ELSEVIER

CrossMark

Alzheimer's & Dementia 10 (2014) 562–570

Alzheimer's & Dementia

Midlife risk score for the prediction of dementia four decades later

Lieza G. Exalto[a,b], Charles P. Quesenberry[a], Deborah Barnes[c], Miia Kivipelto[d], Geert Jan Biessels[a], Rachel A. Whitmer[b,*]

[a]*Kaiser Permanente Division of Research, Oakland, CA, USA*

[b]*Department of Neurology, Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, Utrecht, Netherlands*

[c]*University of California, San Francisco, CA, USA*

[d]*Karolinska Aging Research Centre, Karolinska University, Stockholm Sweden*

Abstract

Objective: The objective of this study was to obtain external validation of the only available midlife dementia risk score cardiovascular risk factors , aging and dementia study (CAIDE) constituting age, education, hypertension, obesity, and hyperlipidemia in a larger, more diverse population. Our second aim was to improve the CAIDE risk score by additional midlife risk factors.

Methods: This retrospective cohort study was conducted in an integrated health care delivery system. A total of 9480 Kaiser Permanente members who participated in a health survey study (age range, 40–55 years) from 1964 to 1973 were included in this study. Dementia diagnoses from primary care and medical specialist visits were collected from January 1, 1994 to January 16, 2006, using International Classification of Diseases 9 codes 290.0, 290.1 for "possible dementia," and 331.0 and 290.4 for "specialist confirmed dementia." Risk model prediction and validation were examined with the C statistic, net reclassification improvement, and integrated discrimination improvement. Dementia risk per sum score was calculated with Kaplan-Meier estimates.

Results: A total of 2767 participants (25%) were diagnosed with any type of dementia, of which 1011 diagnoses (10.7%) were specialist-confirmed diagnoses. Average time between midlife examination and end of follow-up was 36.1 years. The CAIDE risk score replicated well with a C statistic of 0.75, quite similar to the original CAIDE C statistic of 0.78. The CAIDE score also predicted well within different race strata. Other midlife risk factors (central obesity, depressed mood, diabetes mellitus, head trauma, lung function, and smoking) did not improve predictability. The risk score allowed stratification of participants into those with 40-year low (9%) and high (29%) dementia risk.

Conclusions: A combination of modifiable vascular risk factors in midlife is highly predictive of the likelihood of dementia decades later. Possible dementia prevention strategies should point to a life course perspective on maintaining vascular health.

Keywords: Dementia; Alzheimer's disease; Vascular dementia; Risk score; Validation; Prevention; Age; Education; Hypertension; Obesity; Hyperlipidemia; Depressed mood; Diabetes mellitus; Head trauma; Lung function; CAIDE; Smoking

1. Introduction

Currently, projections posit there will be a fourfold increase to 106.8 million dementia cases worldwide by 2050 [1], yet there's no curative treatment available. Dementia has a long preclinical period during which there are no noticeable cognitive impairments, but likely neurodegenerative changes are occurring [2]. To prevent dementia, early identification of individuals at high risk of dementia is crucial. Early identification may be achieved by the development of prognostic models or risk scores at midlife. The focus on midlife is particularly germane for dementia prevention for two reasons: (*i*) midlife is early enough to ensure forward temporal associations between risk factors and dementia before neurodegeneration or cognitive changes have

G. J. Biessels consults for and receives research support from Boehringer Ingelheim.

*Corresponding author. Tel.: +510-891-3461; Fax: +510-891-3761.

E-mail address: Rachel.whitmer@kp.org

1552-5260/$ - see front matter

http://dx.doi.org/10.1016/j.jalz.2013.05.1772

commenced and (*ii*) several studies show that the magnitude and direction of risk factors for dementia vary throughout the life course [3–7].

Risk scores have been used successfully in several other fields in medicine. The first and best known example is the Framingham Risk Score [8], which is used to guide intervention or prevention strategies for cardiovascular disease. In 2006, the first dementia risk score was designed to predict 20-year dementia risk among middle-age people. The risk score was created with data from 1449 Finnish participants of the cardiovascular risk factors, aging, and dementia study (CAIDE) study [9,10]. The CAIDE risk score, based on age, education, hypertension, obesity, and hyperlipidemia in midlife, has an area under the curve (receiver–operating characteristic [ROC]) of 0.77. It is critical to evaluate further the predictability in larger, less homogeneous populations and to evaluate whether it can be improved by the consideration of other important midlife risk factors such as diabetes mellitus.

The objective of our study was twofold: (*i*) to validate externally the CAIDE risk score in a large (n = 9480), diverse population of members of an integrated health care delivery system in the United States and (*ii*) to try to improve the predictability with the testing of additional midlife risk factors.

2. Subjects and methods

2.1. Population

The study population consists of members of the Kaiser Permanente Medical Care Program of Northern California (KPNC) who participated in voluntary periodic multiphasic health checkups (MHCs) in San Francisco and Oakland, CA, between 1964 and 1973 when they were middle-aged [11]. The MHC was performed as part of routine medical care and included a comprehensive questionnaire (sociodemographic, behavioral, medical history, and current health questions), a clinical examination (including anthropometry at some sites), and a standardized blood draw. KPNC is a nonprofit group/practice integrated health delivery system that covers more than one-third of the population in the geographic areas served. Kaiser Permanente members are representative of the sociodemographics of the local population, except for the extreme tails of low- and high-income distribution [12].

