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CAIDE Dementia Risk Score and biomarkers of neurodegeneration in memory clinic patients without dementia

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ABSTRACT

The aim of this study was to explore cross-sectional associations between Cardiovascular Risk Factors, Aging and Dementia Study (CAIDE) Dementia Risk Score and dementia-related cerebrospinal fluid and neuroimaging biomarkers in 724 patients without dementia from the Memory Clinic at Karolinska University Hospital, Huddinge, Sweden. We additionally evaluated the score's capacity to predict dementia. Two risk score versions were calculated: one including age, gender, obesity, hyperlipidemia, and hypertension; and one additionally including apolipoprotein E (APOE) ε4 carrier status. Cerebrospinal fluid was analyzed for amyloid β (Aβ), total tau, and phosphorylated tau. Visual assessments of medial temporal lobe atrophy (MTA), global cortical atrophy-frontal subscale, and Fazekas scale for white matter changes (WMC) were performed. Higher CAIDE Dementia Risk Score (version without APOE) was significantly associated with higher total tau, more severe MTA, WMC, and global cortical atrophy-frontal subscale. Higher CAIDE Dementia Risk Score (version with APOE) was associated with reduced Aβ, more severe MTA, and WMC. CAIDE Dementia Risk Score version with APOE seemed to predict dementia better in this memory clinic population with short follow-up than the version without APOE.

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1. Introduction

Prevention of dementia and Alzheimer's disease (AD) is a major global public health priority (http://www.who.int, 2015). Modifiable vascular and lifestyle-related risk factors have been shown to increase the risk of dementia (Solomon et al., 2014). Dementia risk scores have been developed in general populations (Barnes et al., 2009; Jefferson et al., 2015; Kivipelto et al., 2006), primary care (Barnes et al., 2014), or specialized units (Buratti et al., 2015) for the

purpose of identifying at-risk individuals who could benefit from preventive interventions (Ngandu et al., 2015).

The Cardiovascular Risk Factors, Aging and Dementia Study (CAIDE) Dementia Risk Score was developed in a Finnish population for predicting the risk of dementia 20 years later in middle-aged individuals (Kivipelto et al., 2006). It includes easily measurable factors like age, gender, education, body mass index (BMI), systolic blood pressure, total cholesterol, and physical activity. A second version of the risk score additionally included apolipoprotein E (APOE) genotype but without significantly improved predictive performance compared to the original score. The CAIDE Dementia Risk Score was validated in a large multiethnic population from the USA followed for 40 years (Exalto et al., 2014). Adding several other factors to the risk score (e.g., central obesity, diabetes mellitus, head

trauma, lung function, depressed mood, and smoking) did not improve the prediction capacity of the original score (Exalto et al., 2014).

A higher CAIDE Dementia Risk Score in midlife was shown to relate to more severe white matter changes (WMC) and medial temporal lobe atrophy (MTA) on brain magnetic resonance imaging (MRI) up to 30 years later in a population-based study (Vuorinen et al., 2015). However, the risk score has not been tested in memory clinic patients in relation to markers of neurodegeneration and amyloid beta (Aβ) deposition, or dementia development. AD, the most common form of dementia, is histopathologically characterized by Aβ plaques and neurofibrillary tangles (NFT), and changes can be detected years before dementia diagnosis (Jack et al., 2010). AD-related biomarkers have been divided into 2 main categories: markers of brain Aβ deposition (e.g., cerebrospinal fluid [CSF] Aβ42), and markers of neurodegeneration (e.g., CSF total tau [t-tau] or phosphorylated tau [p-tau], atrophy on structural MRI; Jack et al., 2013). WMC have been related to small vessel disease and are known to have effects on cognitive functioning (Prins and Scheltens, 2015). Memory clinic patients with subjective cognitive impairment (SCI) or mild cognitive impairment (MCI) are very heterogeneous groups. SCI patients report subjective changes in cognitive performance without objective measurable impairment (Jessen et al., 2014a; Sperling et al., 2011). MCI has been defined as both subjective and objective cognitive impairment in patients without dementia (Petersen et al., 2014). The risk for converting to dementia from SCI or MCI has been estimated to 10% and 25%–40%, respectively, depending on study design, duration of the follow-up, and population type (clinic-based or general population; Jessen et al., 2014b; Maioli et al., 2007; Mitchell et al., 2014).

Risk scores including easily available and modifiable risk factors could help identify patients who are most at risk for dementia development, and who may benefit most from preventive interventions. The aim of this study was to explore cross-sectional associations between CAIDE Dementia Risk Score and dementia-related CSF and MRI markers in memory clinic patients without dementia, as well the predictive value of the score for the development of dementia.

2. Methods

2.1. Study population

The study included 724 patients (412 with SCI and 312 with MCI) referred to the Memory clinic at the Department of Geriatrics, Karolinska University Hospital, Huddinge, Stockholm, Sweden during 2007–2012. The study was approved by the Regional Ethical Review Board in Stockholm. Written informed consent was obtained from all participants.

