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Association of hippocampal calcification and cardiovascular risk factors in two patient cohorts

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HIGHLIGHTS

- Older age is a risk factor for presence and severity of hippocampal calcification
- Other cardiovascular risk factors are not associated with hippocampal calcification
- A cumulative risk score was not associated with hippocampal calcification
- These results are new and unexpected compared to other calcification locations

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ABSTRACT

Background and aims: Hippocampal calcification is a recently described type of intracranial calcification and might be a risk factor for ischemic stroke and dementia. Data on its risk factors and insight into the etiology are limited. We aimed to investigate the association of risk factors for hippocampal calcification in two independent cohorts in the Netherlands.

Methods: Unenhanced CT scans of the brain were scored for the presence and severity of hippocampal calcification in two independent prospectively collected patient cohorts, the first consisting of aneurysmal subarachnoid hemorrhage (SAH) patients (N = 741) and the second of patients participating in the Second Manifestation of ARTerial disease (SMART) study (N = 498). We estimated the association of the risk factors age, sex, smoking, dyslipidemia, overweight, hypertension, diabetes, family history, cardiac history, cerebrovascular history, use of vitamin K antagonists and renal disease with the presence and moderate/severe calcification using logistic regression analysis.

Results: In both cohorts, age ≥60 years was associated with the presence of hippocampal calcification (odds ratio (OR) 2.47, 95% confidence interval (CI) 1.37–4.45 in SAH and OR 1.91, 95% CI 1.30–2.82 in SMART); in SMART, age was associated with moderate/severe calcification as well (OR 2.77, 96%CI 2.77 (1.36–3.65). All other risk factors, including a cumulative risk score of 5 or more risk factors, did not show any association with hippocampal calcification presence or severity.

Conclusions: We identified age as a risk factor for hippocampal calcification. All other risk factors studied were not associated with hippocampal calcification. This contradicts findings on arterial calcifications elsewhere in the body. Therefore, more research is needed to understand this discrepancy.

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1. Introduction

Hippocampal calcification is a type of intracranial calcification, which has only recently been described *in vivo,* and was found to be located in precapillaries, capillaries and arteries, mostly in the tail of the hippocampus [1]. This type of calcification is commonly observed in patients above 50 years of age [2]. Scoring of these calcifications on computed tomography (CT) has been validated with histology [1], which means that these calcifications can be detected *in vivo* with CT and that risk factors and outcome can be investigated in cohort studies. The importance of hippocampal calcification on health is not completely clarified. Limited studies focused on the correlation between hippocampal calcification and cognitive decline, where one study showed an association, while in another study, no association was found [3,4]. In contrast, intracranial arterial calcification in general is known to be an independent risk factor for ischemic stroke [5]. While calcifications are widely used as a marker for atherosclerosis [6], intracranial calcifications, including hippocampal calcifications, are not always atherosclerotic in origin [7], raising the question of how these calcifications contribute to stroke. Two recent studies focused on the risk factors of hippocampal calcification, showing, besides age, an association with diabetes [8,9], hyperlipidemia [8] and smoking [9], but the studies were executed in selected patient groups and accounted for a limited number of risk factors.

Risk factors for arterial calcification are studied more extensively for coronary artery calcification and carotid artery calcification. For these different locations of artery calcification, classic cardiovascular risk factors as age [10–12], male sex [12,13], body mass index (BMI) [12–14], hypertension [10,14], hypercholesterolemia [15,16], diabetes [6,17], smoking [12,14] and cardiac history [5,10] were significantly associated with (severe) calcification. For coronary artery calcification, in addition, other calcification risk factors have been identified, like vitamin D deficiency [18,19], chronic kidney disease and renal failure [20,21], use of vitamin K antagonists [22,23], non-alcoholic fatty liver disease [24] and ethnicity [13,16]. For excessive alcohol use (> 20 g/day), results are contradicting [10].

Given the limited data and insights into the etiology of hippocampal calcification, we aimed to investigate the association of risk factors with hippocampal calcification in two independent cohorts of cardiovascular patients in the Netherlands.