2.2. Data collection

During the MHCs, participants were interviewed, and information on demographics, lifestyle, and medical history was collected [11]. A questionnaire was used to screen for head trauma (Have you ever had head injuries bad enough to knock you out?) and for depressed mood (Do you often feel unhappy or depressed?). Study participants who answered yes were classified as having the condition [11,13,14]. Trained technicians performed all anthropometric measures according to the Nutritional Academy of Anthropometry Standards. The sagittal abdominal diameter—the distance between the back surface and the top of the abdomen at the level of the iliac crest—was measured after gentle expiration with the patient in a standing position using an anthropometer. Height and weight were measured using a balance beam scale calibrated to the nearest 8 oz. and a tape measure with standard positioning [14]. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Systolic blood pressure (SBP) was measured according to standard procedures in the supine position [14]. Lung function tests included forced expiratory volume in 1 second (FEV_1) using a Vertek VR5000 Lung Function computer (Electro/Med. Instruments, Houston, TX) according to methods described previously [11]. Blood was drawn for total serum cholesterol, and levels were measured with an autoanalyzer (Technicon Co., White Plains, NY) from 1964 to 1968, with an autochemist (AGA, Stockholm, Sweden) from 1969 to 1972, and with an autoanalyzer (model SMA-12, Technicon) in 1973 [11,14]. Diabetes mellitus was defined by having one of the following: 1) self-report of physician-diagnosed diabetes mellitus, 2) use of insulin, or oral hypoglycemic agents, 3) a fasting glucose level (last food eaten, 8 hours or more) 140 mg/dl or more, or a nonfasting (last food eaten, 4 hours or less) glucose level of 200 mg/dL or more. If all four criteria for diabetes mellitus were negative, it was coded as no diabetes.

2.3. Analytical cohort

Our retrospective cohort was based on mortality and dementia status information in 1994. Dementia diagnosis ascertainment commenced in 1994, when outpatient records became available. Of the 18,231 Kaiser Permanente (KP) members between 40 years and 55 years who participated between 1964 and 1973 in the full MHC (including the anthropometry examination), 14,282 were still a KP member and alive in 1994. Those with missing data in the MHC on education, or any of the following variables—BMI, SBP, cholesterol, diabetes mellitus, depressed mood, pulmonary function, and race (n = 2035)—were excluded, which resulted in a validation cohort of 12,247 subjects. Not considering "possible dementia" diagnosis resulted in a refinement cohort of 9480 subjects. The 2035 KP members that were excluded because of missing MHC data were, on average, 46.4 ± 4.4 (standard deviation) years of age and 57% were female.

2.4. Diagnosis of dementia

Dementia diagnoses were ascertained through electronic medical records from a database that contains diagnoses from all outpatient encounters at Kaiser Permanente medical centers and clinics starting in 1994. Diagnoses included initial diagnoses made in primary care "possible dementia"(International Classification of Diseases, ninth revision (ICD-9) codes

290.0 and 290.1) and dementia diagnosis confirmed by a medical specialist in a memory clinic or neurology department "specialist-confirmed dementia"(ICD-9 codes 331.0, 290.4x, and 290.1x). Diagnoses were ascertained from January 1994 to June 2006, when the MHC participants were, respectively, 61 years to 85 years and 73 years to 97 years. The validation cohort, used for the first aim of our study, included any type of dementia (both possible dementia and specialist-confirmed dementia diagnoses). However, the codes used for possible dementia diagnosis in KPNC's primary care setting can also used for people with milder forms of cognitive impairment and tend to have a lower specificity than specialist diagnoses. To increase the specificity of the dementia diagnosis for the second aim of this study (refinement of the risk score), we created a refinement cohort that only included Alzheimer's disease (AD) (ICD-9 Clinical Modification [CM] code 331.0) and vascular dementia (ICD-9 CM code 290.4) diagnosed by a medical specialist in a memory clinic or neurology department and did not consider "possible dementia" cases.

2.5. Statistical analysis

Differences in midlife characteristics by dementia status were assessed using Student's t test and χ^2 test. Consistent with the CAIDE score methodology, variables were categorized as age, years younger than 47, 47 years to 53 years, or 54 years to 55 years; education, 0 to 6 years, 7 to 9 years, or 10 years or more [10], hypertension as SBP more than 140 mmHg, obesity as a BMI greater than 30 kg/m^2, and total cholesterol greater than 250.9 mg/dL. New variables were defined as central obesity, sagittal abdominal diameter more than 25 cm [15]; and poor pulmonary function as the lowest quintile of forced expiratory volume (0.2–1.8 L). Smoking was defined as never or ever, with the category of ever including current and former.