Inclusion criteria were as follows: age, 40 years or older; available data for CAIDE Dementia Risk Score version without APOE genotype; available measurements of CSF biomarkers (t-tau, tau phosphorylated at threonine 181—p-tau; and Aβ1-42); diagnosis of MCI or SCI. Exclusion criteria were as follows: dementia diagnosis at baseline or within 1 year from baseline; and neurological conditions affecting CSF or MRI assessments (e.g., hydrocephalus, brain tumors, large strokes, or multiple sclerosis). Of 1209 patients without dementia evaluated at the Memory Clinic, 724 fulfilled inclusion criteria (Fig. 1).

The standard evaluation protocol at the Memory Clinic (described in detail in Enache, 2015) included interviews with patients and informants, general physical and neurological examination, standardized neuropsychological test-battery, assessment of depressive and other psychiatric symptoms, routine blood chemistry, CSF analyses including conventional biomarkers of neurodegeneration (t-tau, p-tau, and Aβ1-42), and brain imaging (MRI or computed tomography scans). Diagnoses were established after consensus
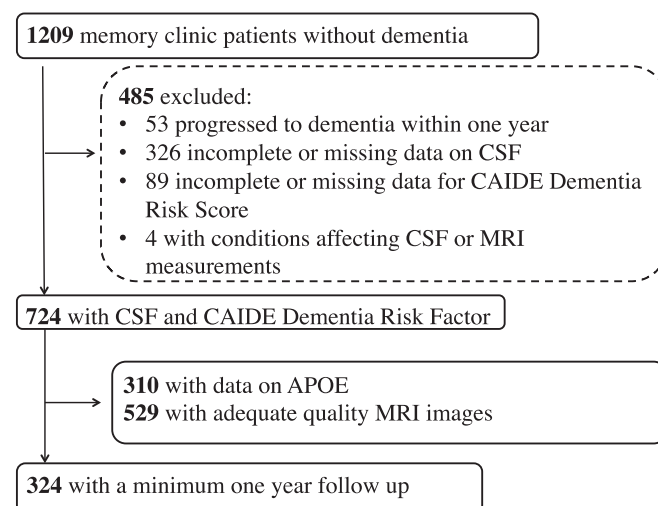
Fig. 1. Study population (flowchart). Abbreviations: APOE, apolipoprotein E; CADINE, Cardiovascular Risk Factors, Aging and Dementia Study; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

meetings using all available information. Dementia diagnoses were made according to International Classification of Diseases 10 revision (ICD 10). MCI was diagnosed according to the Winblad et al., (2004) clinical criteria, which require subjective cognitive complaints, impairment on objective cognitive tests, normal global cognitive function, no significant impairment of activities of daily living, and no dementia. The diagnosis of SCI was made if the assessments did not show evidence of objective cognitive impairment, that is, neither dementia nor MCI criteria were fulfilled, although patients and/or informants reported changes in cognitive performance.

According to the standard protocol at the Memory Clinic, regular annual follow-up visits for patients with MCI or SCI were planned after the initial assessments and diagnosis only if clinically indicated (i.e., high risk of cognitive decline as judged by the physician). Follow-up data until March 2015 were collected from patient files. Altogether 324 (44.8%) patients were followed for at least 1 year (mean, 2.9; standard deviation, 1.6; range, 1–7.8 years). Hundred ten of the 324 patients had SCI at baseline, and 14 (12.7%) developed dementia. Two hundred fourteen of the 324 patients had MCI at baseline, and 86 (40.2%) developed dementia.

2.2. Assessment of CAIDE Dementia Risk Score

The CAIDE Dementia Risk Score (Table 1) was calculated for each patient using data from the baseline visit (first referral to the Memory Clinic). Points were given for elevated total cholesterol or systolic blood pressure if the patient had a diagnosis and received treatment for hyperlipidemia or hypertension. No systematically collected data were available for leisure time physical activity, and this variable was not included in the risk score (Exalto et al., 2014). A second version of the risk score was calculated adding points for the presence of the APOE ε4 allele. APOE genotype was analyzed from blood leucocytes using polymerase chain reaction and HhaI digestion (Garcia-Ptacek et al., 2014; Tsukamoto et al., 1993). The maximum number of points for the CAIDE Dementia Risk Score in the present study was 14 (version without APOE) or 17 (version with APOE), 1 point less than in the original publication (Kivipelto et al., 2006).

