Hippocampal Calcifications: Risk Factors and Association with Cognitive Function

Esther J. M. de Brouwer, MD • Remko Kockelkoren, MD • Jules J. Claus, MD, PhD • Annemarieke de Jonghe, MD, PhD • Mirjam I. Geerlings, PhD • Thomas E. F. Jongsma, MD • Willem P. T. M. Mali, MD, PhD • Jeroen Hendrikse, MD, PhD • Pim A. de Jong, MD, PhD • Huiberdina L. Koek, MD, PhD

From the Department of Geriatrics (E.J.M.d.B., H.L.K.), Department of Radiology (R.K., W.P.T.M.M., J.H., P.A.d.J.), and Julius Center for Health Sciences and Primary Care, Department of Epidemiology (M.I.G.), University Medical Center Utrecht, Room B05.2.25, PO Box 85500, 3508 GA Utrecht, the Netherlands; and Departments of Neurology (J.J.C.), Geriatrics (A.d.J.), and Radiology (T.E.F.J.), Tergooi Hospital, Hilversum, the Netherlands. Received November 5, 2017; revision requested January 2, 2018; final revision received March 19; accepted March 28. **Address correspondence to** E.J.M.d.B. (e-mail: *E.J.M.deBrouwer-8@umcutrecht.nl*).

Conflicts of interest are listed at the end of this article.

Radiology 2018; 288:815–820 • https://doi.org/10.1148/radiol.2018172588 • Content code: NR

Purpose: To identify risk factors for hippocampal calcifications and to investigate the association between hippocampal calcifications and cognitive function.

Materials and Methods: For this retrospective study, consecutive patients visiting a memory clinic at a Dutch general hospital between April 2009 and April 2015 were identified. All individuals underwent a standard diagnostic work-up including cognitive tests and brain CT. The following vascular risk factors were assessed: hypertension, diabetes mellitus, hyperlipidemia, and smoking. Cognitive screening consisted of the Cambridge Cognitive Examination, which includes the Mini-Mental State Examination. CT scans were analyzed for the presence and severity (absent, mild, moderate, severe) of hippocampal calcifications. One measure per patient, only the most severe score, was used. Logistic regression was used to identify risk factors for hippocampal calcifications, and linear regression was used for the association between hippocampal calcifications (patient level) and cognitive function.

Results: A total of 1991 patients (mean age, 78 years; range, 45–96 years) were included. The mean age of women was 79 years (range, 47–96 years), and the mean age of men was 77 years (range, 45–95 years). Of the 1991 patients, 380 (19.1%) had hippocampal calcifications. Older age (odds ratio [OR] per year, 1.05; 95% confidence interval [CI]: 1.03, 1.06), diabetes mellitus (OR, 1.50; 95% CI: 1.12, 2.00), and smoking (OR, 1.49; 95% CI: 1.05, 2.10) were associated with the presence of hippocampal calcifications. No associations were found between presence and severity of hippocampal calcifications and cognitive function.

Conclusion: Older age, diabetes mellitus, and smoking were associated with an increased risk of hippocampal calcifications. A greater degree of hippocampal calcifications was not associated with lower cognitive function in patients with memory complaints.

Online supplemental material is available for this article.

Dementia is a substantial health problem, with 46.8 million people having this condition worldwide (1). Dementia mostly appears to result from a combination of factors, including Alzheimer disease (AD), vascular lesions, Lewy bodies, and inflammation, which eventually lead to atrophy of the cortex and hippocampus (2). The hippocampus is an important area of interest in dementia research. Current research into hippocampal abnormalities in dementia focuses more on neurodegenerative causes and less on vascular causes. Hippocampal calcifications were first described in a pathology study in 2002 as a vasculopathy with fibrosis and calcifications with a predilection for the middle hippocampal artery (3). These calcifications can spread from the tail to the body of the hippocampus and occasionally to the head and may lead to patchy neuronal loss. Accordingly, it has been hypothesized that hippocampal calcifications may be a manifestation of vascular abnormalities that could contribute to hippocampal atrophy and, consequently, cognitive deterioration (3).

