score components from questionnaire and clinical examination data at phase 5 (1997–199) in those free of stroke. Blood pressure was taken twice in the sitting position with a Hawksley random-zero sphygmomanometer after a 5-minute rest (Lynjay Services Ltd.,Worthing, United Kingdom). The average of the two readings was used in the analysis. Antihypertensive medication included diuretics, beta blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers. Diabetes was defined by a fasting glucose level of $\geq$ 7.0 mmol/L, a 2-hour postload glucose level of $\geq$ 11.1 mmol/L, reported doctor-diagnosed diabetes, or use of diabetes medication [29]. Participants were categorized with respect to cigarette smoking status as current smokers or past/nonsmokers. History of cardiovascular disease was based on clinical examination at phases 1, 3, or 5 (via electrocardiograms and angiograms) and corroborated records obtained from general practitioners or hospitals. The diagnosis of atrial fibrillation and left ventricular hypertrophy was made using a standard 12-lead electrocardiogram and the Minnesota code classification system for electrocardiographic findings (atrial fibrillation, code 3-1 for High Amplitude R-waves; left ventricular hypertrophy, code 8-3-1 for Arrhythmias). The stroke risk profile expressed as a predicted 10-year probability of incident stroke (measured as a percentage), was computed using beta coefficients based on the Cox proportional hazards regression model in the Framingham study [26,27].

2.3. Assessment of cognitive function

The cognitive test battery consisted of five standard tasks to assess performance in various cognitive domains. In our cohort, these tests were shown to be sensitive to detecting small changes in cognitive function over time in participants as young as 45 to 49 years of age [30].

The Alice Heim 4-I is composed of a series of 65 verbal and mathematical reasoning items of increasing difficulty [31]. It tests inductive reasoning, measuring the ability to identify patterns and infer principles and rules. The time allowed for this test was 10 minutes. Short-term verbal memory was assessed with a 20-word free recall test. Participants were presented a list of 20 one- or two-syllable words at

2-second intervals and were then asked to recall, in writing, as many of the words in any order, and they had 2 minutes to do so.

We used two measures of verbal fluency: phonemic and semantic. Phonemic fluency was assessed via "S" words and semantic fluency via "animal" words [32]. 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, used in its multiple-choice format, consisting of a list of 33 stimulus words ordered by increasing difficulty and six response choices [33]. In addition, a global cognitive score was created using all five of these tests by first standardizing raw scores on each test to z scores (mean, 0; standard deviation (SD), 1) using the baseline mean and SD value in the entire cohort for each test. Z scores were then averaged to yield the global cognitive score.

2.4. Covariates

Our analyses were adjusted for important demographic and health-related factors, including age, sex, ethnicity, education, depressive symptoms, physical activity, and alcohol use. Although age and sex are both components of the FSRP, we included them as covariates because of their established association with cognitive function. Age was centered at the mean value for the analytical sample. Ethnicity was categorized into (*i*) white and (*ii*) other ethnic groups. Education was measured as highest level of education achieved. Categories included (*i*) elementary or lower secondary, (*ii*) higher secondary (A' levels), and (*iii*) first university degree or higher. We also assessed the effect of occupational position, classified as administrative, professional or executive, and clerical or supportive position. We also adjusted the analyses for depressive symptoms and health behaviors that in our cohort were shown to be associated with cognitive outcomes [34,35]. Depressive symptoms were assessed using the four-item depression subscale of the General Health Questionnaire and had two categories (0–3 and $\geq$4). Alcohol consumption was assessed using questions on the number of alcoholic drinks consumed during the past 7 days. This information was divided into "measures" of spirits, "glasses" of wine, and "pints" of beer, and was converted to number of units of alcohol, with each unit corresponding to 8 g ethanol. For example, a standard measure of spirits and a glass of wine are considered to contain 8 g alcohol, and a pint of beer, 16 g alcohol. Participants' alcohol consumption was categorized as follows: none (0 unit/week), moderate (1–14 units/week for women and 1–21 units/week for men), and heavy ($>$14 units/week for women and $>$21 units/week for men). Physical activity level was determined from phase 5 questionnaires that included 20 items on frequency and duration of participation in different leisure-time physical activities (e.g., walking, general housework, cycling, sports) that were used to compute hours per week of each intensity level. Physical activity level was categorized as follows: high, more than 2.5 hours/week of moderate or more than 1 hour/week of vigorous physical activity; moderate, between 1 hour/week and 2.5 hours/week of moderate physical activity; and low, less than 1 hour/week of moderate and less than 1 hour/week of vigorous physical activity.