2.3. CSF and MRI measurements

CSF samples were obtained in connection to the baseline visit (first referral) at the Memory Clinic. Lumbar puncture was done in

the L3/L4 or L4/L5 intervertebral space, using a 25-gauge needle, and collected in 12-mL polypropylene tubes. Samples were centrifuged within 2 hours. CSF was aliquoted in polypropylene tubes of 0.5 or 1 mL, and stored at $-80\,^{\circ}$C until further analysis. CSF $A\beta_{1\text{-}42}$, t-tau, and p-tau (p-tau at threonine 181) were measured by commercially available sandwich enzyme linked immunoabsorbent assays (Innogenetics, Ghent, Belgium) as previously reported (Kramberger et al., 2012). Memory Clinic physicians have access to CSF measurements, which may be used as supportive information for differential diagnosis in dementia cases. However, clinical diagnostic criteria always have priority due to lack of established CSF-based criteria for regular clinical practice. In the present study, patients were not selected based on CSF biomarker levels, and a researcher without clinical ties to the Memory Clinic (Daniela Enache) collected data on primary clinical diagnoses (SCI, MCI, dementia). Medical record comments on CSF markers, and specific diagnostic codes for dementia types (e.g., AD dementia) were not considered. This approach also matches the original design of the CAIDE Risk Score for predicting dementia in general, without focus on specific causes of dementia.

MRI scans were performed either shortly before the referral to the Memory Clinic at different radiology departments in Stockholm region as part of the routine dementia assessment by the general practitioner or at the Department of Radiology, Karolinska University Hospital during the assessment procedure at our Memory clinic. All images were routinely collected in a common electronic database at the Department of Radiology, Karolinska University Hospital-Huddinge. Images related to the baseline visit (first referral) at the Memory Clinic were used in the present study. Because scanners and protocols were not identical in all image sources, only visual assessments were considered.

MRI visual assessments were performed by an experienced rater (Lena Cavallin) who was blinded to all other data. For visual assessment of MTA, T1-weighted MRI images were oriented to oblique coronal sections. MTA was rated using the 5-point Scheltens scale ranging from 0 (no atrophy) to 4 (severe atrophy; Scheltens et al., 1992). The MTA visual assessment included hippocampus proper, dentate gyrus, subiculum, parahippocampal gyrus, entorhinal cortex, and surrounding CSF spaces such as the temporal horns and choroid fissure. WMC were assessed on transverse fluid-attenuated inversion recovery (FLAIR) images according to the modified 4-point Fazekas scale ranging from 0 (no WMC) to 3 (large confluent WMC; Fazekas et al., 1987). Frontal lobe atrophy was assessed on a FLAIR sequence according to the 4-point scale for global cortical atrophy-frontal subscale ranging from 0 (no atrophy) to 3 (severe "knife blade" atrophy; Pasquier et al., 1996). Parietal atrophy (PA) was visually assessed by combining T1-weighted sagittal, T1-weighted coronal, and axial FLAIR sequences, using Koedam score (Koedam et al., 2011), a 4-point scale ranging from 0 (no atrophy) to 3 (severe atrophy).

2.4. Statistical analysis

Between-group comparisons were made using parametric (Student's *t* tests) or nonparametric tests (chi-square tests, Mann-Whitney) as appropriate. CAIDE Dementia Risk Score was categorized into 3 groups of relatively similar size: 0−5 points (lower risk, n = 301 patients), 6−7 points (intermediate risk, n = 214), and 8−14 points (higher risk, n = 209) for the version without APOE; and 0−6 points (lower risk, n = 81 patients), 7−8 points (intermediate risk, n = 98), and 9−17 points (higher risk, n = 131) for the version with APOE. The lower risk category was used as reference in all analyses.

Based on recent studies suggesting that combinations of CSF biomarkers may be more accurate indicators of Alzheimer's disease

(Duits et al., 2014; Leuzy et al., 2015), the $A\beta_{1\text{-}42}$/t-tau and $A\beta_{1\text{-}42}$/p-tau$_{181}$ ratios were calculated. Zero-skewness log-transformation was applied to $A\beta_{1\text{-}42}$, t-tau, p-tau$_{181}$, and $A\beta_{1\text{-}42}$/t-tau and $A\beta_{1\text{-}42}$/p-tau$_{181}$ ratios. Linear regression models with CSF markers as dependent variables were used to investigate associations with CAIDE Dementia Risk Score. Results are shown as standardized beta-coefficients (*p*-values). Ordinal regression was used to explore associations between visual assessment scales on MRI and CAIDE Dementia Risk Score. MTA was visually assessed for right and left hemisphere separately, and the mean MTA score was used in analyses (Pereira et al., 2014). Owing to the smaller number of patients with higher MTA ratings, patients with mean MTA scores 2.5, 3, and 4 were grouped together. Results are shown as odds ratio (95% confidence interval [95% CI]). Stratified analyses were conducted according to diagnosis (SCI or MCI).

The performance of the CAIDE Dementia Risk Score (versions without and with APOE) in predicting dementia was assessed in patients with available follow-up data (n = 324). Results are reported as area under the receiver operating characteristics curve (AUC) and 95% CI. Sensitivity, specificity, likelihood ratios for positive and negative tests, and their 95% CIs were also calculated. To account for missing follow-up data, additional analyses were conducted: (1) assuming that patients without planned follow-up did not develop dementia and (2) assuming that MCI patients without planned follow-up developed dementia.

