Published in final edited form as:

Alzheimers Dement. 2018 January ; 14(1): 35–42. doi:10.1016/j.jalz.2017.04.013.

Practical risk score for 5-year, 10-year, and 20-year prediction of dementia in elderly persons: Framingham Heart Study

Jinlei Li^{a,b}, Matthew Ogronnik^b, Sherral Devine^b, Sanford Auerbach^b, Philip A. Wolf^b, and Rhoda Au^{b,c,*}

^aPeking Union Medical College (No.9 Dongdangantiao, Dongcheng District, Beijing, China, zip code: 100730)

^bBoston University Schools of Medicine/Framingham Heart Study (72 East Concord Street, Boston, MA, US. Zip code: 02118.)

^cBoston University School of Public Health (715 Albany Street, Boston, MA, US. Zip code: 02118.)

1. Introduction

Dementia is a general term used to describe a chronic and/or progressive decline in cognitive and functional ability. It is a disease of worldwide significance; the World Health Organization (WHO) estimated that 47.5 million people worldwide were living with dementia in 2015.(1) Along with the difficulties experienced by those living with the disease, dementia places extremely high stressors on caregivers. The economic impact is also substantial; in the United States alone, the health care costs are estimated at 604 billion dollars per year at present, and are expected to increase.(2) As a result of these wide-ranging impacts, the medical field has devoted much time and resources to studying the causes and prevention of this disease.(1)

Currently, despite substantial efforts, there is no effective treatment for the cure or prevention of dementia. (3) In recent years, attention has turned to the identification of effective early intervention strategies, implemented at a stage when there is the time and potential to modify or slow disease progression.(3–5) The development of a risk profile for dementia is predicated upon evidence that the modification of several potent risk factors will reduce the probability of developing dementia. A similar approach has been followed successfully in the cardiovascular field in the Framingham Heart Study in 1970s(6–8), but its application to dementia has been more limited.

In 2006, the Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study developed a score index to predict the risk of dementia on the basis of risk factor profiles present in

Correspondence to: Rhoda Au, Boston University School of Medicine, 72 East Concord Street, B6, Boston, MA 02118. US, rhodaau@bu.edu, 508-935-3422 (w); 617-638-8086 (fax).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

middle age.(9) This analysis found that midlife vascular risk factors could be combined to predict the risk of dementia, but at that time, there was still a lack of research about other potential types of risk factors that could be used to improve the model and more accurately predict dementia risk in late life. To fill this gap, Barnes et al. developed a dementia risk index for use in late life based on 6 years of follow-up in the larger Cardiovascular Health Study (CHS).(10) However, this index includes measures that may not be readily available from all patients, such as cerebral magnetic resonance imaging and Doppler sonography of the carotid arteries.(11) Following these efforts, other researchers focused on developing a simpler risk score to enable primary care clinicians to determine the risk of developing dementia in elderly populations. Using 8 years of follow-up data from a New York-based sample, a score system was developed for predicting late-onset Alzheimer disease risk in elderly individuals using more commonly available measures.(11) More recently, research on dementia risk scores was conducted by analyzing four separate longitudinal cohorts in the United States, including the Framingham Heart Study. (12) This analysis identified high-risk patients by defining a cutoff on scores, and targeted this high-risk group as those most likely to benefit from increased cognitive screening in a primary care setting.(12) However, for individual patients and their primary care physicians, it may be more useful to predict their future dementia probability risk with a personalized risk score system. This type of prediction system requires lengthier follow-up data to capture the relevant risk factors and the corresponding dementia incidence. The Framingham Heart Study has monitored the cognitive status of original Cohort participants since 1976, and detailed dementia surveillance data have been collected over the last 30 years.(13–15) In this study, we purposely centered our analysis on potential predictors that are readily available to the general practitioner (GP), and avoided risk factors, such as APOE status, which are not usually used in general practice to develop a risk score that predicted the 5-year, 10-year and 20-year individual dementia risk in older individuals.