2.5. Statistical analysis

For ease of interpretation, we categorized stroke risk into quartiles, with the first quartile representing lowest risk and the fourth quartile representing highest stroke risk. To allow comparability of the five cognitive tests, they were standardized to z scores, as described previously.

We used linear mixed-effects models to estimate 10-year decline and associated 95% confidence intervals (CI) in each of the five measures of cognitive function. This method uses all available data over the 10 year follow-up, including those with one or two missing cognitive tests, and takes into account the intraindividual correlation inherent in repeated measures. In our models, fixed effects included terms for time, the main effect term for each variable (stroke risk, age, sex, ethnicity, education, depressive symptoms, physical activity, and alcohol use), and interactions between time and each variable. The interaction between a given variable and time represents the effect of that variable on change in cognitive score over time. In addition to these main effects, two random effects were included—one for the intercept and one for the slope.

The stroke risk $\times$ time $\times$ sex interaction did not suggest sex differences in the rate of cognitive decline; thus, our analyses were not stratified by sex. Our final models adjusted for demographic factors included terms for FSRP quartile, time, age, sex, ethnicity, and education, and the interaction between time and each of FSRP quartile, age, sex, ethnicity, and education. An interaction term for FSRP quartile and age was also included. Additional models included terms for the demographics-adjusted models plus physical activity, alcohol use, and depressive symptoms, and their interaction with time. The low stroke risk quartile was used as the referent category to obtain *P* values for the difference in cognitive change in the remaining three quartiles. We conducted supplementary analyses to explore further each FSRP component as an independent risk factor for cognitive decline.

We also undertook sensitivity analyses to test the robustness of our main findings. We modeled the association between FSRP and cognitive decline, taking FSRP as a continuous variable, to represent a broader range of stroke risk. We carried out the same analyses as outlined earlier on log-transformed FSRP scores. We also conducted additional analyses to account for interim events (e.g., incident stroke) and missing cognitive function data in our analyses, and tested for the interaction with *APOE* ε4 carrier status (defined as presence or absence of $\geq$1 *APOE* ε4 allele) in a subset of the study population with these data (n = 4936).

Analyses were performed using Proc Mixed procedure in SAS software (version 9; SAS Institute Inc., Cary, NC, USA).

3. Results

Of 10,308 participants at the inception of the Whitehall II study (1985–1988), 7830 (75.9%) participated in phase 5 (1997–1999), the baseline of the current analysis. We included participants for whom stroke risk could be calculated at phase 5 and who had at least one cognitive test measure during the follow-up (n = 6118). Our analysis is based on 5810 individuals (4153 men and 1657 women), after excluding participants with prevalent stroke (n = 48) or those missing data for covariates (n = 260); 73% of participants had complete data at all three phases and 20.2% at two phases. Restricting the analyses to participants with complete data at all three phases did not change our results significantly. Compared with individuals not included in these analyses, our sample included individuals who were younger (55.6 years vs. 57.5 years at phase 5, $P < .001$) and more educated (28.0% vs. 15% with a university degree, $P < .001$). Among participants who had at least one cognitive measure over three waves, those with data at all three waves were different from those with data at one or two waves; they had a lower FSRP (4.3% vs. 5.1%, $P < .001$), were younger (55.2 years vs. 56.7 years, $P < .001$), and were primarily men (72% vs. 67%, $P < .001$). There was also a higher proportion of individuals with a university education (29.8% vs. 24.9%, $P < .01$). Mean FSRP in our analytical sample was 4.5% (SD, 3.5%; range, 1%–78%). Detailed characteristics of the study population are presented in Table 1 (see Supplementary Table 1 for quartile-specific characteristics).