The level of statistical significance was set to $p < 0.05$ in all analyses. Statistical analyses were performed with SPSS software version 22.0. Analyses of the performance of the CAIDE Dementia Risk Score in predicting dementia were conducted using the *diagt* and *roctab* commands in Stata software version 13, and *rocgold* was used to compare the risk score versions with and without APOE.

3. Results

Formation of the study population is shown in Fig. 1. The study included 724 patients with MCI and SCI, of which 310 had available

Table 1
CAIDE Dementia Risk Score versions used in the study

Risk factors	CAIDE Dementia Risk Score	
	Without APOE	With APOE
Age, years		
<47	0	0
47−53	3	3
>53	4	5
Education, years		
≥10	0	0
7−9	2	3
0−6	3	4
Sex		
Women	0	0
Men	1	1
Hypertension		
No	0	0
Yes	2	2
BMI, kg/m^2		
≤30	0	0
>30	2	2
Hyperlipidemia		
No	0	0
Yes	2	1
APOE ε4		
Noncarrier	—	0
Carrier	—	2
Total points	Max 14 p	Max 17 p

Key: APOE, apolipoprotein E genotype; BMI, body mass index; CAIDE, Cardiovascular Risk Factors, Aging and Dementia Study.

data on APOE genotype, and 529 had available MRI scans. Characteristics of the study population are shown in Table 2. Median (range) for the CAIDE risk score version without APOE was 6 (0–14), and 301 (41.6%) patients had lower dementia risk (0–5 points), 214 (29.6%) intermediate risk (6–7 points), and 209 (28.9%) higher dementia risk (8–14 points). Median (range) for the CAIDE risk score version with APOE was 8 (0–17), and 81 (26.1%) patients had lower dementia risk (0–6 points), 98 (31.6%) intermediate risk (7–8 points), and 131 (42.3%) higher dementia risk (9–17 points).

Table 3 shows the characteristics of the study population compared to patients who did not fulfill inclusion criteria. Excluded patients had significantly lower mini-mental state examination scores, were less likely to be APOE $\varepsilon 4$ carriers, less likely to be diagnosed with SCI and more likely to be diagnosed with MCI.

Associations between CAIDE Dementia Risk Score and CSF markers are shown in Table 4. Compared to patients with lower risk (0–5 points) on CAIDE Dementia Risk Score version without APOE, patients with intermediate risk (6–7 points) and higher risk (8–14 points) had higher CSF t-tau and lower $A\beta_{1-42}$/t-tau and $A\beta_{1-42}$/p-tau_{181} ratios. For the CAIDE Dementia Risk Score including APOE genotype, both intermediate (7–8 points) and higher (9–17 points) risk groups had significantly lower CSF $A\beta_{1-42}$ and lower $A\beta_{1-42}$/t-tau and $A\beta_{1-42}$/p-tau_{181} ratios. The association with higher CSF t-tau was significant for the intermediate but not the higher risk group (Table 4). No significant associations were found with CSF p-tau levels.

Table 2
Baseline characteristics of the study population

Population characteristics	All (n = 724)	APOE genotype available (n = 310)
Age, years[a]	60.8 (8.5)	61.2 (7.7)
Women, n (%)	417 (57.6)	193 (62.3)
Education, years[a]	12.5 (3.7)	12.5 (3.7)
CAIDE Dementia Risk Score	6 (0–14)	8 (0–17)
Hyperlipidemia, n (%)	201 (27.8)	97 (31.3)
Hypertension, n (%)	246 (34.0)	108 (34.8)
BMI, kg/m²[a]	26.2 (4.1)	26.3 (4.2)
MMSE[a]	27.7 (2.6)	27.6 (2.6)
APOE $\varepsilon 4$ carrier, n (%)	—	156 (50.3)
SCI, n (%)	412 (56.9)	163 (52.6)
MCI, n (%)	312 (43.1)	147 (47.4)
Cornell Depression Scale	6 (0–26)	6 (0–24)
Antidepressant treatment, n (%)	192 (26.5)	79 (25.5)
History of depression, n (%)	261 (36.0)	109 (35.2)
CSF markers		
$A\beta_{1-42}$, ng/L	855 (56–1920)	821.5 (56–1680)
t-tau, ng/L	240.5 (41–1030)	254 (41–1030)
p-tau, ng/L	51 (16–183)	53 (16–183)
$A\beta_{1-42}$/t-tau[a]	3.91 (2.3)	3.70 (2.5)
$A\beta_{1-42}$/p-tau_{181}	18.22 (8.9)	16.90 (8.8)
MRI visual ratings	n = 529	n = 235
MTA	1 (0–4)	1 (0–4)
GCA-F	0 (0–1)	0 (0–1)
Parietal atrophy	0 (0–2)	0 (0–2)
WMC	1 (0–3)	1 (0–3)
Follow-up		
Planned follow-up, n (%)	324 (44.8)	168 (54.2)
Follow-up years mean (SD)	2.90 (1.6)	3.00 (1.6)
Conversion to dementia n (%)	100 (13.8)	55 (17.7)