2. Method

2.1 Participants

Initiated in 1948, the Framingham Heart Study is an ongoing, multi-generational longitudinal cohort study. At the time of recruitment, the town of Framingham was considered adequately representative of the U.S. population at that time. (16) Members of the Original Cohort of 5209 residents, which were a 2/3 sample of the entire town population, have undergone biennial examinations, which have included medical history, physical examinations, and laboratory testing since study inception.(17) The first detailed cognitive assessment battery was administered to participants from the Original Cohort between examination cycles 14 and 15 (1976–1978); and the ongoing surveillance for cognitive decline and dementia began with the 15th examination cycle. Therefore, we chose the 15th examination (1977–1979) as baseline, and included 30 years of follow-up data in the analysis.(18) In order to meet the eligibility criteria for this study, participants had to be 60 years or older and dementia-free at the time of the 15th examination cycle. All FHS study protocols and participant consent forms were approved by the Institutional Review Board of Boston University School of Medicine; all participants provided written informed consent.

2.2 Surveillance for dementia

The dementia-free cohort population was established by screening all participants using a brief neuropsychological test battery 1 year prior and concurrent to the 15th examination cycle.(19) Since 1976, participants' cognitive status has been monitored regularly at cycle examinations, as described below.

The Mini-Mental State Examination (MMSE) screening test was administered to participants beginning at the 17th examination cycle.(20) Between 1981 and 1999, a participant was flagged for more detailed cognitive assessment using education adjusted MMSE cutoffs and also by comparing their MMSE performance at each examination to their own scores at previous examinations. A drop of 3 or more points from an immediately preceding exam or a drop of 5 or more points across all exams triggered recommendation for further follow up. Participants were also asked to participate in this additional assessment if they self-reported memory loss, if a family member reported symptoms of memory loss in the participant, or if a FHS physician or study staff member referred them for this assessment. Beginning in 1999 in addition to continued administration of the MMSE at the regular health exam, all surviving members of the cohort were invited for a more extensive cognitive assessment and administered a battery of neuropsychological tests regardless of prevalent cognitive status. The entire cohort continued to be followed for dementia progression until the date of death.

A panel of at least one neurologist and one neuropsychologist reviewed each case of possible dementia. The details of this consensus diagnostic process has been previously described.(21)

2.3 Risk factors

Demographic characteristics, lifestyle factors, and medical histories were collected during the 15th examination through self-report questionnaires, and a physical examination was performed by a physician. The candidate risk factors extracted from the 15th examination included: age, gender, marital status, weight, height, smoking status, alcohol use, daily consumption of coffee and tea, low salt diet, and co-existing conditions. Marital status included five categories (single, married, widowed, divorced, or separated).

Height and weight were measured, and body mass index (BMI) (kg/m²) was calculated. BMI was divided into categories using standardly recommended cutoffs of <18.5, 18.5–25, 25–30, and >30. Persons who smoked regularly during the previous 12 months were classified as smokers. Persons who self-reported consumption of beer, wine, or cocktails were classified as consumers of alcohol. The coexisting conditions included the following: hypertension, diabetes, vascular diseases of the brain, and cancer. Two blood pressure readings were taken after the participant had been sitting at least 5 minutes, and the average was used for analyses. Hypertension was categorized according to blood pressure if the blood pressure was > 140/90 mm Hg. Diabetes was considered present if the participant was under treatment with insulin or oral hypoglycemic agents and/or if casual blood glucose determinations exceeded 150 mg/dL at two previous clinic visits. Vascular diseases of the brain included embolic infarction of brain, intracerebral hemorrhage, subarachnoid

hemorrhage, and other vascular disease of brain. Cancers regardless of type or stage were recorded in “Clinical Diagnostic Impression” section in the questionnaire of the 15th examination. Non-malignant neoplasms and non-melanoma skin cancers were not classified as cancer in this analysis.

2.4 Statistical analysis

To extract the maximum amount of information from this study population, we constructed the risk algorithm using the Cox proportional hazards regression model, with subjects censored at death or the last evaluation. Compared to the logistic regression model, the Cox model has the advantage of accounting for the variable duration of follow-up and time-to-event.(7) We developed models using variables collected in the 15th examination, and each risk factor was divided into the categories described above. We first used univariate models to show the hazard ratio and 95% confident interval for each candidate risk factor. Following this step, we employed a multivariate model to estimate the coefficients of selected risk factors (only involved significant variables). The selected predictors were: age at baseline, marital status, BMI, stroke, diabetes, ischemic attacks, and cancer. Overweight and obese people showed similar risk effects, thus we recalibrated BMI into statistically significant clinical groups: underweight, normal and overweight. Divorced and separated people didn’t show significantly different risk effects, and the number of cases was relatively small, and so were combined with widowed person as a group of “formerly married” (no longer with spouse).