Mean cognitive test scores (z scores) at baseline (phase 5) by FSRP quartile are presented in Fig. 1. Persons in the highest stroke risk quartile had lower mean cognitive test scores compared with those in the lowest risk quartile, and there was a negative trend in cognitive test scores across the four stroke risk groups (P for trend = .001 on all tests except vocabulary, when $P = .07$).

Estimates of 10-year change in cognitive z scores as a function of stroke risk at baseline are presented in Table 2. In models adjusted for demographic factors, increased stroke risk was associated with faster cognitive decline for verbal fluency, vocabulary, and global cognition. For example, compared with a decline of −0.32 SD unit per 10 years in phonemic fluency test, for persons in the lowest stroke risk quartile, cognitive decline was −0.39 SD (95% CI, −0.46 to −0.32) and −0.41 SD (95% CI, −0.48 to −0.34) over 10 years for those in the third and fourth quartile, respectively. Similarly, in models adjusted for demographic and health-related factors, those in the fourth FSRP quartile showed faster decline in verbal fluency, vocabulary, and global cognition. Compared with the lowest stroke risk quartile, there was a 0.04-SD unit faster decline in global cognition in the fourth stroke risk quartile compared with the lowest risk quartile ($P = .03$). These differences were evident only when comparing the fourth quartile (FSRP ≥ 6%) with the lowest risk referent quartile. Adjusting associations for occupation, an indicator of socioeconomic status (instead of education), did not change the results considerably.

Table 1
Characteristics of the study sample (phase 5, 1997–1999)

Variable	Data
Framingham Stroke Risk Profile (FSRP), mean (SD)	4.5 (3.5)
FSRP components	
Age, y, mean (SD)	55.6 (6.0)
Men, n (%)	4153 (71.5)
Systolic blood pressure, mmHg, mean (SD)	123.0 (16.4)
Antihypertensive medications, n (%)	733 (12.6)
Diabetes, n (%)	225 (3.9)
Current smoker, n (%)	563 (9.7)
History of CVD, n (%)	331 (5.7)
Atrial fibrillation, n (%)	29 (0.5)
Left ventricular hypertrophy, n (%)	290 (5.0)
Covariates	
Education, n (%)	
Lower primary/secondary	2554 (43.9)
A levels	1522 (26.2)
University	1734 (29.8)
White ethnicity, n (%)	5370 (92.4)
Depressive symptoms, n (%)	716 (12.3)
Alcohol use, n (%)	
None	871 (14.9)
Moderate	3522 (60.6)
Heavy	1417 (24.4)
Physical activity, n (%)	
Low	1737 (29.9)
Moderate	975 (16.8)
High	3098 (53.3)

Abbreviations: CVD, cardiovascular disease; SD, standard deviation.

We investigated further individual FSRP components as independent risk factors for cognitive decline over 10 years, relating each of the FSRP components to global cognitive function. In models adjusted for demographics and health-related factors, only diabetes (β = − 0.06; 95% CI, −0.01

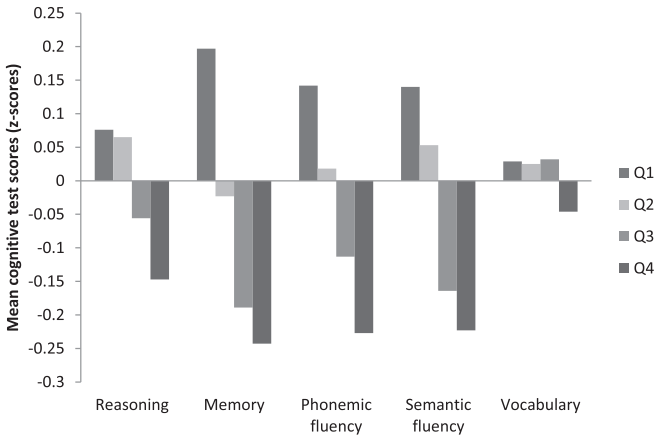

Fig. 1. Mean cognitive test scores at phase 5 by Framingham Stroke Risk Profile (FSRP) quartile. Q1, Q2, Q3, and Q4, quartiles 1 through 4, respectively.