2.6. External validation of CAIDE risk score

Variables were allocated the points of the original risk score. The validation of the CAIDE risk score was performed with logistic regression analyses, with CAIDE risk score as the only predictor, paralleling the original analysis in the CAIDE cohort. Analyses were also stratified by race. The Kaplan-Meier method was used to provide point and interval estimates of observed 40-year population-level dementia risk for each level of the CAIDE risk score.

2.7. Predictive accuracy

Predictive accuracy of the model was assessed based on discrimination and calibration. Discrimination refers to the ability of the model to distinguish accurately between those who develop dementia from those who do not. For comparison with the original study, we calculated the C statistic for the dichotomous outcome of ever/never dementia as the area under the ROC curve [16]. In addition, we assessed discrimination more appropriately in the context of survival analysis using Harrell's C statistic [17], which can be interpreted as the probability that a subject from the event group has a higher predicted probability of having an event than a subject from the nonevent group. Calibration refers to the extent to which predicted risk agrees with observed risk. We assessed this by calculating the Hosmer-Lemeshow χ^2 test [17].

2.8. Testing of additional midlife risk factors

First we added the "new" potential risk factors separately to a model with all the CAIDE risk factors in both a logistic regression and a Cox proportional hazards ratio analysis. Logistic regression analysis was first used for reasons of direct comparison with the originally published CAIDE logistic regression models. Next, we applied Cox proportional hazard models for prediction modeling, because it accounts for time during the 12+-year period of follow-up for dementia, with appropriate right censoring for (*i*) termination of health plan membership (defined as a lag of 3 months or more), (*ii*) death, or (*iii*) the end of the study period on June 1, 2006. The new midlife risk factors tested were diabetes mellitus, depressed mood, head trauma, central obesity, lung function, and smoking. Although the original CAIDE study used clinically established cut points, the current study had ample power for more discrete categorization of some continuous variables, and prior work in our population has shown associations with even moderately elevated vascular risk factors at midlife [18]. Thus, we also ran analyses with recategorized cholesterol, SBP, and BMI values using the following cut points: cholesterol, less than 200 mg/dL, 200 mg/dL to 239 mg/dL, and more than 239 mg/dL; SBP, less than 120 mmHg, 120 mmHg to 129 mmHg, 130 mmHg to 139 mmHg, and more than 140 mmHg; and BMI less than 18.5 kg/m^2, 18.5 kg/m^2 to 24.9 kg/m^2, 25 kg/m^2 to 29.9, and more than 30 kg/m^2.

Improvements in performance of the CAIDE risk score by adding a new risk factor were measured by the net reclassification improvement (NRI) and the integrated discrimination improvement (IDI) statistics [19,20]. The NRI can be interpreted as a measure of correctness of upward and downward movement of predicted probabilities as a result of adding a new marker. The NRI is calculated by first estimating the difference in probability that the new model improves risk prediction and the probability that the new model worsens risk prediction, separately for both events and for nonevents at 40 years. Positive values indicate that prediction gains exceed losses, using the new covariate. The overall NRI is the sum of the NRIs for events and nonevents [20]. The IDI assesses improvement in risk discrimination (i.e., how well a model separates subjects with disease compared with those without disease) by estimating the change in the difference in the mean predicted probabilities of the outcome between those with and without the outcome (e.g., dementia), after introducing the new risk factor to the model. Positive values indicate improved discrimination.

Alternatively, the IDI can be interpreted as the difference in proportion of variance explained by the model (an R^2-like statistic for survival distributions, similar to that for linear regression), with and without the new predictor [20]. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC). The SAS macro published by Chambless et al. [17] was used for calculating the NRI and IDI statistics and associated bootstrap confidence intervals, and the Hosmer-Lemeshow calibration test. The NRI calculation is dependent on the choice of risk categories; thus, different cut points to define low-, middle-, and high-risk dementia groups (0%–15%, 15%–25%, more than 25% vs. 0%–10%, 10%–20%, and more than 20%) were evaluated.

3. Results

A total of 2767 patients (25%) received a diagnosis of any type of dementia, on average, 36.9 ± 4.1 years after their midlife MHC examination. A total of 1011 patients (11%) received a medical specialist-confirmed dementia diagnosis, of which 816 were AD and 265 were vascular dementia. For the 12,247 individuals in the validation cohort, the mean age at the midlife assessment was 46.4 ± 4.4 years, the mean age at the start of dementia ascertainment was 72.4 ± 4.6 years, and the mean age at end of follow-up was 83.1 ± 4.9 years. For the 9480 individuals also included in the refinement cohort, the mean age at the midlife assessment was 46.1 ± 4.3 years, the mean age at the start of dementia ascertainment was 73.1 ± 4.5 years, and the mean age at end of follow-up was 82.2 ± 5.2 years. All results concern the refinement cohort unless otherwise specified. The mean age at the midlife assessment was 46.1 ± 4.3 years, the mean age at the start of dementia ascertainment was 73.1 ± 4.5 years, and the mean age at end of follow-up was 82.2 ± 5.2 years. Compared with subjects who did not develop dementia during follow-up, subjects that became demented were older, less educated, more likely to be female, and more likely to have central obesity, poor pulmonary function, and to be currently smoking at baseline (Table 1).