2. Patients and methods

2.1. Study population

Two different cohorts are used in this study. The first cohort included a prospectively collected cohort of patients with a subarachnoid hemorrhage (SAH) from an intracranial aneurysm, admitted to the Neurology department of the University Medical Center Utrecht (UMCU), the Netherlands, between 2002 and 2010. In these patients, an unenhanced CT was performed upon admittance to confirm the diagnosis, and in case of neurological deterioration during the admission. In case multiple CT scans were performed, the most recent scan was evaluated. This cohort will be further indicated as the SAH cohort. The second cohort included patients from the Second Manifestation of ARTerial disease (SMART) study [25], a single center prospective cohort study including patients aged 18–80 newly referred to the UMCU with (1) clinically manifest atherosclerotic vessel disease, or (2) marked risk factors for atherosclerosis. We included patients between 2004 and 2016, who underwent an unenhanced CT-scan of the brain for clinical indications, for example in case of clinical symptoms of stroke or transient ischemic attack, within 6 months of the SMART inclusion date. No iterative CT scans were performed within this timeframe. In both cohorts, patients with non-evaluable scans were excluded due to technical limitations (i.e. slice thickness > 1 mm, acquisition artefacts as coiled aneurysms, images not retrievable from the hospital archive). Ethical approval of the study protocol is obtained from the Medical-ethical committee of the UMCU. Written consent was obtained from each patient in this study.

2.2. Imaging

Hippocampal calcification was reviewed on non-enhanced CT of the brain using multi-detector row scanners (16–256 detector rows, Philips Healthcare, Cleveland, Ohio). Scans were analyzed using the 0.625–1 mm slices in axial, coronal and sagittal plane in brain window setting using Sectra IDS 7 (Sectra AB, Sweden) by trained researchers MP and MvdK, who were blinded for the risk factors. Complex cases were discussed in a consensus meeting with an experienced radiologist (PdJ). Hippocampal calcification was scored bilaterally as absent, mild (one dot), moderate (multiple dots) or severe (confluent) as described before [3] (Fig. 1).

