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2018-06

Hooshmand , B , Polvikoski , T , Kivipelto , M , Myllykangas , L , Mäkelä , M , Tanskanen , M , Oinas , M , Paetau , A & Solomon , A 2018 , ' CAIDE Dementia Risk Score, Alzheimer and cerebrovascular pathology : a population-based autopsy study ' , Journal of internal medicine , vol. 283 , no. 6 , pp. 597-603 . https://doi.org/10.1111/joim.12736

http://hdl.handle.net/10138/304262
https://doi.org/10.1111/joim.12736

JIM Rapid Communication

doi: 10.1111/joim.12736

CAIDE Dementia Risk Score, Alzheimer and cerebrovascular pathology: a population-based autopsy study

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Abstract. Hooshmand B, Polvikoski T, Kivipelto M, Tanskanen M, Myllykangas L, Mäkelä M, Oinas M, Paetau A, Solomon A (Karolinska Institute, Stockholm, Sweden; Ulm University Hospital, Ulm, Germany; Newcastle University, Newcastle upon Tyne, UK; Karolinska Institute, Stockholm, Sweden; University of Eastern Finland, Kuopio, Finland; Karolinska University Hospital, Stockholm, Sweden; Imperial College London, London, UK; Helsinki University Hospital, Helsinki, Finland). CAIDE Dementia Risk Score, Alzheimer and cerebrovascular pathology: a population-based autopsy study. *J Intern Med* 2018; **283**: 597–603.

Background. CAIDE Dementia Risk Score is a tool for estimating dementia risk in the general population. Its longitudinal associations with Alzheimer or vascular neuropathology in the oldest old are not known.

Aim. To explore the relationship between CAIDE Dementia Risk Score at baseline and neuritic plaques, neurofibrillary tangles, cerebral infarcts and cerebral amyloid angiopathy (CAA) after up to 10-year follow-up in the Vantaa 85 + population.

Methods. Study population included 149 participants aged ≥85 years, without dementia at baseline, and with available clinical and autopsy data. Methenamine silver staining was used for β-amyloid and modified Bielschowsky method for neurofibrillary tangles and neuritic plaques. Macroscopic infarcts were identified from cerebral hemispheres, brainstem and cerebellum slices. Standardized methods were used to determine microscopic infarcts, CAA and α-synuclein pathologies. The CAIDE Dementia Risk Score was calculated based on scores for age, sex, BMI, total cholesterol, systolic blood pressure, physical activity and *APOE*ε4 carrier status (range 0–18 points).

Results. A CAIDE Dementia Risk Score above 11 points was associated with more cerebral infarctions up to 10 years later: OR (95% CI) was 2.10 (1.06–4.16). No associations were found with other neuropathologies.

Conclusion. In a population of elderly aged ≥85 years, higher CAIDE Dementia Risk Score was associated with increased risk of cerebral infarcts.

Keywords: Alzheimer pathology, CAIDE Dementia Risk Score, cerebrovascular pathology, dementia, elderly.

Introduction

Dementia risk scores have been developed for identifying at-risk individuals who could benefit from preventive interventions [1]. CAIDE Dementia Risk Score is the first validated tool estimating the risk of dementia 20 years later [2, 3]. It takes into account age, sex, education, systolic blood pressure, body mass index (BMI), cholesterol, physical activity and *APOE*ε4 status (maximum 18 points, Table S1). Two longitudinal studies reported associations of CAIDE Dementia Risk Score with white matter changes and grey matter atrophy on brain MRI [4, 5]. A cross-sectional study reported associations with CSF amyloid-β/tau ratio [6]. The aim of this study was to investigate links between CAIDE Dementia Risk Score and post-mortem neuropathological findings up to 10 years later in the Vantaa 85 + population including people aged ≥85 years.