Risk factor variables predictive of dementia were developed from the β -coefficients of Cox proportional hazard models in conjunction with the average 5-year, 10-year, and 20-year survival ($S(t = 5, 10, 20)$), which were estimated using Kaplan-Meier.(22) and converted into points. The use of points rather than beta coefficients facilitates the practical ease of use of this risk score. To make the scores approach an integer and easier to understand, all coefficients were transformed. Because the lowest β value was 0.17, all coefficients were divided by 0.17 so that the lowest score had a value of 1 and others were rounded to the closest integers. Model discrimination was estimated by C statistic (23), and calibration was assessed by agreement between risk predictions using the point score system and multivariable model. The risks associated with each point were estimated using Cox model:

$$p=1 - S_0(t)^{\exp\left(\sum_{i=1}^p \beta_i X_i - \sum_{i=1}^p \beta_i \bar{X}_i\right)}. \quad (22)$$
 All analyses were performed using STATA version 11.0.

3. Results

There were 2383 dementia-free participants (age ≥ 60 years) at baseline at the time of the 15th examination, ranging in age from 60 to 88 years. During the 30 years of follow-up, 778 dementia events were observed in this cohort. The probability of dementia in an individual subject depended on the presence and level of the measured risk factors. The hazard ratio (adjusted by age and gender), 95% CI, and proportions of various factors are shown in Table 1. As expected, advanced age was strongly associated with a higher risk of dementia. We divided age into three groups; not surprisingly the risk of dementia in the groups aged 70–79 years and over 80 years were 2.23 times and 7.92 times higher than the group aged 60–69.

The single and widowed group had significantly higher risks than married people. Higher BMI was associated with a reduced risk of dementia; while some coexisting conditions increased the risk of developing dementia. Gender and lifestyle factors (such as smoking, alcohol drinking, low salt diets, and coffee/tea consumption) were not significantly related to dementia risk.

Age, marital status, BMI, stroke, diabetes, ischemic attacks, and cancer were found to be independently predictive of event risk in the final multivariate model and were used to construct the risk algorithm. Table 2 showed the coefficients of variables in the final Cox proportional hazards model, as well as the average 5-year, 10-year and 20-year survival which were needed for computations. Hazard ratios and 95% confidence intervals were also included to enhance interpretability. The c-statistic of the final model was 0.716.

Different points were given for each risk factor according to their β -coefficients in the final Cox proportional hazards model, and score sheets were developed to predict dementia (Table 3). The total score ranged from -1 to 31. Because there were few individuals in the upper ranges of distribution, we cut off the risk table so as not overstate the precision in the risk estimates. The cutoff points were 23 for 5-years prediction, 19 for 10-year prediction, and 15 for 20-year prediction. For 10-year risk prediction, for example, there was a 14-fold difference in dementia risk between the lowest sum score [-1 (5.8%)] and the highest sum score [19 and more (80%)].

The risk of dementia for 5 years, 10 years, and 20 years from each of the risk factors was computed with both the score prediction system and the Cox model (Examples of calculation process are shown in Appendix). Figure 1 demonstrated the comparisons between those two methods, and the differences were all less than 10% except the 5-year prediction with the highest score.

4. Discussion

The dementia risk score presented here permits prediction of an individual's risk of developing dementia within 5-year, 10-year, and 20-year increments based upon selected risk factors that are presumed known to a GP: age, marital status, BMI, stroke, diabetes, history of ischemic attack and cancer. This score system uses total points ranging from -1 to 31, and stratifies individuals into 25 levels of risk from -1 to over 22 in the 5-year prediction; 21 levels from -1 to over 18 in the 10-year prediction; and 17 levels from -1 to over 14 in the 20-year prediction. C statistics was 0.716, which is consistent with other similar risk indices studies. (11, 12)

This score system is intended to be used as a practical tool. The calculation does not require extensive, specialized testing or expensive and/or labor intensive procedures, such as a full neuropsychological test battery or brain imaging, in order to provide a predictive score.(3, 24) All of the included predictors are readily accessible and reliably applied, and therefore this system could be used in a primary care setting, or by individuals who are not medical professionals. General practitioners or lay people are able to predict a person's potential

dementia risk factors by this score system simply based upon demographics, lifestyle characteristics, coexisting conditions, and medical history.