Values are medians (range) unless otherwise specified.
Key: APOE, apolipoprotein E genotype; $A\beta_{1-42}$, amyloid β_{1-42}; BMI, body mass index; CAIDE, Cardiovascular Risk Factors, Aging and Dementia Study; GCA-F, global cortical atrophy-frontal subscale; MCI, mild cognitive impairment; MMSE, mini-mental state examination; MTA, medial temporal lobe atrophy (mean MTA scores of both hemispheres); parietal atrophy, Koedam score for parietal atrophy; p-tau_{181}, phosphorylated tau at threonine 181; SCI, subjective cognitive impairment; SD, standard deviation; t-tau, total tau; WMC, white matter changes measured with Fazekas scale for white matter changes.
[a] Values are means (SD).

Table 3
Included versus excluded patients

Characteristics	Included (n = 724)	Excluded (n = 485)
Age, years[a]	60.8 (8.5)	60.7 (11.6)
Women, n (%)	417 (57.6)	294 (60.6)
Education, years[a]	12.6 (3.7)	12.2 (3.9)
MMSE[a]	27.7 (2.6)*	26.9 (3.2)
Cornell Depression Scale	6 (0–26)	7 (0–25)
Use of antidepressants, n (%)	192 (26.6)	149 (30.7)
History of depression, n (%)	262 (36.2)	200 (41.2)
APOE $\varepsilon 4$ carrier, n (%)/total number	156 (50.3)/310*	65 (42.0)/155
CAIDE Dementia Risk Score	6 (0–14)	
SCI, n (%)	412 (56.9)*	233 (48.0)
MCI, n (%)	312 (43.1)*	252 (52.0)

Values are medians (range) unless otherwise specified.
*$p < 0.05$; p-values for the comparisons between excluded and included patients were based on t test, Mann-Whitney, chi-squared tests as appropriate.
Key: APOE, apolipoprotein E genotype; CAIDE, Cardiovascular Risk Factors, Aging and Dementia Study; MCI, mild cognitive impairment; MMSE, mini-mental state examination; SCI, subjective cognitive impairment.
[a] Values are means (SD).

Table 4 illustrates associations between CAIDE Dementia Risk Score and MRI visual ratings. Compared to patients with lower dementia risk (0–5 points) on CAIDE Dementia Risk Score version without APOE, patients with intermediate risk (6–7 points) and higher risk (8–14 points) had significantly more severe WMC. For the CAIDE Dementia Risk Score including APOE genotype, the association with more severe WMC was significant in the higher risk group (9–17 points). More severe MTA was found in the higher risk group compared to the lower risk group for both CAIDE Dementia Risk Score versions (without and with APOE). Patients in the higher risk group (both risk score versions) were also more likely to have higher global cortical atrophy-frontal subscale ratings. No significant associations were found with PA ratings.

Additional analyses were conducted stratifying for diagnosis group (SCI and MCI separately; data not shown). In SCI patients, no significant associations were found between CAIDE Dementia Risk Score versions and CSF markers. However, the higher risk group (both risk score versions) had significantly more severe WMC. In MCI patients, the intermediate and higher risk groups according to both CAIDE Dementia Risk Score versions had more severe $A\beta$ and tau pathology (CSF markers). Patients with MCI and higher dementia risk according to both risk score versions had significantly more severe WMC on MRI.

The performance of CAIDE Dementia Risk Score versions in predicting dementia in patients with planned follow-up after at least 1 year is shown in Table 5. AUCs (95% CIs) were 0.64 (0.56–0.73) for the version with APOE, 0.58 (0.51–0.65) for the version without APOE, and 0.61 (0.53–0.68) for APOE alone. Comparison of ROC areas was conducted in 168 patients with verified follow-up and available data on both APOE and CAIDE score: CAIDE Dementia Risk Score version with APOE seemed to be significantly better than the version without APOE ($p = 0.049$); neither version was significantly different than APOE alone ($p > 0.4$). The version with APOE had good sensitivity in predicting dementia, but poor specificity. Results from additional analyses accounting for missing follow-up data are shown in Supplementary Tables 1 and 2.

4. Discussion

This is the first study assessing associations of CAIDE Dementia Risk Score with CSF and MRI markers for neurodegeneration and amyloid deposition, as well as the performance of the risk score in predicting dementia in memory clinic patients with SCI and MCI.