The C statistic associated with the CAIDE risk score logistic regression model for specialist-confirmed dementia

Table 1
Sociodemographic and risk factor characteristics of the study population stratified by dementia diagnosis and by race

	Dementia		Race		
Characteristics	Yes (n = 1011)	No (n = 8469)	Asian (n = 474)	Black (n = 1401)	White (n = 7605)
Population information					
Race, n (%)					
Asian	39 (4)	435 (5)*			
Black	209 (21)	1192 (14)*			
White	763 (75)	6842 (81)*			
Dementia diagnosis, n (%)			39 (8)	209 (15)	763 (10)
Age at dementia diagnosis, years; mean (SD)	81.8 (5.0)		82.33 (4.8)*	80.8 (4.7)*	82.0 (5.1)*
The original variables					
Age at baseline, years; mean (SD)	47.9 (4.3)	45.9 (4.3)*	44.8 (4)*	45.6 (4.1)*	46.2 (4.3)*
Education, n (%)					
>9 years	440 (44)	4041 (48)*	246 (52)*	343 (24)*	3892 (51)*
7–9 years	376 (37)	3067 (36)*	158 (33)*	655 (47)*	2630 (35)*
0–6 years	195 (19)	1361 (16)*	70 (15)*	403 (29)*	1083 (14)*
Men, n (%)	408 (40)	3846 (45)*	243 (51)*	567 (40)*	3444 (45)
Cholesterol, >250.9 mg/dL; n (%)	298 (29)	2101 (25)*	115 (24)	396 (28)*	1888 (25)*
BMI, >30 kg/m^2; n (%)	97 (10)	751 (9)	9 (2)*	264 (19)*	575 (8)*
SBP, >140 mm/Hg; n (%)	189 (19)	1547 (18)	67 (14)*	413 (29)*	1256 (17)*
Time from MHC, years; mean (SD)†	33.9 (4.1)	36.4 (4.3)*	37.1 (4)*	35.9 (4.4)*	36.1 (4.3)
Other new variables, n (%)					
Central obesity‡	161 (16)	1155 (14)*	27 (6)*	343 (24)*	946 (12)*
Depressed mood	190 (19)	1621 (19)	55 (12)*	316 (23)*	1440 (19)
Diabetes mellitus	152 (15)	1186 (14)	85 (18)*	201 (14)	1052 (14)
Head trauma	68 (7)	515 (6)	6 (1)*	52 (4)*	525 (7)*
Poor pulmonary function§	262 (26)	1781 (21)*	171 (36)	518 (37)*	1357 (18)*
Smoking¶	530 (52)	4865 (57)*	189 (40)*	776 (55)	4430 (58)*

Abbreviations: SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; MHC, multiphasic health checkup.
NOTE. *P* values were calculated using the χ^2 test.
*Significant *P* value less than .05.
†Time from MHC to end of follow-up (including censor).
‡Central obesity: sagittal abdominal diameter, more than 25 cm.
§Poor pulmonary function: forced expiratory volume, 0.2 to 1.8 liters (lowest quintile).
¶Smoking: current and former.

diagnosis in our refinement cohort was 0.747, and for any dementia diagnosis in our validation cohort was 0.688. The CAIDE score also performed well by race subtypes. Race stratification of the risk score model showed a C statistic of 0.812 for Asian, 0.750 for black, and 0.735 for white.

The odds ratio and the hazard ratio, and the size and direction of the β coefficient of the risk score are shown for the six CAIDE risk score variables in one model (Table 2). The β coefficient of age is larger based on the Cox proportional hazard model compared with the β coefficient of the logistic model (e.g., 0.90 vs. 0.15 for the age category 47 years–53 years). The odds ratio and the hazard ratio of the six additional new risk factors based on six different models with the CAIDE model plus one additional new risk factor are shown in Table 2.

The added value of all the new variables was very modest, with the C statistic almost unaffected (Table 3). The C statistic of the original CAIDE score generated from the Cox proportional hazards model is less than the one from the logistic model (0.665 vs. 0.747). This difference likely represents a slight overfitting of the logistic model; Cox models account more accurately for right censoring and loss to follow-up. The lower C statistic in the validation cohort (0.688) compared with the refinement cohort (0.747) can be explained by more false-positive dementia cases in the "possible dementia" diagnosis in the validation cohort. The C statistic of both the logistic and the Cox models did not change with the addition of new risk factors. More discrete categorization of BMI, SBP, and cholesterol also did not improve prediction (data not shown here).

NRI and IDI statistics were also used to evaluate potential predictive improvement. Table 3 shows that similar to the C statistic, the NRI (cut points, 0%–15%, 15%–25%, more than 25%) and IDI calculations show no model improvements. For example, the addition of central obesity causes a reclassification toward incorrect assignment, shown by a decrease in the net reclassification by 1.5%. The calibration decreased, as shown by the increase in the Hosmer Lemeshow χ^2 value from 17 to 28.5. Adding smoking improved the calibration slightly; the Hosmer Lemeshow χ^2 value decreased from 17 to 7.2; however, there was no reclassification. The NRI analysis with the cut points 0% to 10%, 10% to 20%, and more than 20%, to define the low-, middle-, and high-risk group generated similar results (not shown).