Advances in radiologic imaging have provided opportunities to explore the role of hippocampal calcifications in dementia. In a study in which multiplanar brain CT scans were used, hippocampal calcifications were frequently observed and appeared to increase with age, with hippocampal calcifications detected in more than 20% of individuals older than 50 years (4). Hippocampal calcifications may be difficult to distinguish from plexus calcifications because of the proximity of these structures, and before multiplanar CT became available, hippocampal calcifications may have been mistaken for choroidal calcifications. The literature on the association between hippocampal calcifications and cognitive impairment is limited to a small case-control study in which hippocampal calcifications were found more often in patients from a memory clinic than in matched control subjects. Moreover, individuals with hippocampal calcifications were found to have a lower score on the Mini-Mental State Examination (MMSE) (5).

We hypothesized that patients with hippocampal calcifications are more likely to have vascular risk factors and that hippocampal calcifications are associated with lower scores on cognitive tests.

The aim of our study was to identify vascular risk factors for hippocampal calcifications in a large cohort of individuals who visited an outpatient memory clinic.

Abbreviations

AD = Alzheimer disease, CAMCOG = Cambridge Cognitive Examination, CI = confidence interval, DM = diabetes mellitus, MMSE = Mini-Mental State Examination, OR = odds ratio

Summary

Older age, diabetes mellitus, and smoking appear to be associated with an increased risk of hippocampal calcifications on CT scans.

Implications for Patient Care

- Hippocampal calcifications are associated with older age, diabetes mellitus, and smoking.
- The clinical relevance of hippocampal calcifications is still unknown.

Furthermore, we aimed to evaluate the clinical importance of hippocampal calcifications by studying the association between hippocampal calcifications and cognitive function.

Materials and Methods

Study Population

Our retrospective cross-sectional study consisted of 2000 consecutive patients who visited the memory clinic of Tergooi Hospital, a general hospital in the Netherlands, between April 2009 and April 2015. All 2000 patients were included in a previously published article (6) investigating the prevalence of mixed dementia in patients with late-onset AD. Herein, we report the risk factors of hippocampal calcifications and the association with cognitive function.

The inclusion criterion for this study was referral to the memory clinic of Tergooi Hospital between April 2009 and April 2015 because of memory complaints. All patients underwent a standard diagnostic work-up, including brain CT. The only exclusion criterion for our study was absence of a brain CT scan, which led to exclusion of nine patients. None of the CT scans had to be excluded because of motion artifacts. Of the 1991 remaining patients, 40.3% were male and the mean patient age was 78 years (range, 45–96 years).

The local medical ethics committee of Tergooi Hospital approved our study and waived the requirement to obtain informed consent.

Diagnostic Procedures

All patients referred to the memory clinic underwent a standard diagnostic work-up including history taking; medical and neurologic examinations; assessment of vital functions; assessment of education level according to Verhage (details in Appendix E1 [online]) (7); cognitive screening including the Cambridge Cognitive Examination (CAMCOG), which contains the MMSE (full details in Appendix E1 [online]) (8,9); electrocardiography; laboratory tests; head CT; and history taking with a relative or other acquaintance. The CAMCOG is a well-validated cognitive evaluation and includes the most important cognitive domains that might be impaired in dementia. It has a high sensitivity and specificity (92% and 96%, respectively) for the detection of cognitive decline (8,9). Vascular risk factors including hypertension, diabetes mellitus (DM), hyperlipidemia, and smoking status were assessed during history taking (yes/no). Smoking status was classified into smoking or nonsmoking (also including previous smoking). Finally, a diagnosis was established, including mild cognitive impairment, AD, or vascular dementia, according to the standard clinical diagnostic criteria (10–12) (further details are in Appendix E1 [online]).

CT Protocol

All patients underwent brain CT. A 64–detector row CT scanner (Somatom Definition AS; Siemens Healthineers, Erlangen, Germany) was used to scan patients from the base of the skull to the vertex. The acquisition parameters were as follows: 120 kV; 260 mAs; collimation, 64 × 0.6 mm; pitch, 0.55; window center, 40 HU; and window width, 80 HU. The CARE kV tool (dose optimization slider for noncontrast examinations) was used. Scans were reconstructed as oblique coronal sections of 3.0 mm, axial sections of 5 mm with soft-tissue window, and 1.5-mm axial sections in bone window.