Table 2
Cognitive change as a function of stroke risk (FSRP)

	10-Year cognitive change (95% CI) per FSRP quartile			
Cognitive tests	1 (mean, 2.4%)	2 (mean, 4.0%)	3 (mean, 5.0%)	4 (mean, 9.3%)
Adjusted for demographics				
Reasoning	−0.31 (−0.34, −0.28)	−0.30 (−0.34, −0.26)	−0.33 (−0.38, −0.29)	−0.33 (−0.37, −0.29)
Memory	−0.23 (−0.29, −0.17)	−0.18 (−0.26, −0.10)	−0.23 (−0.32, −0.14)	−0.20 (−0.24, −0.08)
Phonemic fluency	−0.32 (−0.37, −0.27)	−0.34 (−0.40, −0.28)	−0.39 (−0.46, −0.32)	−0.41 (−0.48, −0.34)*
Semantic fluency	−0.22 (−0.27, −0.17)	−0.26 (−0.33, −0.22)	−0.26 (−0.33, −0.19)	−0.30 (−0.36, −0.24)*
Vocabulary	0.05 (0.02, 0.08)	0.06 (0.02, 0.09)	0.03 (−0.004, 0.08)	−0.008 (−0.04, 0.03)†
Global cognition	−0.21 (−0.23, −0.18)	−0.21 (−0.23, −0.18)	−0.23 (−0.26, −0.21)	−0.24 (−0.27, −0.21)*
Adjusted for demographics and health related factors				
Reasoning	−0.33 (−0.36, −0.29)	−0.32 (−0.36, −0.28)	−0.35 (−0.40, −0.30)	−0.35 (−0.40, −0.30)
Memory	−0.25 (−0.32, −0.18)	−0.20 (−0.28, −0.12)	−0.25 (−0.34, −0.16)	−0.18 (−0.27, −0.009)
Phonemic fluency	−0.33 (−0.39, −0.27)	−0.34 (−0.41, −0.28)	−0.39 (−0.47, −0.32)	−0.42 (−0.48, −0.13)*
Semantic fluency	−0.21 (−0.27, −0.16)	−0.27 (−0.33, −0.20)	−0.25 (−0.32, −0.18)	−0.29 (−0.36, −0.22)*
Vocabulary	0.04 (0.01, 0.08)	0.05 (0.01, 0.09)	0.03 (0.01, 0.08)	−0.01 (−0.05, 0.03)†
Global cognition	−0.21 (−0.24, −0.19)	−0.16 (−0.24, −0.18)	−0.24 (−0.27, −0.20)	−0.25 (−0.28, −0.21)*

Abbreviations: CI, confidence interval; FSRP, Framingham Stroke Risk Profile.

NOTE. Estimates derived from linear mixed models using three assessments over 10 years. Models adjusted for demographics include age centered at the mean, sex, ethnicity, and education. Health-related factors include depressive symptoms, physical activity, and alcohol consumption.

*$P < .05$, difference in mean cognitive change compared with referent quartile 1.

†$P < .01$, difference in mean cognitive change compared with referent quartile 1.

to −0.003; $P = .03$) was associated independently and inversely with decline in global cognition over 10 years (Table 3).

Last, we obtained similar results in analyses of stroke risk as a continuous variable. Here, too, verbal fluency, vocabulary, and global cognition were associated with cognitive decline over 10 years (see Supplementary Table 2). Other sensitivity analyses to test the robustness of our results indicated that accounting for interim stroke events (n = 146) did not influence the findings greatly. Restricting the analyses to participants with complete cognitive data at all three phases (n = 4258) did not alter the results qualitatively. In addition, the association between 10-year risk of stroke and cognitive decline was not modified by *APOE* ε4 status.