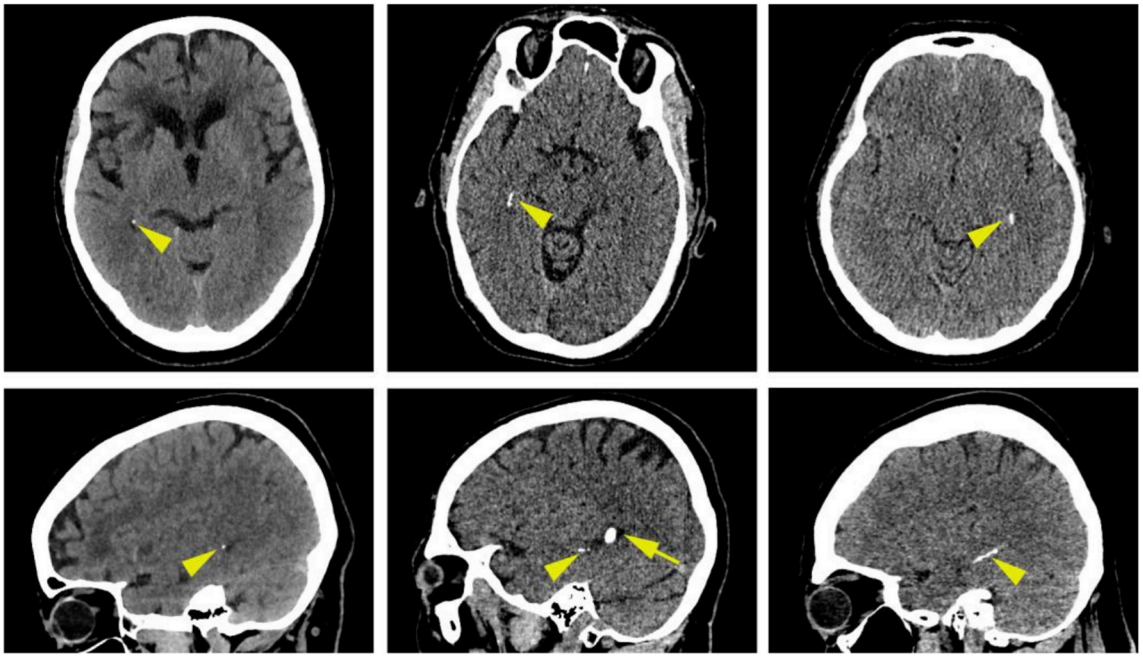

Fig. 1. Examples of mild, moderate and severe hippocampal calcifications on computed tomography (CT).
Hippocampal calcification on thin unenhanced CT examinations (arrowheads), left image mild calcification, middle moderate, right severe. Arrow: choroid plexus calcification.

2.3. Risk factor definitions

In this study, the following risk factors were investigated: age, sex, smoking, dyslipidemia, overweight, hypertension, diabetes, family history, cardiac history, cerebrovascular history, use of vitamin K antagonists and renal disease. Age was analyzed as continuous variable and dichotomized in < 60 and ≥60 years. Smoking was categorized into ever and never smokers. Dyslipidemia was defined as total cholesterol > 6.5 mmol/l and/or HDL < 1.0 mmol/l and/or statin use. Use of antihypertensives and/or clinical diagnosis and/or systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg was scored as hypertension. Diabetes was defined as present in the case of use of antidiabetic drugs and/or fasting glucose > 7.0 mmol/l and/or clinical diagnosis. Family history was scored as positive when a family member was diagnosed with cardiovascular disease or a stroke below the age of 65. A myocardial infarction and/or angina pectoris and/or cardiac bypass/stent operation in the previous medical history was scored as a positive cardiac history. A positive cerebrovascular history was defined as ischemic stroke and/or transient ischemic attack in the previous medical history. The use of vitamin K antagonists was scored positive in case of the use of acenocoumarol or fenprocoumon. In the SAH cohort a BMI > 25 kg/m^2 and/or clinical diagnosis of overweight or obesity was defined as overweight, while in the second SMART cohort only a BMI > 25 kg/m^2 was used for the definition. In the SAH cohort renal disease was defined as clinical diagnosis end stage chronic kidney disease and/or kidney failure and/or dialysis and/or glomerular filtration rate (GFR) < 30 mL/min; in the SMART cohort renal disease was defined as a GFR < 30 mL/min.

2.4. Data analysis

Data analysis was performed with IBM SPSS Statistics 22. The baseline characteristics of the two cohorts were compared using Student's t-test for the continuous variable age and chi-square test for all categorical variables. Age difference between the group with (severe) calcification and the group without (severe) calcification was assessed using the Student's t-test. The association of the dichotomous risk factors with hippocampal calcification was assessed by univariable logistic regression analysis to calculate crude odds ratio's (OR) with corresponding 95% confidence intervals (CI). Multivariable logistic regression was used to adjust for possible confounding by age and sex. The presence *versus* absence of hippocampal calcification as well as moderate/severe calcification *versus* none/mild calcification was assessed. As an additional analysis, we also tested the association of a cumulative risk score of all the risk factors, excluding age and sex, with hippocampal calcification. This cumulative risk score was dichotomized in the presence of < 5 or ≥5 risk factors. Missing data (shown in Supplementary Table 1) were imputed using multiple imputation, with 10 iterations.

2.5. Power calculation

The sample size of both the SAH and the SMART cohort is based on our inclusion criteria and includes 741 and 498 patients, respectively. Based on our sample size and an estimation of 10% prevalence of hippocampal calcification based on previous literature [2,8,9], we calculated the detectable OR of a risk factor on hippocampal calcification, using significance level $\alpha = 0.05$ and power $\beta = 0.80$.