In the final model, as expected, age is strongly associated with an increased risk of dementia. Individuals with a marital status of single or widowed had an increased risk of developing dementia, as compared with other marital statuses. These indicated that living alone was associated with an increased dementia risk potentially due to lack of emotional or other forms of support from spouses. (25) Similar to several recent studies, gender had did not contribute significantly to risk of incident dementia.(26) It may be because gender differences are attenuated in these elderly groups through other mitigating factors, such as including women who are most likely post-menopause. (26) Higher BMI demonstrated some protective effects in this study. This result does support similar findings regarding BMI from another recent large retrospective study on dementia risk.(27) Overall, the mechanisms at work behind these association require further investigation, and many potential issues related to frailty, genetic factors, and weight change may play a part.(27) The associations between stroke/diabetes and an increased risk of dementia were consistent with findings from several previous studies.(28–30) It may suggest that a combination of vascular and degenerative pathologies may underlie the development of dementia after stroke and diabetes.(3, 28) These associations are in agreement with previous findings using data from this cohort.(11) Prior research suggested that earlier diagnosis and more effective treatment of stroke and heart disease may result in a lower incidence of dementia (particularly vascular dementia); and that a continuing decline in the incidence of dementia over the last thirty years has occurred in parallel with improvements in cardiovascular health (notwithstanding the increasing prevalence of diabetes and obesity)(11). This further supports the need for the early identification of at-risk individuals, as many of the risk factors we have examined represent modifiable health and lifestyle behaviors. Cancer was also related to an increased risk of dementia, which may be due to changes in mental health after the illness, and/or as a result of the adverse effects of cancer treatment. However, there was a discrepancy with a previous study using Framingham Heart Study data.(31) This is likely due to the fact that the previous study analyzed different types of cancer, while our study looked across all cancers.

These Framingham data has also previously been used by researchers to create a dementia screening instrument (29). By including age, medical history (stroke, diabetes, hypertension, and coronary heart disease), depression, BMI, and functional difficulties in their model, these investigators generated a tool to identify high-risk patients to target for cognitive screening. Our study has some important differences from this previous work, however. While both analyses employed Cox regression models to create the score systems, the previous analysis used scores to stratify individuals into high-risk and low-risk groups. By grouping individuals in this manner, these researchers determined that the maximum practical benefit derives from implementing cognitive screening for individuals identified as high-risk. In this analysis, we estimated 5-year, 10-year and 20-year risk of dementia, and incorporated these into a more easily calculable points system. Further, we tested across a range of readily obtainable information, which led to the inclusion of marital status into the model. Marital status is a straightforward variable to measure, and as demonstrated by the association we found between single or widowed/divorced/separated status and an increased risk of dementia, this factor may represent a worthwhile addition.(32)

A major strength of this study is the longitudinal cohort with more than 30 years of follow-up data. We also present a simple point-scoring scheme for predicting dementia risk that has significant practical utility. However, there are several limitations in this study. First, although Figure 1 showed part of the internal validation methods. However the results need to be externally validated with other cohorts, for example, assessing predictive accuracy based on both discrimination and calibration. Calibration could be assessed by comparing observed risk and estimated risk, while discrimination could be assessed by plotting the receiver operating characteristic (ROC) curve and calculating the area under the ROC curve (AUC). (33) It is possible that the identified risk scores may not be fully generalizable outside of the Framingham Heart Study because the cohort was only comprised of those with European ancestry. Careful considerations should be taken before applying these risk scores to other races and ethnic backgrounds, as they are not represented in this cohort. Second, our analyses focused on dementia incidence without regard for dementia subtype. It is likely, for example, that risk factors may be different for Alzheimer's disease and vascular dementia. We chose to focus this study on dementia more generally because the potential clinical utility targets general practitioners and lay people who do not have significant clinical training. Assessing these potential differences will be an important next step for future research that can serve as a tool for specialists. Third, other established or potential risk factors of dementia, such as family history, education, depression, and physical activity were not assessed in the 15th examination; and therefore, we were not able to incorporate them into this analysis. The inclusion of these additional factors, on which we did not have information, may have further improved the predictive accuracy of the dementia risk score. We also did not consider APOE status because although it is a well-established risk factor for dementia, particularly Alzheimer's disease (10, 11, 34), it does not meet the criteria of clinical utility for a general practice. Another important consideration in use of our score is that survival bias may affect results. If dementia were more prevalent during life in persons who died before the baseline of the study than in persons who were included in the study, our score would underestimate the effects of the individual risk factors. If those who died before inclusion in the study had worse risk factor profiles while dementia was less prevalent, there would be an overestimation on risk factors' effects. (11)