4. Discussion

In this large cohort of middle-aged men and women, we found higher risk of stroke to be associated with faster decline in multiple cognitive domains assessed using a battery of cognitive tests administered three times over 10 years. There was faster decline in phonemic and semantic fluency, vocabulary, and global cognition in the highest risk quartile compared with the referent lowest risk quartile. Our study, based on longitudinal data, provides a less biased estimate of the causal association between stroke risk and cognitive decline than cross-sectional data. The relationship between vascular risk factors and cognition is likely to be bidirectional; cross-sectional data on elderly subjects do not allow the direction of the association to be established. In this study, we addressed whether stroke risk in mid life, when stroke is rare, is associated with more rapid cognitive decline. Our findings add to the literature linking vascular risk to cognitive impairment by providing evidence for the association between stroke risk in mid life and long-term cognitive decline. Using the FSRP as an aggregate measure of risk factors, we found that mid to low risk levels on more than one component of the stroke risk score can lead to

Table 3
Association of vascular risk factor components of the Framingham Stroke Risk Profile and cognitive change

	10-Year change in global cognition					
	Adjusted for demographics			Adjusted for demographic and health related factors		
Risk factor	β	95 % CI	*P* value	β	95 % CI	*P* value
SBP	−0.01	(−0.04, 0.02)	.39	−0.01	(−0.04, 0.02)	.41
Diabetes	−0.04	(−0.10, 0.003)	.05	−0.06	(−0.10, −0.003)	.03
Smoking	−0.03	(−0.07, 0.003)	.07	−0.03	(−0.07, 0.003)	.08
History of CVD	0.002	(−0.04, 0.05)	.93	0.001	(−0.04, 0.05)	.94
AF	−0.05	(−0.22, 0.12)	.53	−0.07	(−0.20, 0.11)	.54
LVH	−0.04	(−0.08, 0.003)	.08	−0.04	(−0.08, −0.0004)	.05

Abbreviations: AF, atrial fibrillation; CI, confidence interval; CVD, cardiovascular disease; LVH, left ventricular hypertrophy; SBP, systolic blood pressure.

NOTE. Estimates derived from linear mixed models using three assessments over 10 years. Models adjusted for demographics include age centered at the mean, sex, ethnicity, and education. Health-related factors include depressive symptoms, physical activity, and alcohol consumption.

a threshold of risk that is detrimental to cognitive aging. We found that, even in our relatively low-risk middle-aged population, this led to a detectable decline in cognitive performance over 10 years. Although our data do not allow us to determine an exact cutoff for stroke risk that clearly confers a greater risk of cognitive decline, we observed a faster rate of cognitive decline only in the highest risk quartile (FSRP $\geq$ 6%; mean, 9.3%) compared with the referent lowest risk quartile. Thus, it appears that in our study sample a stroke risk $\geq$6% is associated with more rapid cognitive decline.

Among individual risk factors, only diabetes was associated independently with cognitive decline. Although this association has not been found in some studies [21], the observed relation between diabetes and cognitive decline in our study is supported by a number of studies reporting associations of diabetes with longitudinal changes on magnetic resonance imaging markers of vascular brain injury [17], incident cognitive impairment and cognitive decline [13,36,37], and incident dementia [38]. There is compelling evidence for a causal relationship between alterations in glycemic control and subsequent brain ischemic and atrophic changes [39]. Although the absence of an independent association between other risk factors for stroke and cognitive decline may be related to study population attributes (e.g., lower prevalence of risk factors in the current study), it can also substantiate the suggestion that the combined influence or clustering of these risk factors may be particularly important in this association. Indeed, stroke risk factors are correlated highly with each other. Overall, it appears that FSRP is a good predictor of cognitive impairment and cognitive decline. Our findings support further the notion that stroke risk factors begin to exert their influence on cognition early and that they may act in an additive manner in affecting cognitive decline. Furthermore, although in our study the differences in rate of cognitive decline between risk groups may seem small, they are nonetheless important from a pathogenetic stand point, especially considering that the mean age in our population at stroke risk assessment was only 55 years.