Methods

Study population

The Vantaa 85 + study has been described in detail [7]. In brief, the study included 553 participants who were clinically examined at baseline and represented 92% of the 601 individuals aged ≥85 years and living in Vantaa, Finland, in 1991. A total of 149 individuals without dementia at baseline underwent consented post-mortem examination and had complete CAIDE Dementia Risk Score data. They were older at death (mean (standard deviation SD)) 92.8 (3.5) vs. 91.9 (3.4) years; $P = 0.021$), had longer follow-up (4.7 (2.5) vs 3.7 (2.3) years; $P < 0.001$) and more incident dementia over 10 years (36.9% vs. 24.2% ($P = 0.011$) compared with the rest of the study population (Table 1). The Vantaa 85 + study was approved by the Ethics Committee of the Health Centre of the city of Vantaa and by the Coordinating Ethics Committee of Helsinki University Hospital. The Finnish Health and Social Ministry approved the use of the health and social work records and death certificates. Blood samples were collected only after subjects or their relatives gave informed consent. The National Authority for Medicolegal Affairs (VALVIRA) approved the tissue sample collection at autopsy and their use for research. Written consent for autopsy was obtained from the nearest relative.

Clinical assessment

Evaluation included an interview by a trained nurse using questionnaires concerning health, health-related behaviour and clinical examination by a physician. Data on socio-demographic characteristics and medical history were collected according to a structured protocol, and dementia was diagnosed according to the DSM-III-R criteria. BMI was assessed. Blood pressure was measured from the right arm after sitting for 5 min [8]. Serum cholesterol levels were determined by enzymatic techniques [8]. *APOE*ε4 status was determined as previously described [7]. Being physically active was defined as engaging in light walking or moderate exercise several times per week. CAIDE Dementia Risk Score was calculated as specified previously [2].

Neuropathology

Paraffin-embedded brain tissue samples were assessed for neuropathology blind to clinical status. The sampling procedures and quantification of the Alzheimer's and cerebrovascular pathologies were previously described in detail [7, 9]. In brief, the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) protocol was employed for neocortical neuritic plaque score [10]. Methenamine silver staining was used for amyloid-β and modified Bielschowsky method for neurofibrillary tangles (NFT) and neuritic plaques. The average area fraction of cortex covered by methenamine silver-positive plaques and NFT per standard cortical area was determined. Gallyas silver stain was used for the Braak staging, which was carried out as originally described [10, 11].

Macroscopic infarcts were identified from cerebral hemispheres, brainstem and cerebellum slices. Microinfarcts were analysed in the haematoxylin and eosin-stained tissue sections in six brain regions (frontal, parietal, temporal and occipital lobes, hippocampus and cerebellum) [12]. Cerebral amyloid angiopathy diagnosis was based on Congo red staining within these six regions and confirmed using immunohistochemistry against amyloid-β peptide [13]. Sections of substantia nigra stained with the haematoxylin and eosin method and sections of substantia nigra and hippocampus stained with antibodies against α-synuclein were used to screen for Lewy-related pathology [14]. If any Lewy-related pathology was detected in screened areas, the immunohistochemistry for α-synuclein was performed on cortical samples [15].

Statistical analysis

Comparisons between autopsy population with available CAIDE Dementia Risk Score ($n = 149$) and the remaining study population without dementia at baseline were performed using chi-square and t-test as appropriate. Associations of CAIDE Dementia Risk Score with neuropathological variables were assessed with ordinal or logistic regressions and association with incident dementia with Cox proportional hazard regression (age as timescale). The tangle count, amyloid-β load and cerebral amyloid angiopathy were not normally distributed and were categorized into three groups: no neuropathology, and values below or above the median level of these pathologies. Dichotomous variables were created for brain infarctions (macroscopic, microscopic and all). The presence of α-synuclein pathology was categorized into three groups: none, brain stem or limbic predominant and diffuse neocortical α-synuclein. Additional analyses were performed to investigate effects of each CAIDE Dementia Risk Score component, and