There are currently no effective treatments for dementia, and preclinical dementia may be present in a patient decades before symptoms emerge.(35, 36) Therefore, creating an easily understandable and practical score system for providing an estimated risk of dementia represents an important area of research. This risk estimate system not only affords general practitioners the opportunity to utilize complex statistical models in a clinic setting (37), but also helps individuals to identify their potential risk profile, and prevent or delay the future incidence of dementia.

Acknowledgments

Funding This work was supported by the Milstein Medical Asian American Partnership Foundation Irma & Paul Milstein Program for Senior Health Fellowship; Framingham Heart Study's National Heart, Lung, and Blood Institute contract [N01-HC-25195; HHSN2682015000011]; the National Institute on Aging [grants number R01-AG016495, R01-AG008122, R01-AG033040], and the National Institute of Neurological Disorders and Stroke [grant number R01-NS017950].

Reference list

1. WHO. WHO | 10 facts on dementia [Internet]. WHO; [cited 2016 Jun 15]. Available from: <http://www.who.int/features/factfiles/dementia/en/>
2. Etters L, Goodall D, Harrison BE. Caregiver burden among dementia patient caregivers: a review of the literature. *J Am Acad Nurse Pract*. 2008; 20(8):423–8. [PubMed: 18786017]
3. Exalto LG, Biessels GJ, Karter AJ, Huang ES, Katon WJ, Minkoff JR, et al. Risk score for prediction of 10 year dementia risk in individuals with type 2 diabetes: a cohort study. *Lancet Diabetes Endocrinol*. 2013; 1(3):183–90. [PubMed: 24622366]
4. Carrillo MC, Brashear HR, Logovinsky V, Ryan JM, Feldman HH, Siemers ER, et al. Can we prevent Alzheimer's disease? Secondary "prevention" trials in Alzheimer's disease. *Alzheimers Dement J Alzheimers Assoc*. 2013; 9(2):123–131 e1.
5. The European Dementia Prevention Initiative —IIS1474442213700309.pdf [Internet]. [cited 2016 Jun 17]. Available from: <http://www.thelancet.com/pdfs/journals/lanneur/PIIS1474442213700309.pdf>
6. D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study. *Stroke J Cereb Circ*. 1994; 25(1):40–3.
7. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke J Cereb Circ*. 1991; 22(3):312–8.
8. FHS. Risk Functions | Framingham Heart Study [Internet]. 2016. [cited 2016 Jun 17]. Available from: <https://www.framinghamheartstudy.org/risk-functions/index.php>
9. Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *Lancet Neurol*. 2006; 5(9):735–41. [PubMed: 16914401]
10. Barnes DE, Covinsky KE, Whitmer RA, Kuller LH, Lopez OL, Yaffe K. Predicting risk of dementia in older adults: The late-life dementia risk index. *Neurology*. 2009; 73(3):173–9. [PubMed: 19439724]
11. Reitz C, Tang M-X, Schupf N, Manly JJ, Mayeux R, Luchsinger JA. A summary risk score for the prediction of Alzheimer disease in elderly persons. *Arch Neurol*. 2010; 67(7):835–41. [PubMed: 20625090]
12. Barnes DE, Beiser AS, Lee A, Langa KM, Koyama A, Preis SR, et al. Development and validation of a brief dementia screening indicator for primary care. *Alzheimers Dement J Alzheimers Assoc*. 2014; 10(6):656–665 e1.
13. Seshadri S, Beiser A, Au R, Wolf PA, Evans DA, Wilson RS, et al. Operationalizing diagnostic criteria for Alzheimer's disease and other age-related cognitive impairment-Part 2. *Alzheimers Dement J Alzheimers Assoc*. 2011; 7(1):35–52.
14. Seshadri S, Wolf PA, Beiser A, Au R, McNulty K, White R, et al. Lifetime risk of dementia and Alzheimer's disease. The impact of mortality on risk estimates in the Framingham Study. *Neurology*. 1997; 49(6):1498–504. [PubMed: 9409336]
15. Satizabal CL, Beiser AS, Chouraki V, Chêne G, Dufouil C, Seshadri S. Incidence of Dementia over Three Decades in the Framingham Heart Study. *N Engl J Med*. 2016; 374(6):523–32. [PubMed: 26863354]
16. Seshadri S, Wolf PA, Beiser A, et al. Elevated midlife blood pressure increases stroke risk in elderly persons: the Framingham Study. *Archives of Internal Medicine*. 2001; 161(19):2343–50. [PubMed: 11606150]
17. Dawber TR, Meadors GF, Moore FE. Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health Nations Health*. 1951; 41(3):279–81. [PubMed: 14819398]
18. FHS. Phenotypic Data Table of Exams | Framingham Heart Study [Internet]. 2016. [cited 2016 Jun 17]. Available from: <https://www.framinghamheartstudy.org/researchers/description-data/index.php>
19. Farmer ME, White LR, Kittner SJ, Kaplan E, Moes E, McNamara P, et al. Neuropsychological test performance in Framingham: a descriptive study. *Psychol Rep*. 1987; 60(3 Pt 2):1023–40. [PubMed: 3628637]

20. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975; 12(3):189–98. [PubMed: 1202204]
21. Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Au R, Kannel WB, et al. The lifetime risk of stroke: estimates from the Framingham Study. *Stroke J Cereb Circ.* 2006; 37(2):345–50.
22. Sullivan LM, Massaro JM, D'Agostino RB. Presentation of multivariate data for clinical use: The Framingham Study risk score functions. *Stat Med.* 2004; 23(10):1631–60. [PubMed: 15122742]
23. Chambless LE, Cummiskey CP, Cui G. Several methods to assess improvement in risk prediction models: extension to survival analysis. *Stat Med.* 2011; 30(1):22–38. [PubMed: 20827726]
24. Pankratz VS, Roberts RO, Mielke MM, Knopman DS, Jack CR, Geda YE, et al. Predicting the risk of mild cognitive impairment in the Mayo Clinic Study of Aging. *Neurology.* 2015; 84(14):1433–42. [PubMed: 25788555]
25. Fratiglioni L, Wang HX, Ericsson K, et al. Influence of social network on occurrence of dementia: a community-based longitudinal study. *The Lancet.* 2000; 355(9212):1315–1319.
26. Peters R, Beckett N, Geneva M, Tzekova M, Lu FH, Poulter R, et al. Sociodemographic and lifestyle risk factors for incident dementia and cognitive decline in the HYVET. *Age Ageing.* 2009; 38(5):521–7. [PubMed: 19553357]
27. Qizilbash N, Gregson J, Johnson ME, Pearce N, Douglas I, Wing K, et al. BMI and risk of dementia in two million people over two decades: a retrospective cohort study. *Lancet Diabetes Endocrinol.* 2015; 3(6):431–6. [PubMed: 25866264]
28. Kalaria RN, Maestre GE, Arizaga R, Friedland RP, Galasko D, Hall K, et al. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. *Lancet Neurol.* 2008; 7(9):812–26. [PubMed: 18667359]
29. Ivan CS, Seshadri S, Beiser A, Au R, Kase CS, Kelly-Hayes M, et al. Dementia after stroke: the Framingham Study. *Stroke J Cereb Circ.* 2004; 35(6):1264–8.
30. Booker A, Jacob LE, Rapp M, Bohlken J, Kostev K. Risk factors for dementia diagnosis in German primary care practices. *Int Psychogeriatr IPA.* 2016; 28(7):1059–65.
31. Driver JA, Beiser A, Au R, Kreger BE, Splansky GL, Kurth T, et al. Inverse association between cancer and Alzheimer's disease: results from the Framingham Heart Study. *BMJ.* 2012; 344:e1442. [PubMed: 22411920]
32. Fratiglioni L, Wang HX, Ericsson K, et al. Influence of social network on occurrence of dementia: a community-based longitudinal study. [J]. *Lancet.* 2000; 355(9212):1315–9.
33. Goh LG, Welborn TA, Dhaliwal SS. Independent external validation of cardiovascular disease mortality in women utilising Framingham and SCORE risk models: a mortality follow-up study. *BMC Women's Health.* 2014; 14(1):118. [PubMed: 25255986]
34. Jessen F, Wiese B, Bickel H, Eiffländer-Gorfer S, Fuchs A, Kaduszkiewicz H, et al. Prediction of Dementia in Primary Care Patients. *PLOS ONE.* 2011; 6(2):e16852. [PubMed: 21364746]
35. Pike KE, Savage G, Villemagne VL, Ng S, Moss SA, Maruff P, et al. Beta-amyloid imaging and memory in non-demented individuals: evidence for preclinical Alzheimer's disease. *Brain J Neurol.* 2007; 130(Pt 11):2837–44.
36. Price JL, Morris JC. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. *Ann Neurol.* 1999; 45(3):358–68. [PubMed: 10072051]
37. Schnabel RB, Sullivan LM, Levy D, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. [J]. *Lancet.* 2009; 373(9665):739–45.