Although the neuropsychological tests used in various studies are not identical, it appears that stroke risk commonly assessed using the FSRP is associated with cognitive function in multiple cognitive domains [7,22–24]. We found that higher stroke risk was associated with decline in all cognitive domains except memory and reasoning. A 3-year follow-up study of 235 healthy older men showed an association between FSRP and decline only on verbal fluency; no associations between FSRP and decline in memory or visual–spatial function were reported [24]. In contrast, in a study of 23,752 stroke-free individuals monitored for an average of 4 years, a higher FSRP was found to be related to incident cognitive impairment in global cognitive function that focused on memory [21]. Several studies suggest that vascular disease does not always affect memory, and that vascular risk factors may have a particularly detrimental effect on frontally mediated cognitive functions such as verbal fluency [13,40,41]. Deficits in executive function have long been recognized as a salient feature of cognitive impairment of vascular origin. In relation to FSRP, at least three other cross-sectional studies report similar associations between stroke risk and cognitive function. Elias et al. [7] reported associations between higher FSRP and deficits in multiple domains, including abstract reasoning and visual–spatial memory, but not verbal memory, in 2175 participants of the Framingham Offspring Study. Seshadri et al. [23] found similar associations between FSRP and visual–spatial and executive function, but not with verbal memory. These results conflict with another study that found an association between FSRP and both immediate and delayed verbal memory, and semantic verbal fluency [22]. However, it is important to note that the comparison of our findings with these studies is limited because of important differences in study methods, particularly their cross-sectional design.

The mechanisms underlying the association between vascular risk factors and cognitive function remain to be elucidated fully. However, studies suggest that subclinical cerebrovascular disease may present an important link between major risk factors for stroke and cognitive function. These mechanisms include silent cerebral infarctions, brain atrophy, and white matter abnormalities [23,42–44]. Hypertension in mid life is associated with accelerated white matter hypterintensity volume (WMHV); diabetes and smoking are linked to a more rapid increase in temporal horn volume, which is a surrogate marker of accelerated hippocampal atrophy. Smoking has also been linked to a marked decrease in total brain volume [17]. The presence of silent brain infarcts on magnetic resonance imaging is associated with worse performance on neuropsychological tests and a steeper decline in global cognitive function, memory performance, and psychomotor speed [43].

The strengths of our study include its large sample size, three cognitive measures over 10 years to study longitudinal cognitive decline, and use of a representative battery of cognitive tests, permitting examination of different and distinct aspects of cognition. However, there are several limitations. First, because Whitehall II participants were office-based staff, they may not be representative of the British population, thus potentially limiting the generalizability of our findings. Second, it is possible that observed associations between stroke risk and cognitive decline are underestimations because our study sample included participants with a more favorable demographic and stroke risk profile than those excluded from the analysis and the general population.

In conclusion, the observed associations between an elevated risk of stroke and long-term cognitive decline in multiple cognitive domains have important implications. Our findings provide some evidence that an aggregation of vascular risk is especially important in this association, and suggest that vascular risk assessment may be better determined using a multifactorial risk score. That this association is

evident in a relatively young population indicates early neurological consequences of vascular risk factors leading to cognitive decline. Public health implications are in the domain of early prevention and treatment of stroke risk factors in middle age to reduce or forestall cognitive decline and dementia. Dementia is characterized by a long preclinical phase; individuals who develop dementia later may show subtle cognitive changes as early as two decades before diagnosis [45]. Currently, there are no specific treatments for cognitive impairment or dementia. Given the important vascular contribution to cognitive impairment, detection and treatment of risk factors particularly at mid life may be most effective in the prevention or progression of cognitive impairment. Indeed, recent projections suggest that as many as half of the cases of Alzheimer's disease might be prevented by risk factor reduction and could potentially prevent up to 3 million cases of Alzheimer's disease worldwide [46].

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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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Dr. Elbaz provided methodologic expertise and edited 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 reasoning, memory, verbal fluency, vocabulary and global cognition, assessed three times over ten years.

Results: Higher cardiovascular risk and higher stroke risk were associated with greater 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; 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 risk 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 to predict risk of late life dementia has recently been proposed. [19] 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.[20] 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. [21]

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 ε4* genotype. There are two versions of the dementia risk score, the difference being the inclusion of *APOE* in one version.[19] 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. [19, 22-24]

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, 7to <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). Cardiovascular risk 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 online 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* ε4 (online 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.