Hippocampal Calcifications

CT scans were analyzed for hippocampal calcifications by one physician (E.J.M.d.B. or R.K.) who was blinded to clinical outcomes and all risk factors except age and sex. All CT scans were analyzed during a time span of 2 weeks. One physician (E.J.M.d.B.) had 5 years of clinical experience in geriatrics. The other physician (R.K.) had 3 years of experience in the assessment of CT images during his doctoral degree program. These investigators were trained by a vascular radiologist (P.A.d.J., with 10 years of experience) and by a neuroradiologist (J.H., with 15 years of experience). Images were analyzed in axial and coronal planes in the brain window setting (center, 40 HU; width, 80 HU) with use of a previously established scoring system (5). Calcifications were scored according to presence and severity, as follows: absent, mild (one high-attenuation area) (Fig 1), moderate (multiple high-attenuation areas) (Fig 2), or severe (confluent) (Fig 3). Both hippocampi were scored separately. In the analysis of severity, the more severe calcification score, either for right or for left hippocampi, was used. In the analysis of the presence of hippocampal calcifications, hippocampal calcifications were considered present if a calcification was scored in at least one hippocampus. In this way, we used only one measure for hippocampal calcification presence and one measure for hippocampal calcification severity per patient.

Statistical Analysis

Descriptive statistics were used to summarize the baseline characteristics. The χ^2 test (for trend) and Mann-Whitney *U* test were performed to compare categorical and continuous variables, respectively, between individuals with and individuals without hippocampal calcifications. Logistic regression was performed to identify risk factors (explanatory variables) associated with the presence of hippocampal calcifications (outcome variable), including univariable analyses (model 1), age- and sex-adjusted analyses (model 2), and analyses adjusted for age, sex, hypertension, DM, hyperlipidemia, and smoking sta-

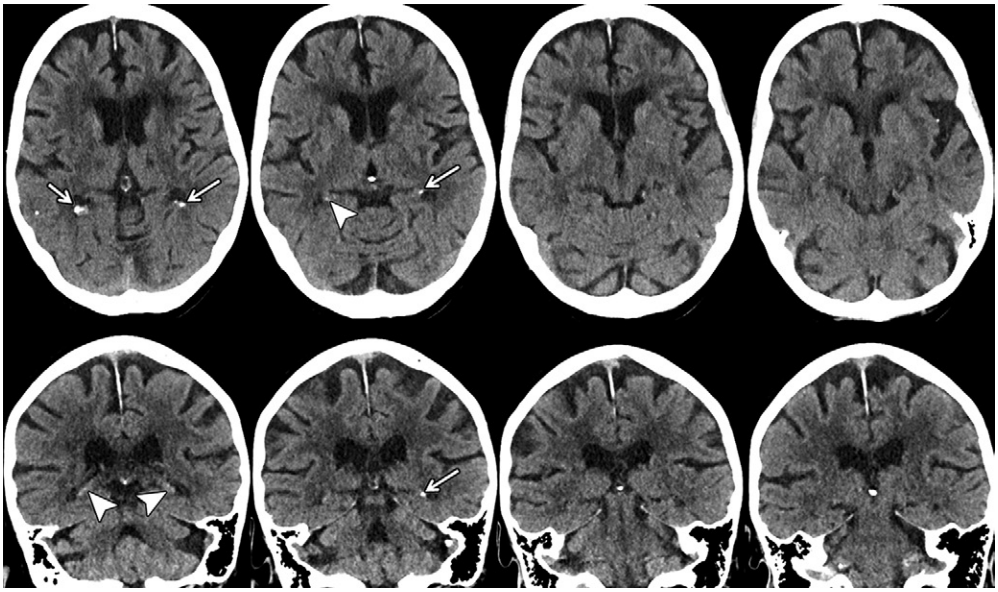

Figure 1: Axial and coronal CT images in 88-year-old woman show mild hippocampal calcifications (arrowheads). Arrows indicate calcifications of choroid plexus.