Table 4
Associations of CAIDE Dementia Risk Score with CSF and MRI markers at baseline

CSF markers (dependent variable)	CAIDE risk score (without APOE)		CAIDE risk score (with APOE)	
	Standardized beta-coefficients (*p*-values)			
Aβ_{1-42}, pg/L	0–5 points (n = 301)	Ref	0–6 points (n = 81)	Ref
	6–7 points (n = 214)	−0.04 (0.37)	7–8 points (n = 98)	**−0.22 (0.002)**
	8–14 points (n = 209)	−0.07 (0.10)	9–17 points (n = 131)	**−0.27 (<0.001)**
t-tau, pg/l	0–5 points (n = 301)	Ref	0–6 points (n = 81)	Ref
	6–7 points (n = 214)	0.08 (0.06)	7–8 points (n = 98)	**0.14 (0.04)**
	8–14 points (n = 209)	**0.09 (0.04)**	9–17 points (n = 131)	0.10 (0.17)
p-tau, pg/l	0–5 points (n = 301)	Ref	0–6 points (n = 81)	Ref
	6–7 points (n = 214)	0.06 (0.17)	7–8 points (n = 98)	0.05 (0.49)
	8–14 points (n = 209)	0.05 (0.22)	9–17 points (n = 131)	0.05 (0.43)
Aβ_{1-42}/t-tau	0–5 points (n = 301)	Ref	0–6 points (n = 81)	Ref
	6–7 points (n = 214)	**−0.08 (0.04)**	7–8 points (n = 98)	**−0.21 (0.002)**
	8–14 points (n = 209)	**−0.12 (0.004)**	9–17 points (n = 131)	**−0.23 (0.001)**
Aβ_{1-42}/p-tau	0–5 points (n = 301)	Ref	0–6 points (n = 81)	Ref
	6–7 points (n = 214)	−0.07 (0.09)	7–8 points (n = 98)	**−0.16 (0.02)**
	8–14 points (n = 209)	**−0.10 (0.02)**	9–17 points (n = 131)	**−0.23 (0.001)**
MRI visual ratings (dependent variable)	OR (95% CI)			
MTA	0–5 points (n = 226)	Ref	0–6 points (n = 57)	Ref
	6–7 points (n = 150)	1.11 (0.76–1.62)	7–8 points (n = 78)	1.50 (0.80–2.78)
	8–14 points (n = 153)	**1.47 (1.01–2.15)**	9–17 points (n = 100)	**2.71 (1.48–5.95)**
WMC	0–5 points (n = 226)	Ref	0–6 points (n = 57)	Ref
	6–7 points (n = 150)	**1.80 (1.16–2.77)**	7–8 points (n = 78)	1.78 (0.87–3.65)
	8–14 points (n = 153)	**3.41 (2.20–5.27)**	9–17 points (n = 100)	**3.91 (1.93–7.92)**
GCA-F	0–5 points (n = 226)	Ref	0–6 points (n = 57)	Ref
	6–7 points (n = 150)	1.14 (0.47–2.73)	7–8 points (n = 78)	1.48 (0.26–8.40)
	8–14 points (n = 153)	**2.40 (1.11–5.10)**	9–17 points (n = 100)	4.47 (0.99–20.47)
Parietal atrophy	0–5 points (n = 226)	Ref	0–6 points (n = 57)	Ref
	6–7 points (n = 150)	0.88 (0.52–1.49)	7–8 points (n = 78)	0.81 (0.36–1.84)
	8–14 points (n = 153)	1.36 (0.84–2.20)	9–17 points (n = 100)	1.46 (0.70–3.05)

Standardized beta-coefficients (*p*-values) are from linear regression with Aβ_{1-42}, t-tau, and p-tau as dependent variable. Odds ratios and 95% confidence interval (OR and 95% CI) are from ordinal logistic regression with MTA, WMC, CGA-F, and parietal atrophy as dependent variable. Statistically significant values are marked in bold.
Key: APOE, apolipoprotein E genotype; Aβ_{1-42}, amyloid β_{1-42}; CSF, cerebrospinal fluid; CAIDE, Cardiovascular Risk Factors, Aging and Dementia Study; GCA-F, global cortical atrophy-frontal subscale; MRI, magnetic resonance imaging; MTA, medial temporal lobe atrophy (mean MTA scores of both hemispheres); parietal atrophy, Koedam score for parietal atrophy; p-tau$_{181}$, phosphorylated tau at threonine 181; t-tau, total tau; WMC, white matter changes measured with Fazekas scale for white matter changes.

A higher risk level according to the CAIDE Dementia Risk Score (version with APOE) was associated with lower Aβ_{1-42}, higher t-tau, lower Aβ_{1-42}/t-tau and Aβ_{1-42}/p-tau$_{181}$ ratios, and more severe MTA and WMC at baseline. The CAIDE Dementia Risk Score version without APOE showed a similar pattern of associations, although these were somewhat weaker, and the relation to Aβ_{1-42} was not significant. In addition, an association with frontal lobe atrophy was found only for the risk score version without APOE. Neither risk score version had any relation to p-tau levels and PA. These results are in line with recent findings from a population-based study where higher CAIDE Dementia Risk Score in midlife was associated with more severe WMC and MTA up to 30 years later (Vuorinen et al., 2015).