Notable strengths of this study include its cohort of middle aged individuals and 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 dementia [28-30] 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, ≥160 mm Hg) but only two categories (≤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. The good performance of Framingham primary event cardiovascular risk scores in different populations has indicated 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 prevent or delay cognitive decline 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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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
CAIDE dementia risk score		
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/m2	12.8	13.8
Total cholesterol > 6.5 mmol/L	25.9	26.4
Physical activity, inactive	56.9	58.7
Framingham risk scores	***CVD***	***Stroke***
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				Standardized risk	
	Low	Intermediate	High			
	10-year cognitive change (95% CI)			*p trend*	β (95% CI)	Δ (95% CI) [a]
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				Standardized risk	
	Low	Intermediate	High			
	10-year cognitive change (95% CI)			*p trend*	β (95% CI)	Δ (95% CI) [a]
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.

Cognitive Aging: Role of Cardiovascular Disease Risk Factors

ABSTRACT

Several cardiovascular disease risk factors including, dyslipidemia, high blood pressure, and diabetes have been proposed as important modifiable risk factors for cognitive decline and dementia. These risk factors often co-occur and their aggregation is associated with increased risk of cardiovascular disease and dementia. However, studies of composite measures of cardiovascular disease risk in relation to cognitive outcomes in non-elderly populations are scarce. The aim of this thesis was to examine composite measures of risk relation to cognition and longitudinal cognitive change among middle-aged adults. Data from the Whitehall II study were used to study the associations between the metabolic syndrome, two Framingham risk scores; the Framingham stroke and general cardiovascular disease risk scores, and cognition, based on three cognitive assessments over 10 years. In addition, these two (cardio)vascular risk scores were compared with the CAIDE dementia risk score. Of all composite measures of risk examined, the two Framingham risk scores were the best predictors of 10-year cognitive decline. Higher cardiovascular risk was associated with faster 10-year decline in multiple cognitive tests including verbal fluency, vocabulary and global cognition. These results suggest that multiple cardiovascular disease risk factors contribute to cognitive decline starting in midlife and that multi-risk factor models such as cardiovascular risk scores may be better suited to assessing risk of cognitive decline. Early identification and treatment of cardiovascular disease risk factors may offer the possibility of markedly delaying or preventing cognitive decline.

Key words: Aging, cognition, cardiovascular disease risk factors, risk scores

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Vieillissement Cognitif: Rôle des Facteurs de Risque Cardiovasculaire

RESUME

De nombreux facteurs de risque cardiovasculaire comme l'hypercholestérolémie, l'hypertension, et le diabète sont comptés parmi les facteurs de risque modifiables les plus importants pour le déclin cognitif et la démence. L'exposition à ces facteurs de risque au cours de la vie en particulier avant l'âge de 65 ans ainsi que leur agrégation contribuent de manière plus importante au déclin cognitif. Peu d'études se sont intéressées aux mesures composites de risque cardiovasculaire par rapport à la fonction cognitive chez les sujets de moins de 65 ans. L'objectif de cette thèse était d'étudier l'association entre les mesures composites de risque et le déclin cognitif au cours de la phase précoce du vieillissement. Les données de la cohorte Whitehall II dans laquelle les fonctions cognitives ont été mesurées à trois reprises ont été utilisées pour étudier l'association entre le syndrome métabolique et deux scores de risque de Framingham (de maladie cardiovasculaire globale et d'AVC), et la fonction cognitive et le déclin cognitif sur 10 ans. Les scores de risque cardiovasculaire de Framingham ont aussi été comparés avec un score de risque de démence. De toutes les mesures composites de risque étudiées, les scores de risque de Framingham montraient la plus forte association avec le déclin cognitif. Un risque cardiovasculaire plus élevé était associé à un déclin plus rapide dans de multiples tests cognitifs dont la fluence verbale, le vocabulaire et la cognition globale. Ces résultats suggèrent d'une part qu'un risque cardiovasculaire plus élevé contribue au déclin cognitif dès la phase précoce de vieillissement et d'autre part que l'estimation du risque cardiovasculaire et son effet sur la fonction cognitive nécessite une approche multifactorielle. L'identification et la réduction de facteurs de risque cardiovasculaire peuvent avoir un impact important sur la réduction du déclin cognitif et de la démence.

Mots clés: Vieillissement, cognition, facteurs de risque cardiovasculaire, scores de risques