In the SAH cohort, for risk factors with a prevalence of 50%, which is expected for smoking, hypertension and older age, our study was powered to detect an association of the risk factor with an OR ≥ 1.86. For risk factors with a prevalence of 5% (expected for kidney failure and diabetes), we are able to detect an OR ≥ 3.05. Since the SMART cohort is a cardiovascular risk cohort, we expect higher prevalences of risk factors. Assuming a prevalence of 70%, we are able to detect an OR ≥ 2.34. For risk factors with a prevalence of 50% our study is powered to detect an OR ≥ 2.11, and when the prevalence is 10% we can detect an OR ≥ 2.81.

3. Results

In the SAH cohort, 741 patients were included, while in the SMART cohort, 498 patients were included. Of the 741 patients of the SAH cohort, 51 (6.9%) patients had uni- or bilateral hippocampal calcification, compared to 153 of the 498 (30.5%) patients of the SMART cohort. The baseline characteristics of all patients are shown in Table 1. Upon comparing these characteristics between the two cohorts, the prevalence of all risk factors, except age and smoking, and the presence of mild and moderate hippocampal calcification are higher in the SMART cohort.

3.1. SAH cohort

In the SAH cohort, age was associated with hippocampal calcification. The mean age was higher in the group with calcification (62 ± 12 yr) compared to the group without calcification (56 ± 11 yr, $p < 0.001$), while in patients of 60 years or older, hippocampal calcification was present more often (10.9%) than in patients younger than 60 years (4.5%; adjusted OR 2.39, 95% CI 1.33–4.31). For the group with moderate/severe calcification, the mean age was higher (63 ± 9 yr) compared to the group with none/mild calcification (56 ± 11 yr, $p < 0.005$). We were not able to demonstrate a statistically significant association of all other calcification risk factors, sex, lipid disorder, overweight, smoking, family history, hypertension, diabetes, cardiac history, ischemic stroke history, vitamin K antagonist use, and kidney disorder, with the presence or severity of hippocampal calcification (Tables 2 and 3). In addition, we did not find a statistically significant association of the cumulative risk score of all risk factors with hippocampal calcification (Tables 2 and 3).

To further examine the influence of age on the presence of hippocampal calcification, the cumulative prevalence of hippocampal calcification as a function of age was studied, which showed an increasing prevalence of hippocampal calcification above the age of 45 (Fig. 2A).

Table 1
Baseline characteristics.

Characteristic	SAH cohort *n* (%)	SMART cohort *n* (%)	Comparison SAH-SMART (*p*-value)
No. of patients	741	498	
Age (mean ± SD) yr	56 ± 11	57 ± 11	0.12
Age ≥60yr	275 (37.1%)	226 (45.4%)	**0.004**
Male sex	223 (30.1%)	284 (57.0%)	< **0.0001**
Lipid disorder	255 (34.4%)	375 (75,2%)	< **0.0001**
Overweight	281 (37.9%)	272 (54.6%)	< **0.0001**
Smoking	508 (68.6%)	348 (69.8%)	0.65
Family history	209 (28.2%)	180 (36.2%)	**0.0029**
Hypertension	342 (46.2%)	342 (68.6%)	< **0.0001**
Diabetes	39 (5.2%)	59 (11.8%)	< **0.0001**
Cardiac history	43 (5.9%)	82 (16.2%)	< **0.0001**
Ischemic stroke history	45 (6.1%)	410 (82.3%)	< **0.0001**
Vit K antagonist use	22 (3.0%)	58 (11.6%)	< **0.0001**
Kidney failure	15 (2.1%)	2 (0.3%)	**0.008**
Cumulative risk ≥5	68 (9.2%)	209 (42.0%)	< **0.0001**
Calcification presence	51 (6.9%)	152 (30.5%)	< **0.0001**
None	690 (93.1%)	346 (69.5%)	< **0.0001**
Mild	34 (4.6%)	111 (22.3%)	< **0.0001**
Moderate	8 (1.1%)	38 (7.6%)	< **0.0001**
Severe	9 (1.2%)	2 (0.6%)	0.29

SAH = subarachnoid hemorrhage; SD = standard deviation; SMART = second manifestation of arterial disease study.
Bold = significant difference on $\alpha < 0.005$.