Aβ deposition and NFT are the histopathological hallmarks of AD. According to Braak and Braak (1991) stages, extracellular Aβ deposition begins in the frontal lobe, whereas NFT appear first subcortically in the entorhinal cortex and medial temporal lobe. The hypothetical model of dynamic biomarkers in AD suggests that Aβ and tau pathologies can begin independently from each other, and both are necessary but not sufficient to produce clinical symptoms of AD (Jack et al., 2013). Other pathologies (e.g., small vessel disease, Lewy body accumulation; Nelson et al., 2010), genetic factors, and brain resilience or cognitive reserve are also important. CSF t-tau and p-tau, and MTA on MRI are considered markers of neurodegeneration, and they have been associated with NFT burden (Jack et al., 2013). Atrophy of the medial temporal lobe is a common finding in sporadic AD, while more pronounced frontal or parietal lobe atrophy tends to be present primarily in atypical forms of AD, or early onset AD (Lam et al., 2013). Importantly, Aβ and tau often coexists with cerebrovascular pathology, particularly small vessel

Table 5
Performance of the CAIDE Dementia Risk Score in predicting dementia

Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95%CI)	LR− (95% CI)	AUC (95% CI)
CAIDE Dementia Risk Score (version without APOE)					
4/5	82.0 (73.1–89.0)	26.3 (20.7–32.6)	1.11 (0.99–1.26)	0.68 (0.43–1.10)	0.58 (0.51–0.65)
5/6	70.0 (60.0–78.8)	41.5 (35.0–48.3)	1.20 (1.01–1.42)	0.72 (0.52–1.01)	
6/7	51.0 (40.8–61.1)	60.3 (53.5–66.7)	1.28 (1.00–1.65)	0.81 (0.65–1.02)	
7/8	39.0 (29.4–49.3)	72.8 (66.4–78.5)	1.43 (1.03–1.98)	0.84 (0.70–1.00)	
CAIDE Dementia Risk Score (version with APOE)					
5/6	96.4 (87.5–99.6)	15.0 (9.0–23.0)	1.13 (1.03–1.24)	0.24 (0.06–1.01)	0.64 (0.56–0.73)
6/7	92.7 (82.4–98.0)	27.4 (19.5–36.6)	1.28 (1.12–1.46)	0.27 (0.10–0.71)	
7/8	83.6 (71.2–92.2)	42.5 (33.2–51.2)	1.45 (1.19–1.77)	0.39 (0.20–0.73)	
8/9	60.0 (45.9–73.0)	61.1 (51.4–70.1)	1.54 (1.12–2.11)	0.66 (0.46–0.93)	
APOE alone					
0/1	69.1 (55.2–80.9)	52.2 (42.6–61.7)	1.45 (1.11–1.88)	0.59 (0.38–0.91)	0.61 (0.53–0.68)

Key: APOE, apolipoprotein E genotype; AUC, area under the receiver operating characteristics curve; CAIDE, Cardiovascular Risk Factors, Aging and Dementia Study; CI, confidence interval; LR+, likelihood ratio for positive test; LR−, likelihood ratio for negative test.

disease (Prins and Scheltens, 2015), and interactions between the 2 pathology types have been described (Kester et al., 2014). WMC are common at older ages, are often found in AD (Prins and Scheltens, 2015), and may potentiate the effects of cortical atrophy on cognitive impairment (Zi et al., 2014).

Because CAIDE Dementia Risk Score is mainly based on vascular risk factors, the association with WMC is not surprising. In addition, midlife hypertension and hypercholesterolemia have been associated with increased risk of AD neuropathology in previous population-based autopsy studies (Petrovitch et al., 2000; Toledo et al., 2013), whereas obesity has been related to lower brain volumes on MRI (Willette and Kapogiannis, 2015).

Cardiovascular risk factors, confluent white matter lesions, MTA, and central atrophy have been shown to increase the AD likelihood of SCI subjects (Garcia-Ptacek et al., 2014). The association of lower $A\beta_{1-42}$ with higher CAIDE Dementia Risk Score including APOE (but not the risk score version without APOE) could be explained by the well-known contribution of the APOE ε4 allele to Aβ deposition and neurodegeneration (Liu et al., 2013). APOE ε4 seems to be related to increased Aβ deposition independently of cognitive performance (e.g., normal cognition or MCI; Risacher et al., 2013).