Systematic review

We reviewed the literature using PubMed. The major key words were dementia, risk, prediction, risk index, and risk score. These relevant citations are appropriately cited.

Interpretation

Analyses resulted in stratifying individuals into 33 categories from which we derived a point system. We estimated 5-year, 10-year, and 20-year dementia risk prediction, and incorporated these into the points system. This risk score system provides a practical tool since all included predictors are easy to assess for both practitioners and patients. It can be used to estimate future probabilities of dementia for individuals, as well as guide clinician and/or patient decision-making regarding the implementation of preventative strategies, such as lifestyle changes based upon modifiable risk factors.

Future directions

Additional studies are needed to validate the risk scores using external longitudinal data. Furthermore, assessing potential different risk scores for dementia subtypes will be an important next step for future research.

Figure 1.

Comparison of the risk prediction of dementia by points system and Cox model in 5-year, 10-year, and 20 years (for the 5th case in 20-year prediction, score of 20 was higher than the cut-off point 15, so we didn't predict its risk and omitted it in the graph). * Marital status, Coexisting conditions.

Table 1

Total number and dementia cases (aged over 60 years) at the 15th examination, and hazard ratios in Cox proportional regression (adjusted by age and gender) for 30 years follow-up

	Total		Cases		Hazard Ratio	95% CI
	Number	Proportion	Number	%		
Age at baseline	2383	1	778	32.65		
60–69	1341	0.56	388	28.93	1	
70–79	766	0.32	282	36.81	3.23	2.74–3.80
Over 80	276	0.12	108	39.13	8.92	7.03–11.33
Gender						
Male	942	0.40	242	25.69	1	
Female	1441	0.60	536	37.20	1.10	0.94–1.28
Marital status						
Single	184	0.08	72	39.13	1.33	1.03–1.72
Married	1510	0.63	456	30.20	1	
Widowed	613	0.26	229	37.36	1.19	1.00–1.42
Divorced	61	0.03	17	27.87	1.07	0.66–1.74
Separated	15	0.01	4	26.67	1.05	0.31–2.22
BMI						
<18.5	34	0.01	14	41.18	1.89	1.10–3.23
18.5–25	903	0.38	325	35.99	1	
25–30	989	0.42	314	31.75	0.84	0.71–0.98
>30	457	0.19	125	27.35	0.93	0.76–1.15
Smoking	1460	0.61	430	29.45	1.05	0.90–1.23
Alcohol	1401	0.59	451	32.19	0.98	0.84–1.13
Daily consumption of						
Coffee	1815	0.76	578	31.85	0.95	0.81–1.12
Tea	1225	0.51	420	34.29	1.02	0.88–1.17
Low salt diet	160	0.07	44	27.50	0.98	0.72–1.33
Coexisting conditions						
Hypertension	1222	0.51	374	30.61	0.95	0.82–1.10