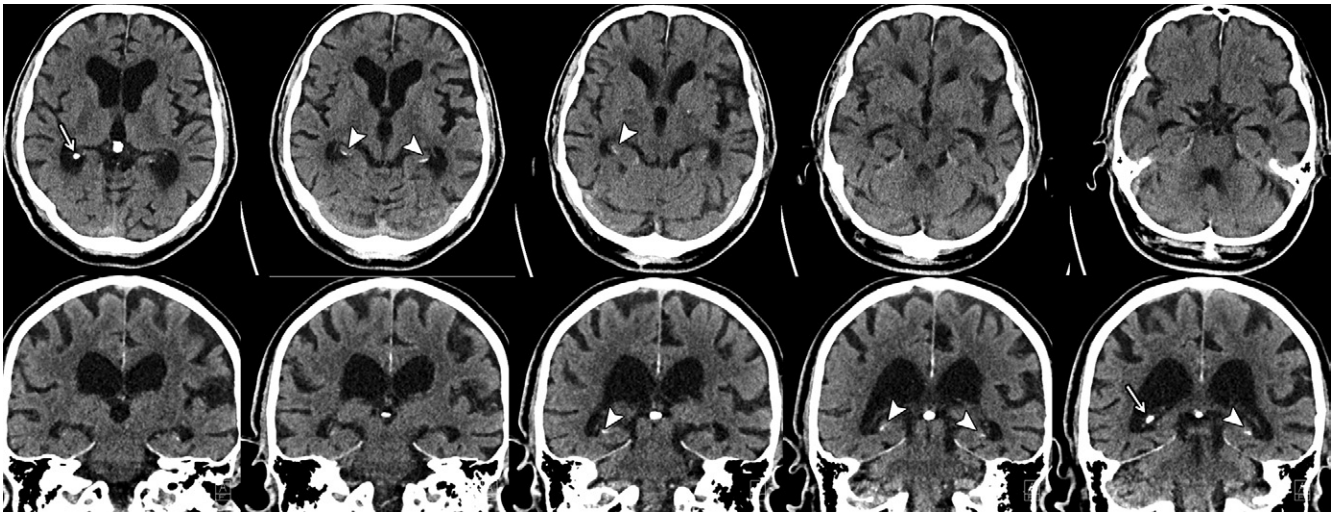

Figure 2: Axial and coronal CT images in 74-year-old woman show moderate hippocampal calcifications (arrowheads). Arrows indicate calcifications of choroid plexus.

tus (model 3). The χ^2 test was used to analyze whether number of risk factors (age >80 years, DM, and smoking) was associated with severity of hippocampal calcifications. Linear regression was used to analyze whether hippocampal calcifications (explanatory variable) were associated with cognitive function (outcome variable). A reflect and square root transformation ($\sqrt{}$[largest value of outcome variable + 1] − original value of outcome variable) was used to obtain a normal distribution, checked with the Q-Q plot, of the CAMCOG and MMSE outcomes. The β levels obtained after transformation of the outcome variables (MMSE or CAMCOG) to a normal distribution are presented in the Cognitive Outcomes section. Univariable analyses (model 1), age- and sex-adjusted analyses (model 2), and analysis adjusted for age, sex, and education level (model 3) were performed. In addition, subgroup analyses were performed for patients with mild cognitive impairment, AD, or vascular dementia. Patients with missing values on the cognitive tests were excluded from the regression analyses.

Two-sided $P < .05$ was considered indicative of a statistically significant difference. The Cohen κ was used to estimate the interobserver agreement of hippocampal calcification presence (yes or no) in a sample of 50 CT scans. Statistical analyses were performed with software (SPSS, version 24; IBM, Armonk, NY).

Results

Patients

The cohort consisted of 2000 patients. Nine patients were excluded from the analysis because there was no CT scan of the brain present. This resulted in a total of 1991 patients. Of the 1991 patients, 380 (19.1%) had hippocampal calcifications