Although the APOE ε4 allele is the strongest known genetic risk factor for dementia, adding APOE genotype to the midlife CAIDE Dementia Risk Score did not improve the ability to predict dementia 20 years later in the general population (Kivipelto et al., 2006). However, in the present study the CAIDE Dementia Risk Score version with APOE seemed to perform better than the version without APOE in predicting dementia in memory clinic patients with SCI and MCI. The ability of the CAIDE Dementia Risk Score to predict dementia short term (up to 7 years) in memory clinic patients was nevertheless lower than the ability to predict dementia long-term (20–40 years) in a middle-aged general population where AUC (95% CI) was 0.77 (0.71–0.83; Exalto et al., 2014; Kivipelto et al., 2006). Although performance of CAIDE Risk Score versions did not seem to be different from APOE alone in the present study, the CAIDE Risk Score version including APOE has the advantage of additionally including modifiable risk factors that can be targeted with preventive interventions (e.g., lifestyle and vascular risk monitoring).

In the present study, cutoffs were 1 point lower than in the original publication (Kivipelto et al., 2006), but they were chosen to be higher than for points given for age alone. Sensitivity remained high in the memory clinic population (above 80% for the version including APOE), but specificity was lower. The risk score may thus be useful for identifying individuals with higher dementia risk who could benefit more from preventive lifestyle interventions and vascular and metabolic risk management, similarly to the selection of participants in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability prevention trial (Ngandu et al., 2015).

Risk profiles for dementia have been shown to differ between midlife and older ages (Barnes et al., 2009; Kivipelto et al., 2006). Blood pressure, BMI, and cholesterol tend to decline after midlife in individuals who develop dementia later on (Solomon et al., 2014). The CAIDE Dementia Risk Score was formulated based on a midlife risk profile (mean population age around 50 years; Kivipelto et al., 2006). The Memory clinic at Karolinska University Hospital, Huddinge, is known to have a relatively young population of patients (Andersson, 2007), with a mean age of 61 years in the present study. However, patients in most memory clinics tend to be older, and a late-life risk score for shorter-term dementia prediction may work better in this type of population (e.g., modifying the list of vascular and lifestyle factors included in the score, and the number of points given to each factor).

The present study has a number of methodological limitations. First, associations between CAIDE Dementia Risk Score, CSF, and MRI markers could only be evaluated cross-sectionally at baseline because data on risk factors before the memory clinic referral were not available. Second, physical activity was not routinely assessed, and could not be used for calculating CAIDE Dementia Risk Score according to the original versions. Reduced physical activity has been associated with Aβ deposition and neurodegeneration (Brown et al., 2013). However, the CAIDE Dementia Risk Score version used in the present study is the same as in a previous validation study which did not include physical activity (Exalto et al., 2014). Third, the study population consisted of memory clinic patients, who have a more advanced stage of Aβ pathology, neuronal injuries, or small vessel pathology, and an increased prevalence of the APOE ε4 allele compared to the general population (Garcia-Ptacek et al., 2014). Associations with CSF markers of Aβ deposition and neurodegeneration cannot thus be extrapolated to the general population based on the present study. However, the associations with MTA and WMC on MRI found in memory clinic patients are in line with a previous population-based longitudinal study (Vuorinen et al., 2015). Fourth, follow-up data on dementia development after more than 1 year were available only for patients considered to have a high risk of cognitive and functional decline after the initial comprehensive assessments. According to the routine Memory clinic protocol, if follow-up beyond 1 year is not considered necessary in a patient with SCI or MCI, the general practitioner (or referring physician) is instructed to send a new referral if there are signs of cognitive decline. We have tried to account for missing data by conducting additional analyses of dementia prediction performance based on this protocol (assuming that patients without follow-up did not develop dementia), and also considering the progression of MCI to dementia (assuming that all MCI patients without planned follow-up developed dementia). CAIDE Dementia Risk Score is not used for risk assessment at the Memory clinic, thus circularity was avoided.

5. Conclusions

A higher CAIDE Dementia Risk Score, particularly the version including APOE genotype, tends to identify patients who are more likely to have brain pathology (e.g., neurodegeneration, Aβ deposition, and/or cerebrovascular changes). This suggests that the previously shown ability of the CAIDE Dementia Risk Score to predict dementia may be explained by its links to AD/neurodegenerative and/or cerebrovascular pathological processes. The CAIDE Dementia Risk Score version including APOE seems to be better at predicting dementia up to 7 years later in memory clinic patients compared to the version without APOE. The risk score does not perform as well in a memory clinic setting as it does in the general population, particularly due to lower specificity. However, high sensitivity could make the risk score useful for identifying patients with higher risk who may benefit most from preventive lifestyle interventions. This is particularly important in a memory clinic setting because no therapeutic measures are currently available for patients with SCI or MCI. However, the risk score must not be used as a diagnostic tool (it was not designed to predict or diagnose specific types of dementia), or for excluding dementia development within short term. An adjusted prediction model for use in older memory clinic patients with SCI and MCI should be formulated in future studies to test whether the dementia prediction performance of the CAIDE Risk Score can be improved.

Disclosure statement

The authors report no conflicts of interest.

Acknowledgements

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version at http://dx.doi.org/10.1016/j.neurobiolaging. 2016.03.007.

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