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

	Total		Cases		Hazard Ratio	95% CI
	Number	Proportion	Number	%		
Diabetes	227	0.10	61	26.87	1.40	1.07–1.82
Stroke	31	0.01	11	35.48	2.11	1.16–3.85
Vascular disease of brain	132	0.06	41	31.06	1.33	0.96–1.83
Ischemic attack	16	0.01	8	50.00	1.97	0.98–3.97
Cancer	177	0.07	60	33.90	1.37	1.05–1.78

Table 2

Cox proportional regression coefficients and hazard ratios for significant risk factors

Risk factor	Number of cases	Coefficient	P value	Hazard Ratio	95% CI
Age at baseline					
60–69	388	Base		1	
70–79	282	1.1091	<0.001	3.03	2.56–3.59
Over 80	108	2.0881	<0.001	8.07	6.28–10.37
Marital status					
Single	72	0.2721	0.034	1.31	1.02–1.69
Married	456	Base		1	
Formerly married	250	0.1713	0.043	1.19	1.01–1.40
BMI					
<18.8	14	0.6659	0.015	1.95	1.14–3.33
18.5–25	325	Base		1	
>25	439	–0.1484	0.045	0.86	0.75–0.99
Stroke					
No	766	Base		1	
Yes	11	0.3204	0.008	2.27	1.24–4.15
Diabetes					
No	717	Base		1	
Yes	61	0.3484	0.011	1.42	1.08–1.85
Ischemic attack					
No	8	Base		1	
Yes	8	0.6961	0.052	2.01	1.00–4.05
Cancer					
No	716	Base		1	
Yes	60	0.2872	0.034	1.33	1.02–1.74

average 5-year survival = 0.9618; 10-year survival = 0.8722; 20-year survival = 0.6731

Table 3
Score system and probability of dementia within 5, 10 and 20 year for individuals aged over 60 years: Framingham Heart Study *

Risk factors	Categories	Points
Age at baseline	60–69	0
	70–79	6
	Over 80	12
Marital status	Single	2
	Married	0
	Formerly married	1
BMI	Underweight	4
	Normal	0
	Overweight	–1
Stroke	No	0
	Yes	5
Diabetes	No	0
	Yes	2
Ischemic attack	No	0
	Yes	4
Cancer	No	0
	Yes	2

5-year		10-year		20-year	
Point total	Estimate of risk	Point total	Estimate of risk	Point total	Estimate of risk
–1	1.7%	–1	5.8%	–1	15.8%

5-year			10-year			20-year		
Point total	Estimate of risk	Point total	Estimate of risk	Point total	Estimate of risk	Point total	Estimate of risk	Estimate of risk
0	2.0%	0	6.8%	0	18.5%	0	18.5%	
1	2.4%	1	8.0%	1	21.5%	1	21.5%	
2	2.8%	2	9.4%	2	25.0%	2	25.0%	
3	3.3%	3	11.1%	3	28.9%	3	28.9%	
4	3.9%	4	13.0%	4	33.3%	4	33.3%	
5	4.6%	5	15.3%	5	38.1%	5	38.1%	
6	5.5%	6	17.9%	6	43.5%	6	43.5%	
7	6.4%	7	20.8%	7	49.2%	7	49.2%	
8	7.6%	8	24.2%	8	55.2%	8	55.2%	
9	9.0%	9	28.0%	9	61.4%	9	61.4%	
10	10.5%	10	32.3%	10	67.7%	10	67.7%	
11	12.4%	11	37.1%	11	73.9%	11	73.9%	
12	14.5%	12	42.3%	12	79.7%	12	79.7%	
13	17.0%	13	48.0%	13	84.9%	13	84.9%	
14	19.8%	14	53.9%	14	89.4%	14	89.4%	
15	23.1%	15	60.1%	15-31	>90%			
16	26.7%	16	66.4%					
17	30.9%	17	72.6%					
18	35.5%	18	78.5%					
19	40.5%	19-31	>80%					
20	46.1%							
21	51.9%							
22	58.1%							
23-31	>60%							

* two tables are combined to predict individual's dementia risk. For example, a 71-year-old person with low BMI (<18.5) and a history of diabetes would have a calculated dementia risk score of 14 points, and therefore a 19.8% risk of dementia in the next 5 years; an 63-year-old single person with stroke would have a risk score of 7 points and a 20.8% risk of dementia in the next 10 years.