The risk of dementia is reported per sum score (Fig. 1). Sum scores greater than 7 points (i.e., 8–14 points) were relatively rare; thus, the risk estimates were less stable for the very highest scores. Therefore, scores greater than 7 points were merged into one category for the Kaplan-Meier estimated dementia risk. There was a threefold difference in dementia risk between the lowest sum score of 1 point (associated Kaplan-Meier estimate, 9%) and the highest sum score of 8 points or more (associated Kaplan-Meier estimate, 29%). The summary of the risk score for dementia is shown in Fig. 2.

Table 2
Multivariate analysis of possible risk factors for dementia

Variables	Logistic		Cox proportional hazard	
	Odds ratio (95% CI)	β	Hazard ratio (95% CI)	β
Original variables				
Age, years				
<47	1	0 (ref)	1	0 (ref)
47–53	1.58 (1.37–1.83)	0.15*	2.46 (2.15–2.81)	0.90*
>53	1.61 (1.27–2.06)	0.17*	4.44 (3.59–5.49)	1.49*
Education, years				
0–6	1.14 (0.94–1.37)	0.07	1.20 (1.01–1.43)	0.18*
7–9	1.04 (0.90–1.22)	−0.01	1.06 (0.93–1.22)	0.06
>9	1	0 (ref)	1	0 (ref)
Gender				
Male	0.74 (0.64–0.85)	−0.15*	0.96 (0.84–1.09)	−0.04
Cholesterol, mg/dL				
>250.9	1.09 (0.94–1.27)	0.04	1.21 (1.06–1.39)	0.19*
BMI, kg/m^2				
>30	0.98 (0.77–1.23)	−0.01	1.19 (0.96–1.48)	0.18
SBP, mm/Hg				
>140	0.75 (0.63–0.89)	−0.15*	1.02 (0.87–1.21)	0.02
New variables				
Central obesity†				
Yes	1.05 (0.84–1.31)	0.17	1.27 (1.04–1.56)	0.24*
Depressed mood				
Yes	0.88 (0.74–1.05)	−0.06	1.02 (0.87–1.20)	0.02
Diabetes mellitus				
Yes	1.07 (0.89–1.30)	0.03	1.05 (0.88–1.24)	0.04
Head trauma				
Yes	1.05 (0.80–1.39)	0.14	1.22 (0.95–1.57)	0.20
Poor lung function‡				
Yes	0.96 (0.81–1.15)	−0.02	0.85 (0.72–1.00)	−0.16*
Smoking§				
Yes	0.70 (0.61–0.81)	−0.18	1.00 (0.89–1.14)	0.00

Abbreviations: CI, confidence interval; ref, reference; BMI, body mass index; SBP, systolic blood pressure.

NOTE. Original variables are from all six CAIDE variables in one model. The next section, New variables, presents six different models: the six CAIDE variables plus one new variable.

*Significant at *P* less than .05.

†Central obesity: sagittal abdominal diameter, more than 25 cm.

‡Poor pulmonary function: forced expiratory volume, 0.2 to 1.8 liters (lowest quintile).

§Smoking: current and former.

4. Discussion

The CAIDE midlife dementia risk score replicated well in our large, diverse cohort. Indeed, it was possible to stratify participants into those with 40-year low (9%) and high (29%) dementia risk. The predictability of the risk score in our cohort (C statistic, 0.75) was quite comparable with the original CAIDE cohort (0.78). The CAIDE risk score also performed well within race subtypes: Asian C statistic, 0.81; black C statistic, 0.75; and white C statistic, 0.74.

Somewhat surprisingly, the addition of several "new" midlife risk factors, not available in CAIDE, did not enhance the predictability of the risk score as tested by the C statistic. The application of novel statistical methods to investigate clinical meaningful improvement by NRI and IDI also did not show an improvement. There are some potential reasons why additional midlife risk factors did not improve the risk

Table 3
Added value of adding a variable to the original CAIDE model

		Discrimination		Calibration		Reclassification improvement					
		C statistic		HL		NRI*				IDI	
No.	Model name	Logistic†	Cox‡	χ^{2}§	*P* value	Event	Nonevent	Estimate	95% CI	Estimate	95% CI
1.	CAIDE	0.747	0.665	17.0084	.0300						
2.	1 + central obesity	0.747	0.668	28.5453	.0004	−.0242	.0096	−.0145	−.0233 to .0257	.0014	.0000–.0050
3.	1 + depressed mood	0.747	0.665	20.7744	.0078	−.0204	.0110	−.0093	−.0270 to .0344	.0000	−.0000 to .0015
4.	1 + DM	0.747	0.665	22.1899	.0046	−.0353	.0199	−.0153	−.0234 to .0311	.0000	−.0001 to .0001
5.	1 + head trauma	0.747	0.665	24.4681	.0019	−.0210	.0149	−.0060	−.0204 to .0253	.0005	−.0000 to .0026
6.	1 + poor lung function¶	0.747	0.666	5.1746	.7388	−.0104	.0021	−.0082	−.0268 to .0355	.0006	−.0000 to .0030
7.	1 + smoking#	0.749	0.665	7.1978	.5155	0**	0**	0**		0**	

Abbreviations: HL, Hosmer Lemeshow goodness of fit test; NRI, net reclassification improvement; IDI, integrated discrimination improvement; CI, confidence interval: CAIDE, cardiovascular risk factors, aging and dementia; DM, diabetes mellitus.