Table 2
Influence of risk factors on presence of hippocampal calcification in two cohorts.

Risk factor	SAH cohort				SMART cohort			
	HC *n* (%)	No HC *n* (%)	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)	HC *n* (%)	No HC *n* (%)	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Age ≥ 60 yr	30 (10.9%)	21 (4.5%)	**2.60 (1.45–4.63)**	**2.39 (1.33–4.31)**	86 (38.1%)	66 (24.2%)	**1.92 (1.30–2.82)**	**1.91 (1.30–2.82)**
Male sex	14 (6.3%)	37 (7.1%)	0.87 (0.46–1.65)	0.88 (0.46–1.71)	89 (31.3%)	63 (29.4%)	1.09 (0.74–1.61)	0.98 (0.66–1.46)
Lipid disorder	23 (8.9%)	28 (5.8%)	1.59 (0.86–2.97)	1.25 (0.66–2.38)	118 (31.5%)	34 (27.6%)	1.21 (0.77–1.90)	0.97 (0.60–1.56)
Overweight	21 (7.4%)	30 (6.5%)	1.14 (0.58–2.25)	1.02 (0.49–2.15)	85 (31.3%)	67 (29.6%)	1.08 (0.74–1.58)	1.10 (0.74–1.63)
Smoking	33 (6.5%)	18 (7.6%)	0.85 (0.45–1.61)	1.07 (0.53–2.12)	107 (30.8%)	45 (29.9%)	1.04 (0.69–1.58)	1.02 (0.66–1.55)
Family history	12 (5.7%)	39 (7.4%)	0.76 (0.35–1.65)	0.73 (0.33–1.60)	58 (32.2%)	94 (29.6%)	1.13 (0.76–1.67)	1.12 (0.75–1.68)
Risk factor	HC *n* (%)	No HC *n* (%)	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)	HC *n* (%)	No HC *n* (%)	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Hypertension	28 (8.2%)	23 (5.8%)	1.45 (0.82–2.58)	1.20 (0.66–2.16)	110 (32.2%)	42 (26.9%)	1.29 (0.85–1.97)	1.09 (0.71–1.69)
Diabetes	4 (10.3%)	47 (6.7%)	1.61 (0.55–4.74)	1.06 (0.35–3.22)	22 (37.3%)	130 (29.6%)	1.41 (0.80–2.49)	1.21 (0.68–2.16)
Cardiac history	6 (13.8%)	45 (6.5%)	2.33 (0.93–5.83)	1.29 (0.45–3.71)	25 (30.9%)	127 (30.4%)	1.02 (0.61–1.72)	0.87 (0.51–1.49)
Ischemic stroke history	5 (11.0%)	46 (6.6%)	1.75 (0.66–4.65)	1.21 (0.44–3.34)	125 (30.5%)	27 (30.7%)	0.99 (0.60–1.63)	0.97 (0.58–1.62)
Vit K antagonist use	5 (22.6%)	46 (6.4%)	**4.30 (1.49–12.49)**	2.95 (0.97–8.96)	18 (31.0%)	134 (30.5%)	1.03 (0.57–1.86)	0.89 (0.48–1.63)
Kidney disorder	2 (13.2%)	49 (6.8%)	2.10 (0.46–9.59)	2.27 (0.47–10.88)	1 (66.7%)	151 (30.4%)	NA	NA
Cumulative risk ≥ 5	8 (11.9%)	43 (6.4%)	1.96 (0.77–5.00)	1.28 (0.45–3.62)	69 (33.0%)	83 (28.7%)	1.22 (0.83–1.79)	1.07 (0.72–1.60)

95% CI = 95% confidence interval; bolt = significant result; HC = hippocampal calcification; NA = not applicable; OR = odds ratio; SAH = subarachnoid hemorrhage; SMART = second manifestation of arterial disease study.
[a] Adjusted for age, sex and unadjusted significant risk factors.

Table 3
Influence of risk factors on moderate/severe hippocampal calcification in two cohorts.