Table 1 *Characteristics of the study population without dementia at baseline*

	N	Autopsy data available	*N*	Autopsy data not available	*P*
Age at baseline, mean (SD), year	149	88.1 (2.7)	190	88.0 (2.7)	0.675
Age at death, mean (SD), year	149	92.8 (3.5)	159	91.9 (3.4)	0.021
Follow-up time, mean (SD), year	149	4.7 (2.5)	159	3.7 (2.3)	<0.001
Women, *N.* (%)	149	121 (81.2%)	190	145 (76.3%)	0.277
Education, mean (SD), year	149	4.3 (2.9)	186	4.2 (2.9)	0.912
Systolic blood pressure, mean (SD), mmHg	149	154.5 (23.8)	184	156.2 (28.7)	0.563
Diastolic blood pressure, mean (SD), mmHg	149	84.5 (12.2)	184	82.6 (11.8)	0.148
Cholesterol, mean (SD), mmol L^{-1}	149	5.8 (1.3)	167	5.6 (1.3)	0.102
Low-density lipoprotein, mmol L^{-1}	137	3.8 (1.1)	157	3.7 (1.2)	0.533
High-density lipoprotein, mmol L^{-1}	149	1.0 (0.3)	166	1.0 (0.3)	0.268
Triglycerides, mmol L^{-1}	149	2.2 (1.4)	166	1.9 (1.0)	0.018
Obesity, *N.* (%)[a]	149	34 (22.8%)	189	39 (20.6%)	0.628
Physical activity (inactive), *N.* (%)	149	97 (65.1%)	187	122 (65.2%)	0.979
*APOE*ε4, *N.* (%)	149	30 (20.1%)	181	39 (21.5%)	0.753
CAIDE Dementia Risk Score, mean (SD)	149	11.9 (2.0)	158	12.0 (1.0)	0.966
CAIDE Dementia Risk Score without APOE, mean (SD)	149	9.9 (1.9)	158	9.7 (1.7)	0.558
Dementia at death, *N.* (%)	149	55 (36.9%)	190	46 (24.2%)	0.011

APOE, apolipoprotein E genotype, CAIDE, Cardiovascular Risk Factors, Aging and Dementia Study.
[a]Obesity was defined here as body mass index (BMI) ≥28 as previously described [29].

also diastolic blood pressure, triglycerides, HDL and LDL on neuropathological outcomes. As elevated homocysteine was previously related to neuropathology in the Vantaa 85 + study [7], further analyses were conducted to assess the links between CAIDE Dementia Risk Score and neuropathological outcomes according to homocysteine values above or below the cut-off of 20 μmol L^{-1} [16]. We used Stata software for the analysis.

Results

Associations between baseline CAIDE Dementia Risk Score and neuropathological measurements are shown in Table 2. Individuals with higher CAIDE Dementia Risk Score tended to have higher risk of cerebral infarcts ($P = 0.08$). This association was most evident in participants with CAIDE Dementia Risk Score above 11 points ($n = 93$) compared with below 11 points ($n = 56$): OR (95% CI) was 2.10 (1.06–4.16; $P = 0.035$). Individuals with higher CAIDE Dementia Risk Score and homocysteine >20 μmol L^{-1} tended to have higher risk of amyloid-β load: OR (95% CI) was 1.26 (0.96–1.65), $P = 0.099$. No association between CAIDE Dementia Risk Score and incident dementia was found (hazard ratio (95% confidence interval) was 1.03 (0.92–1.17)). CAIDE Dementia Risk Score without APOE was not associated with neuropathological outcomes (results not shown).

Among individual CAIDE Dementia Risk Score components, there were more amyloid-β accumulation and NFT in *APOE*ε4 carriers compared with noncarriers (Table 2). Elevated triglycerides were associated with increased NFT count and more severe Braak stage at death. Furthermore, higher HDL was related to less severe Braak stage and amyloid-β accumulation (Table 3).

Discussion

Our results indicated that a higher CAIDE Dementia Risk Score was associated with increased cerebral infarcts risk over 10 years in the oldest old. No associations with NFT burden, amyloid-β load or incident dementia were found. The CAIDE

Table 2 *Association of CAIDE Dementia Risk Score with neuropathology (OR, 95% CI)*[a]

	Continuous	Dichotomous (cut-off > 11)
Tangle count	1.03 (0.88–1.21)	0.64 (0.34–1.22)
Braak stage	*1.15 (0.98–1.34)*	0.92 (0.50–1.68)
Amyloid-β load	1.13 (0.97–1.33)	1.01 (0.54–1.87)
CERAD score	1.12 (0.95–1.33)	0.96 (0.49–1.87)
Cerebral amyloid angiopathy	1.06 (0.90–1.24)	0.77 (0.31–1.46)
Cerebral macroinfarcts	1.11 (0.94–1.32)	1.62 (0.82–3.21)
Cerebral microinfarcts	1.21 (0.96–1.53)	2.01 (0.76–5.59)
All cerebral infarcts	*1.17 (0.98–1.40)*	**2.10 (1.06–4.16)**
α-synuclein pathology	1.05 (0.87–1.27)	0.76 (0.35–1.66)

CERAD, The Consortium to Establish a Registry for Alzheimer's Disease.
[a]One hundred and fourty nine participants without dementia at baseline had available data on CAIDE Dementia Risk Score at baseline. Significant results ($P < 0.05$) are in bold, and trends ($P < 0.10$) are in italics.