NOTE. Results of NRI and IDI analysis are expressed as differences in probabilities with 95% CI based on bootstrap procedure.

*NRI was used to compare model 1 (CAIDE) with models 2 through 7, with cut points 15% and 25%.

†C statistic based on logistic regression analyses.

‡C statistic based on Cox proportional hazard regression analyses.

§Hosmer Lemeshow test χ^{2} is presented.

¶Poor pulmonary function with a forced expiratory volume of 0.2 to 1.8 liters (lowest quintile).

#Smoking: current and former.

**Not one member of the cohort had a change in risk prediction category with the addition of smoking to the model—thus, zero for NRI and IDI, and bootstrap CIs were incalculable.

score. Some of our additional risk factors are highly correlated with the original predictors, such as central obesity with BMI. The combination of high BMI, high SBP, and high cholesterol in the original CAIDE risk score likely represents a metabolically risky phenotype. Further addition of midlife vascular risk factors to this metabolic risk phenotype may not amplify predictability. Second, some additional risk factors are known to be risk factors both in midlife and later in life, but have a higher prevalence later in life, such as type 2 diabetes mellitus and head trauma. The population-attributable risk of type 2 diabetes mellitus and head trauma at midlife might be too low. A possible etiological role of any of the midlife risk factors cannot be deduced from the current prediction study.

Our study has several strengths. A wide breadth of detailed midlife information was available for our cohort. Participants could be monitored for up to an average age of 82.2 ± 5.2 years, compared with 71.3 ± 4.0 years in CAIDE. Another benefit of the study design is that the current cohort had more than a 12-year period to ascertain a dementia diagnosis, in contrast to the CAIDE cohort, in which the participants were evaluated for dementia at one time point in late life. The model was tested in different race groups, a significant contribution given the rapidly increasing ethnic diversification in the elderly population in the United States. Last, we used survival analysis techniques (Cox regression and Kaplan-Meier estimates) in a longitudinal follow-up and applied novel risk score testing, including IDI and NRI, not used previously in dementia prediction.

Limitations of the study include the use of diagnostic codes for dementia rather than a standardized assessment given to all

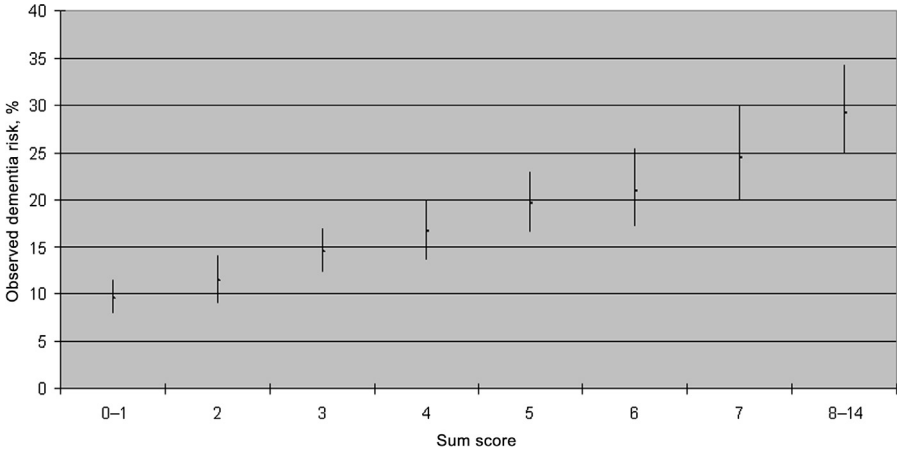

Fig. 1. Plot of probability of dementia in late life according to the risk score categories in midlife. Kaplan-Meier estimates were used to calculate the observed 40-year dementia risk per sum score with a 95% confidence interval.