Risk factor	SAH cohort				SMART cohort			
	HC *n* (%)	No HC *n* (%)	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)	HC *n* (%)	No HC *n* (%)	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Age ≥60 yr	7 (2.5%)	10 (2.1%)	1.19 (0.45–3.17)	0.98 (0.34–2.81)	29 (12.8%)	12 (4.4%)	**3.19 (1.59–6.41)**	**2.76 (1.41–5.39)**
Male sex	5 (2.2%)	12 (2.3%)	0.97 (0.34–2.78)	1.06 (0.37–3.07)	31 (10.9%)	10 (4.7%)	**2.50 (1.20–5.22)**	**2.11 (1.44–3.09)**
Lipid disorder	6 (2.4%)	11 (2.2%)	1.06 (0.36–3.10)	0.86 (0.29–2.55)	31 (8.3%)	10 (8.1%)	1.02 (0.49–2.15)	0.59 (0.27–1.31)
Overweight	7 (2.3%)	11 (2.3%)	1.00 (0.31–3.21)	0.91 (0.27–3.02)	21 (7.7%)	20 (8.8%)	0.86 (0.46–1.63)	0.77 (0.55–1.08)
Smoking	9 (1.7%)	8 (3.5%)	0.48 (0.17–1.37)	0.58 (0.19–1.70)	27 (7.8%)	14 (9.3%)	0.82 (0.42–1.61)	0.74 (0.37–1.48)
Family history	4 (2.0%)	13 (2.4%)	0.82 (0.23–2.90)	0.83 (0.24–2.91)	13 (7.2%)	28 (8.8%)	0.80 (0.41–1.59)	0.84 (0.42–1.70)
Risk factor	HC *n* (%)	No HC *n* (%)	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)	HC *n* (%)	No HC *n* (%)	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Hypertension	6 (1.8%)	11 (2.8%)	0.63 (0.23–1.72)	0.53 (0.19–1.47)	35 (10.2%)	6 (3.8%)	**2.88 (1.19–6.99)**	2.15 (0.87–5.31)
Diabetes	3 (7.8%)	14 (2.0%)	4.14 (1.13–15.11)	3.06 (0.81–11.55)	6 (10.2%)	35 (8.0%)	1.31 (0.53–3.25)	0.80 (0.49–1.29)
Cardiac history	1 (2.3%)	16 (2.3%)	1.01 (0.13–7.77)	0.72 (0.09–5.73)	6 (7.4%)	35 (8.4%)	0.87 (0.36–2.13)	0.52 (0.21–1.33)
Ischemic stroke history	1 (2.2%)	16 (2.3%)	0.96 (0.12–7.38)	0.65 (0.08–5.20)	34 (8.3%)	7 (8.0%)	1.05 (0.45–2.44)	1.21 (0.55–2.65)
Vit K antagonist use	1 (4.5%)	16 (2.2%)	2.09 (0.26–16.61)	1.37 (0.16–11.54)	7 (12.1%)	34 (7.7%)	1.64 (0.69–3.89)	1.05 (0.43–2.59)
Kidney disorder	0 (0%)	17 (2.3%)	NA	NA	0 (0%)	41 (8.3%)	NA	NA
Cumulative risk ≥5	3 (3.7%)	15 (2.2%)	1.70 (0.39–7.48)	1.36 (0.30–6.13)	16 (7.6%)	25 (8.7%)	0.87 (0.45–1.68)	0.63 (0.32–1.25)

95% CI = 95% confidence interval; bolt = significant result; HC = hippocampal calcification; NA = not applicable; OR = odds ratio; SAH = subarachnoid hemorrhage; SMART = second manifestation of arterial disease study.
[a] Adjusted for age, sex and unadjusted significant risk factors.