Dementia Risk Score is so far the only validated dementia risk estimation tool used to select participants in a successful cognitive decline prevention trial testing a multidomain lifestyle intervention [1]. Given the increasing interest in adapting and testing this prevention model worldwide [17], it is essential to determine the full range of properties of the CAIDE Dementia Risk Score.

Because CAIDE Dementia Risk Score is mainly based on vascular risk factors, associations with cerebral infarcts may not be surprising. Furthermore, a dose–response relationship between APOE genotype and stroke has been shown [18], which may partly explain the observed stronger association with the CAIDE Dementia Risk Score including APOE. Our findings add to previous reports linking higher CAIDE Dementia Risk Score to more severe white matter lesions on MRI [4, 5].

While higher CAIDE Dementia Risk Score has been previously linked to lower grey matter and hippocampal volume, lower cortical thickness and more severe MTA on MRI [4, 5], associations with markers of amyloid accumulation seem to be context-dependent. Higher midlife CAIDE Dementia Risk Score did not predict late-life brain amyloid accumulation on PIB-PET scans in individuals from the general population [5], although a cross-sectional association with lower amyloid/tau ratio in CSF was reported in memory clinic patients without dementia [6].

CAIDE Dementia Risk Score did not predict dementia in the present study. This is in line with previous reports of differences between midlife versus late-life risk profiles for dementia [2, 19]. Risk factors such as blood pressure, BMI and cholesterol tend to decline after midlife in individuals who develop dementia later on [20]. Several studies have shown that midlife risk scores tend to perform poorly when applied to older age groups [21, 22]. CAIDE Dementia Risk Score was formulated based on midlife risk profile, while the Vantaa 85 + population was ≥85 years at baseline. A late-life risk score may perform better in this age group regarding both dementia and pathology prediction.

Our findings indicated a relationship between higher HDL and less severe Braak stage and less amyloid-β accumulation. Also, elevated triglycerides were associated with more NFT and more severe Braak stage. This is in line with previous studies showing associations of lower HDL and higher triglycerides with increased risk of neuritic plaques [23] and lower HDL levels with amyloid accumulation on PIB-PET scans [24]. Although other studies reported conflicting findings [21, 22], potentially due to differences in populations and designs, such blood markers would merit further testing as potential candidates in neuropathology prediction models. Another potential candidate would be, for example, homocysteine, which was previously associated with AD pathology in the Vantaa 85 + population [7], as well as dementia risk in several studies [25].

The major strength of this study is the prospective population-based design with comprehensive autopsy data and inclusion of participants aged

Table 3 *Associations of individual components of CAIDE Dementia Risk Score and other vascular factors at baseline with neuropathological outcomes (OR, 95% CI)*[a]