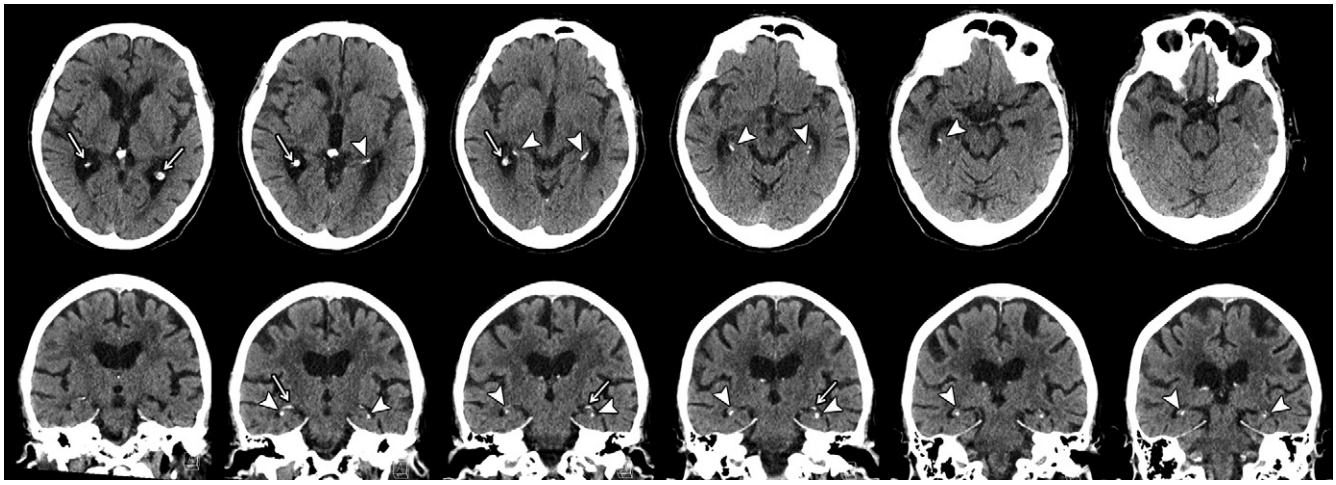

Figure 3: Axial and coronal CT images in 76-year-old man show severe hippocampal calcifications (arrowheads). Arrows indicate calcifications of choroid plexus.

(Table 1). The interobserver agreement was good (κ coefficient of 0.80 and 0.78 when weighted for severity scores).

Table 1: Baseline Characteristics according to Presence of Hippocampal Calcifications

Characteristic	Total (n = 1991)*	HC Present (n = 380)*	HC Absent (n = 1611)*	P Value
Age (y)†	78 (45–96)	81 (62–95)	78 (45–96)	<.01
No. of men	802 (40.3)	164 (43.2)	638 (39.6)	.22
Education level‡	4.34 ± 1.5	4.20 ± 1.5	4.37 ± 1.5	.05
Cerebral infarct	104 (5.2)	13 (3.4)	91 (5.6)	.10
TIA	116 (5.8)	25 (6.6)	91 (5.6)	.47
Hypertension	675 (33.9)	129 (33.9)	546 (33.9)	.99
Diabetes mellitus	317 (15.9)	79 (20.8)	238 (14.8)	.01
Hyperlipidemia	153 (7.7)	27 (7.1)	126 (7.8)	.75
Smoking	228 (11.5)	51 (13.4)	177 (11.0)	.18
MMSE score§	23 (18–26)	22 (18–26)	23 (18–26)	.39
CAMCOG score§	76 (63–85)	75 (61–84)	76 (63–86)	.04

Note.—Age, Mini-Mental State Examination (MMSE) score, and Cambridge Cognitive Examination (CAMCOG) score were analyzed with the Mann-Whitney U test. Other characteristics were analyzed with the χ^2 test, with education analyzed with the χ^2 test for trend. HC = hippocampal calcifications, TIA = transient ischemic attack.

* Except where indicated, data are numbers of patients, with percentages in parentheses.

† Data are means, with interquartile range in parentheses.

‡ Data are means ± standard deviations.

§ Data are medians, with interquartile range in parentheses.

Risk Factors for Hippocampal Calcifications

Before correcting for confounders, we found that patients with hippocampal calcifications were older than those without hippocampal calcifications (mean age, 81 vs 78 years, respectively; $P < .01$) and had a lower education level (mean level, 4.20 vs 4.37, respectively; $P = .05$). More patients with hippocampal calcifications had a history of DM (20.8% vs 14.8%, $P = .01$) (Table 1). Other vascular risk factors were similarly prevalent among both groups. When we corrected for confounders, we found that older age (odds ratio [OR], 1.05; 95% confidence interval [CI]: 1.03, 1.06; $P < .01$), DM (OR, 1.50; 95% CI: 1.12, 2.00; $P < .01$), and smoking (OR, 1.49; 95% CI: 1.05, 2.10; $P = .02$) were associated with the presence of hippocampal calcifications (Table 2, model 2). Education level was no longer associated with the presence of hippocampal calcifications (OR, 0.95; 95% CI: 0.88, 1.02; $P = .17$). Hypertension (OR, 0.91; 95% CI: 0.71, 1.17; $P = .47$) and hyperlipidemia (OR, 0.89; 95% CI: 0.57, 1.39; $P = .60$) were not associated with a higher risk of hippocampal calcifications. The number of risk factors (age >80 years, DM, smoking) was associated with the severity of hippocampal calcifications ($P < .01$). In patients without hippocampal calcifications or with mild calcifications, 11.1% had two risk factors and 0.5% had three risk factors. In patients with moderate or severe calcifications, 17.0% had two risk factors and 3.1% had three risk factors (Table 3).