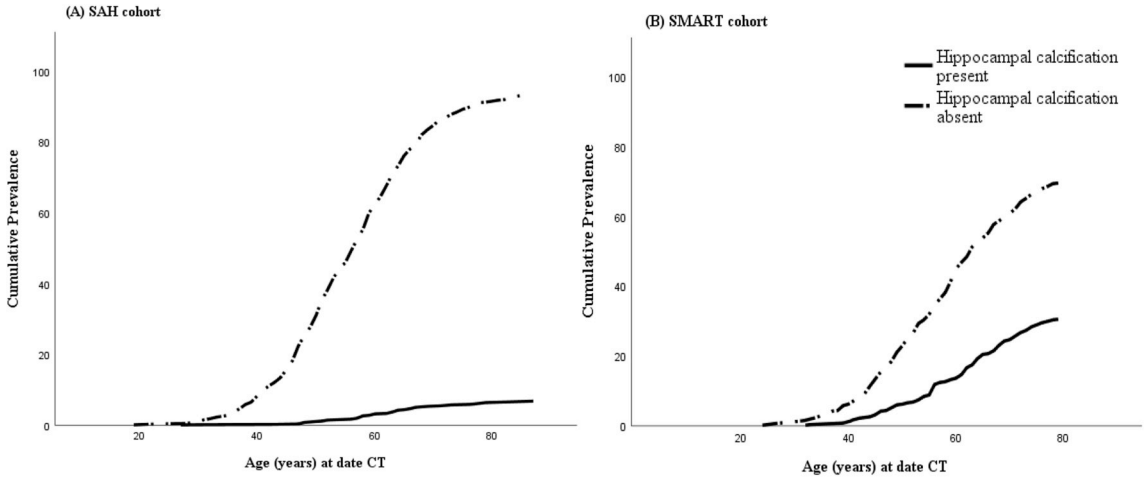

Fig. 2. Cumulative percentage of hippocampal calcification presence and absence as a function of age at date of computed tomography (CT) for both cohorts. (A) Subarachnoid hemorrhage (SAH) cohort. (B) Second manifestation of ARTerial disease study (SMART) cohort.

3.2. SMART cohort

In the SMART cohort, we also found that age was associated with hippocampal calcification, with the mean age being higher in the group with calcification present (60 ± 11 yr) compared to the group without calcification (56 ± 12 yr, $p < 0.001$) and patients ≥60 years having more often hippocampal calcification (38.1%) than patients < 60 years (24.2%; adjusted OR 1.91, 95% CI 1.30–2.82). In this cohort, age was associated with calcification severity as well, with the mean age being higher in patients with moderate/severe calcification (63 ± 9 yr) compared to those with none/mild calcification (57 ± 11 yr, $p = 0.001$) and patients ≥60 years having moderate/severe calcification more often (12.8%) than patients < 60 years (4.4%; adjusted OR 2.76, 95% CI 1.41–5.39). The relationship between age and hippocampal calcification is shown graphically in Fig. 2B, indicating an increase in prevalence starting at age 40. Male sex was not associated with the presence of calcification, but was associated with the presence of moderate/severe calcification, with more men (10.9%) than women (4.7%) having moderate/severe calcification (adjusted OR 2.11, 95% CI 1.44–3.09). For all other risk factors, including for the cumulative risk score of all the risk factors, no significant association with hippocampal calcification was found (Tables 2 and 3).

4. Discussion

In two cohorts of patients after subarachnoid hemorrhage and patients with increased cardiovascular risk, we found that increasing age was associated with both the presence of hippocampal calcification and the presence of moderate/severe hippocampal calcification. The graphical display suggests the increase in prevalence starts at age 40 and increases substantially over the years. No consistent associations were observed with the presence of hippocampal calcification for all other factors sex, lipid disorder, overweight, smoking, family history, hypertension, diabetes, cardiac history, ischemic stroke history, vitamin K antagonist use, and kidney disorder, previously established as risk factor for other types of arterial calcification, being coronary artery calcification [6,12–15,17,20–23] and carotid artery calcification [5,10,11,17,20,21]. For the cumulative risk score of five or more of these risk factors, no association with hippocampal calcification could be established, strengthening our conclusions.