	Tangle count	Braak stage	Amyloid-β load	CERAD score	All cerebral infarcts
Age at death (n = 163)	1.01 (0.91–1.12)	1.02 (0.92–1.12)	0.95 (0.86–1.05)	0.96 (0.87–1.05)	1.04 (0.93–1.16)
Female (n = 163)	1.01 (0.49–2.11)	1.26 (0.61–2.59)	0.73 (0.35–1.55)	0.73 (0.35–1.53)	0.96 (0.43–2.15)
Education (n = 160)	1.02 (0.92–1.12)	0.97 (0.88–1.07)	1.03 (0.93–1.13)	1.05 (0.94–1.17)	0.97 (0.87–1.08)
Systolic blood pressure (n = 161)	0.99 (0.98–1.01)	1.0 (0.99–1.01)	1.00 (0.99–1.02)	1.00 (0.99–1.01)	1.00 (0.99–1.01)
Diastolic blood pressure (n = 161)	0.98 (0.96–1.01)	0.99 (0.97–1.02)	1.00 (0.98–1.02)	0.99 (0.97–1.02)	1.00 (0.98–1.03)
Obesity (n = 162)	0.87 (0.61–1.25)	1.00 (0.70–1.42)	0.76 (0.39–1.51)	0.74 (0.35–1.59)	1.83 (0.82–4.08)
Cholesterol (n = 153)	1.20 (0.92–1.55)	1.19 (0.93–1.53)	1.03 (0.80–1.32)	1.18 (0.91–1.54)	1.00 (0.77–1.30)
High-density lipoprotein (n = 153)	0.42 (0.14–1.27)	**0.23 (0.08–0.66)**	*0.40 (0.13–1.19)*	0.50 (0.16–1.61)	0.45 (0.14–1.51)
Low-density lipoprotein (n = 141)	1.19 (0.87–1.62)	1.16 (0.86–1.56)	1.04 (0.77–1.40)	1.15 (0.83–1.58)	1.01 (0.73–1.40)
Triglycerides (n = 153)	**1.31 (1.03–1.65)**	**1.33 (1.08–1.63)**	1.15 (0.92–1.44)	1.20 (0.96–1.52)	1.09 (0.86–1.38)
Physical inactivity (n = 161)	0.80 (0.43–1.46)	1.41 (0.79–2.52)	0.77 (0.42–1.40)	0.98 (0.58–1.66)	1.23 (0.64–2.35)
*APOE*ε4 (n = 160)	**3.30 (1.59–6.83)**	**2.52 (1.25–5.07)**	**9.07 (3.64–22.63)**	**4.38 (1.89–10.14)**	1.37 (0.62–3.02)

CERAD, The Consortium to Establish a Registry for Alzheimer's Disease, APOE, apolipoprotein E genotype.
[a]All analyses adjusted only for follow-up time, significant results ($P < 0.05$) are in bold, and trends ($P < 0.10$) are in italics. Only participants without dementia at baseline are included in analyses.

≥85 years. Although few studies have investigated the impact of CAIDE Dementia Risk Score on Alzheimer- and cerebrovascular-type neuropathology, none had a longitudinal design with autopsy data. However, selective survival may contribute to underestimating associations with cerebral infarcts, because individual components of CAIDE Dementia Risk Score are associated with increased mortality [26]. Although clinical dementia diagnoses were shown to correlate well with brain autopsy findings in the Vantaa 85+ study [7], association between brain pathologies and dementia is known to be more complex in older compared with younger elderly [27]. Quantitative, systematic methods were used in our study to identify neuropathological changes, but due to the use of traditional silver staining methods, there may be differences compared with studies using immunohistochemistry [28].

In conclusion, CAIDE Dementia Risk Score was related to cerebral infarcts, but not amyloid-β load or NFT count. Different risk scores will need to be developed if the aim is to predict dementia, amyloid or tangle accumulation in the oldest old.

Acknowledgement

This work was supported by Academy of Finland (278457, 287490, 294061), ALF Grants (20130507, 20150589), Alzheimerfonden (Sweden), Center for Innovative Medicine (CIMED) at Karolinska Institute South Campus, Knut and Alice Wallenberg Foundation (Sweden), Stiftelsen Stockholms Sjukhem (Sweden), Konung Gustaf V:s och Drottning Victorias Frimurarstiftelse (Sweden), Loo och Hans Ostermans Stiftelse, Stiftelsen för åldressjukdomar vid Karolinska Institutet and Tore Nilsons Stiftelse För Medicinsk Forskning. The funding

sources had no involvement in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Author contributions

Dr Hooshmand had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Hooshmand, Polvikoski, Kivipelto and Solomon conceived and designed the study. Hooshmand, Polvikoski, Kivipelto, Tanskanen, Myllykangas, Mäkelä, Oinas, Paetau and Solomon participated in acquisition, analysed and interpreted the data. Hooshmand, Polvikoski, Kivipelto and Solomon drafted the manuscript. All authors critically revised the manuscript for important intellectual content. Hooshmand, Kivipelto and Solomon performed statistical analysis. Hooshmand, Kivipelto and Solomon obtained funding. All authors contributed to administrative, technical or material support. Hooshmand, Polvikoski, Kivipelto, Myllykangas and Solomon supervised the study.

Conflict of interest statement

No conflict of interest to declare.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. CAIDE Dementia Risk Score versions used in the study and number of points[1].■