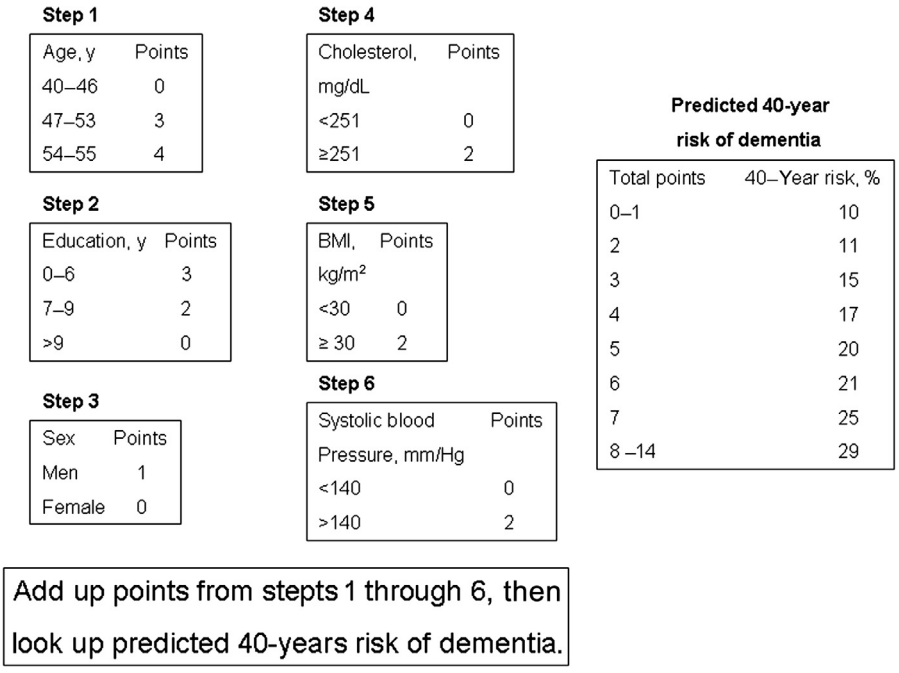

Fig. 2. Risk score to predict 40-year risk of dementia. Steps 1 through 6 are based on the original cardiovascular risk factors, aging and dementia (CAIDE) score; the predicted 40-year risk of dementia is based on the current study.

members of the cohort. This approach can lead to underdetection of dementia (i.e., not all cases of dementia will be diagnosed and recorded) and overdetection (i.e. not all participants with a physician-recorded diagnosis of dementia will have dementia). Nevertheless, based on a recent study, the use of the same ICD-9 codes for dementia was found to have a sensitivity of 77% and a specificity of 95% compared with a consensus diagnosis of dementia based on a neuropsychiatric battery, physical examination, structured interview with informants, and review of medical records in a clinic-based setting [21]. Moreover, an advantage of this passive case identification is the absence of refusal bias. The exclusion of those with a diagnosis of general dementia from a primary care physician who did not, subsequently, get diagnosed by a medical specialist for the second aim of our study (the refinement of the risk score) likely resulted in underrecognition of some dementia cases. However, this approach increases the specificity for the outcome, which we considered particularly important for this second aim. Another limitation of the study is that dementia ascertainment was initiated, on average, 26 years after the baseline assessment, at an average age of 73.1 years. Subjects that participated in the midlife examination (n = 18,231) had to survive and remain a member of KP to be able to be included in the 12-year follow-up starting in 1994 (n = 14,282). This study design is subject to attrition and possible immortal person-year time bias of the interval between midlife (1964–1973) and 1994. Use of the Cox proportional hazards model with censoring for death and gaps in health plan membership during the 12-year dementia ascertainment period minimizes confounding by survival bias from 1994 to 2006, but not before 1994. Another potential weakness is the absence of a physical activity variable similar to the one used in the original CAIDE study [10]. However, in the CAIDE study, midlife physical activity was not associated significantly with dementia risk, but was kept in their final model to highlight its importance as a healthy lifestyle factor.

Other than the CAIDE dementia risk score, three late-life dementia risk scores focusing on short-term prediction in the elderly have been published [22–24]. All risk scores identified older age as an important predictor; however, other findings differed. Predictors in CAIDE (midlife) are primarily cardiovascular risk factors, whereas late-life measures reflect the cumulative long-term impact of vascular risk factors on the brain. A dementia midlife risk score is a screening tool to be used in the general population; therefore, predictors need to be noninvasive, cheap, and easily attainable. Early markers of disease such as magnetic resonance imaging abnormalities can be used for dementia prediction in an elderly population with subjects who already have preclinical stages of dementia, but may be inappropriate for use in a midlife population.

The main use of a risk score is to target preventive measures to those most at risk. A recently published review [25] regarding potentially modifiable risk factors showed that a 10% reduction in midlife obesity prevalence could potentially prevent about 67,000 AD cases worldwide and 36,000 cases in the United States. Unfortunately, most prevention studies have been conducted in the elderly. The few studies in midlife suggest that lipid-lowering drugs [26] and a healthy diet [27] in midlife may have a beneficial effect in dementia prevention. A multicenter, randomized, controlled clinical trial showed there was no difference in decline between elderly patients with mild dementia that received strict cardiovascular treatment vs. patients that

received standard care [28]. This highlights the importance of the timing of prevention trials and suggests a promising role for a midlife dementia risk score.

Even though dementia becomes apparent in older age, recent evidence has illustrated that it is a disease of a lifetime. Early detection of those at increased risk of dementia may help to develop and target preventive treatment strategies. Implications of the CAIDE score suggest that long-term maintenance of vascular health may delay or prevent dementia [25]. It is projected that even a modest 1-year delay in the onset of AD would result in 11.8 million fewer cases after 50 years [1]. The current findings demonstrate that a combination of mostly modifiable vascular risk factors in midlife is highly predictive of the likelihood of dementia four decades later in a large representative population. Application of the current risk score would allow subjects at high risk for dementia to be selected for clinical trials and early intervention or prevention studies as early as midlife.