The influence of age reflects previous studies on hippocampal calcification. The first study on hippocampal calcification, a retrospective cohort study with 300 patients ranging in age from 0 to 99, found a prevalence of 21.7% in patients older than 50 years while no calcification was found in younger subjects [2]. To the best of our knowledge, there are two previous, recent papers on other risk factors of hippocampal calcification besides age. The first study, a prospective multicenter cohort study of 1130 patients of 18 years and older, which had an ischemic stroke, found an association between hippocampal calcification and the risk factors age, diabetes and hyperlipidemia, but no association was found with sex, stroke history, hypertension, family history, smoking, BMI and GFR [8]. The second study, a retrospective cohort study of 1991 patients ranging in age from 45 to 96, who were referred to a memory clinic with cognitive complaints, found age, diabetes, and smoking to be related to hippocampal calcification, while hypertension and hyperlipidemia were not [9]. We have no clear explanation for the discrepancies in the findings on diabetes and smoking. For hyperlipidemia, different definitions were used between different studies, which may explain why in one study an association was found with hippocampal calcifications while others did not. Besides the comparison with other studies on hippocampal calcification, it is interesting to remark the discrepancy in risk factors for hippocampal calcification compared to those for arterial calcifications elsewhere in the body, being the coronary arteries and the carotid arteries. While we found no association of all risk factors studied besides age, all these risk factors are quite undisputed risk factors for calcification of the coronary arteries and the carotid arteries [10–17,20–23]. This suggests that pathophysiology differs between different locations of calcification, which might lead to different optimal treatment options in the prevention of intracranial calcification, if any treatment would be needed.

A recent study validated hippocampal calcifications on CT scan with histology to be located in the adventitial and medial layer of capillaries and arterioles located in the tail of the hippocampus [1]. This might mean the calcifications we found are not atherosclerotic in origin since atherosclerosis mainly occurs in the intima layer [7], which might be a reason why some of the classic cardiovascular risk factors are not risk factors for hippocampal calcification. It has also been suggested that these calcifications are caused by hypoxia [1], with the hypoxia causing damaging of the vessel wall where calcification plaques can start forming. If so, we would expect a higher prevalence in patients with a medical history of ischemic stroke, which was not the case, although the number of these patients was small. Therefore, our results are unexpected and further investigations into the etiology of these calcifications are needed. These investigations may explain why risk factors differ between different locations of calcification.

The strength of this study relies in the large sample size of the study population, combining two different cohorts from one center where calcification was scored in the same way and using the same CT-scanner, scanning protocol and viewer. Although the sample size was large enough to detect clinically relevant ORs, the prevalence of certain risk factors was smaller than expected, causing limited power to state conclusions with certainty for these risk factors. A limitation is the cross-sectional study design, limiting the possibility to detect causal relations. In addition, the scoring of some risk factors was slightly different between the two cohorts: in the SMART cohort, overweight was defined as BMI > 25 kg/m^2 and renal disease as GFR < 30 mL/min, whereas in the SAH cohort, for these factors also the clinical diagnosis was used. However, we do not expect this difference in definitions will have much influence on our results since in the SAH cohort clinical diagnosis of renal disease without a GFR < 30 mL/min or a clinical diagnosis of overweight without a BMI > 25 km/m^2 did not occur often.

4.1. Conclusion

In conclusion, in two cohorts of cardiovascular patients, one with subarachnoid hemorrhage and the other with increased cardiovascular risk, we observed that age was an important risk factor for hippocampal calcification, while other cardiovascular risk factors were not. Our findings suggest that risk factors differ between coronary artery and carotid artery calcification on the one hand, and hippocampal calcification, on the other hand. More research on the pathophysiology of this difference and calcification in other intracranial arteries is needed.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

MJAK, CL, YMR and PAJ designed the study. MJAK, MEMP, MIG and the SMART Study Group participated in data acquisition. MJAK and YMR performed statistical analyses and participated in interpretation of the data. CL made the figure. YMG and PAJ supervised the study. MJAK drafted the article. MEMP, CL, MIG, PAJ, YMG and the SMART study group approved the final version of the manuscript before submission.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.athx.2019.100005.

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