Acknowledgments

This work is supported by Kaiser Permanente Community Benefits Grant (R. A. Whitmer as principal investigator) and a Fulbright fellowship (L. G. Exalto).

RESEARCH IN CONTEXT

1. Systematic review: Dementia prevention trials have not yet shown the desired effect. To increase chances of successful future trials, enrichment of study cohorts through risk stratification is needed. We searched PubMed for dementia risk scores.
2. Interpretation: As a result of the long prodromal stage of dementia, and the potential for risk factor modification, valid dementia risk stratification in midlife is imperative. Although several dementia risk scores using predictors in late life to predict short-term risk of dementia have been published, only the CAIDE score used predictors in midlife to predict dementia in the elderly 20 years later. However, the cardiovascular risk factors, aging and dementia (CAIDE) score has not been validated externally. It is unknown how it performs in larger, diverse populations and whether it can be improved through testing of other midlife risk factors.
3. Future directions: The CAIDE risk score predicted well in our population. Application of the risk score to select subjects in midlife at high risk for dementia is useful for future clinical trials and prevention studies.

References

[1] Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. Alzheimers Dement 2007;3:186–91.
[2] Jack CR Jr., Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010;9:119–28.
[3] Stewart R, Xue QL, Masaki K, Petrovitch H, Ross GW, White LR, et al. Change in blood pressure and incident dementia: a 32-year prospective study. Hypertension 2009;54:233–40.
[4] Stewart R, Masaki K, Xue QL, Peila R, Petrovitch H, White LR, et al. A 32-year prospective study of change in body weight and incident dementia: the Honolulu-Asia Aging Study. Arch Neurol 2005; 62:55–60.
[5] Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L, et al. 15-Year longitudinal study of blood pressure and dementia. Lancet 1996;347:1141–5.
[6] Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol 2006;5:64–74.
[7] Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology 2005; 64:277–81.
[8] Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837–47.
[9] Vartiainen E, Puska P, Jousilahti P, Korhonen HJ, Tuomilehto J, Nissinen A. Twenty-year trends in coronary risk factors in north Karelia and in other areas of Finland. Int J Epidemiol 1994; 23:495–504.
[10] Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. Lancet Neurol 2006;5:735–41.
[11] Collen MF. Multiphasic health testing services. New York: Wiley; 1978.
[12] Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. Am J Public Health 1992;82:703–10.
[13] Collen MF, Rubin L, Neyman J, Dantzig GB, Baer RM, Siegelaub AB. Automated multiphasic screening and diagnosis. Am J Public Health Nations Health 1964;54:741–50.
[14] Collen MF, Davis LF. The multitest laboratory in health care. J Occup Med 1969;11:355–60.
[15] Pouliot MC, Despres JP, Lemieux S, Moorjani S, Bouchard C, Tremblay A, et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol 1994;73:460–8.
[16] Bamber D. The area above the ordinal dominance graph and the area below the receiver operating graph. J Math Psychol 1975;12:387–415.
[17] Chambless LE, Cummiskey CP, Cui G. Several methods to assess improvement in risk prediction models: extension to survival analysis. Stat Med 2011;30:22–38.
[18] Solomon A, Kivipelto M, Wolozin B, Zhou J, Whitmer RA. Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later. Dement Geriatr Cogn Disord 2009; 28:75–80.
[19] Pencina MJ, D'Agostino RB Sr., Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Stat Med 2011;30:11–21.
[20] Pencina MJ, D'Agostino RB Sr., D'Agostino RB Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008; 27:157–72.

[21] Katon WJ, Lin EH, Williams LH, Ciechanowski P, Heckbert SR, Ludman E, et al. Comorbid depression is associated with an increased risk of dementia diagnosis in patients with diabetes: a prospective cohort study. J Gen Intern Med 2010;25:423–9.
[22] 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;73:173–9.
[23] Jessen F, Wiese B, Bickel H, Eifflander-Gorfer S, Fuchs A, Kaduszkiewicz H, et al. Prediction of dementia in primary care patients. PLoS One 2011;6:e16852.
[24] Reitz C, Tang MX, Schupf N, Manly JJ, Mayeux R, Luchsinger JA. A summary risk score for the prediction of Alzheimer disease in elderly persons. Arch Neurol 2010;67:835–41.
[25] Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol 2011;10:819–28.
[26] Solomon A, Sippola R, Soininen H, Wolozin B, Tuomilehto J, Laatikainen T, et al. Lipid-lowering treatment is related to decreased risk of dementia: a population-based study (FINRISK). Neurodegener Dis 2010;7:180–2.
[27] Eskelinen MH, Ngandu T, Tuomilehto J, Soininen H, Kivipelto M. Midlife healthy-diet index and late-life dementia and Alzheimer's disease. Dement Geriatr Cogn Dis Extra 2011;1:103–12.
[28] Richard E, Kuiper R, Dijkgraaf MG, Van Gool WA. Vascular care in patients with Alzheimer's disease with cerebrovascular lesions: a randomized clinical trial. J Am Geriatr Soc 2009; 57:797–805.