Cognitive Outcomes

Of the 1991 patients in our cohort, most (n = 829, 41.6%) had AD, followed by mild cognitive impairment (n = 490, 24.6%) and subjective cognitive impairment (n = 332, 16.7%) (Table E1 [online]). Less than 1% of patients had missing values from the CAMCOG and MMSE.

When analysis was uncorrected for confounders, the total CAMCOG score in patients with hippocampal calcifications was lower than that in patients without calcifications (median score, 75 vs 76; $P = .04$). After correction for confounders, we did not find differences in outcomes of the CAMCOG (β

Table 2: Risk Factors for Presence of Hippocampal Calcifications

	Univariable Analysis (Model 1)			Age- and Sex-adjusted Analysis (Model 2)			Multivariable Analysis (Model 3)		
Risk Factors	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age	1.04	1.03, 1.06	<.01	1.05	1.03, 1.06	<.01	1.05	1.03, 1.06	<.01
Sex	0.86	0.69, 1.08	.20	0.78	0.62, 0.98	.03	0.81	0.64, 1.02	.07
Hypertension	1.00	0.79, 1.27	.98	0.95	0.75, 1.21	.68	0.91	0.71, 1.17	.47
Diabetes mellitus	1.51	1.14, 2.01	<.01	1.47	1.10, 1.95	<.01	1.50	1.12, 2.00	<.01
Smoking	1.25	0.90, 1.75	.18	1.50	1.06, 2.11	.02	1.49	1.05, 2.10	.02
Hyperlipidemia	0.90	0.59, 1.39	.64	0.91	0.59, 1.41	.67	0.89	0.57, 1.39	.60
Education level	0.93	0.86, 1.00	.05	0.94	0.87, 1.01	.10	0.95	0.88, 1.02	.17

Note.—Data were analyzed with logistic regression. Multivariable analysis adjusted for age, sex, hypertension, diabetes mellitus, smoking, and hyperlipidemia. CI = confidence interval, OR = odds ratio.

Table 3: Number of Risk Factors according to Severity of Hippocampal Calcifications

No. of Risk Factors	No HC	Mild HC	Moderate HC	Severe HC	Total
0	600 (85.2)	61 (8.7)	32 (4.5)	11 (1.6)	704 (100)
1	840 (80.7)	117 (11.2)	59 (5.7)	25 (2.4)	1041 (100)
2	160 (69.6)	43 (18.7)	22 (9.6)	5 (2.2)	230 (100)
3	9 (64.3)	0 (0.0)	3 (21.4)	2 (14.3)	14 (100)
Total	1609	221	116	43	1989 (100)

Note.—Data are numbers of patients, with percentages in parentheses. There was a significant difference between the groups ($P < .01$). Data were analyzed with the χ^2 test. Risk factors are age older than 80 years, diabetes mellitus, and smoking. HC = hippocampal calcifications.

= −0.05; P = .48) or MMSE (β = −0.08; P = .09) between patients with and patients without hippocampal calcifications (Table 4). There were also no differences in cognitive function when data were analyzed according to severity (P = .37 for CAMCOG and .07 for MMSE) (Table 4). Analysis according to subgroups of patients with mild cognitive impairment, AD, or vascular dementia yielded the same results, with P values ranging from .11 to .67 (Tables E2–E4 [online]).

Discussion

The results of our cross-sectional study in patients attending a memory clinic showed that older age, DM, and smoking were associated with the presence of hippocampal calcifications. The presence and higher severity of hippocampal calcifications were not associated with lower cognitive function in our cohort of memory clinic patients, which included patients with subjective cognitive impairment, mild cognitive impairment, dementia due to AD, and vascular dementia.

There currently are limited data on risk factors for hippocampal calcifications. To our knowledge, only three previous articles have been published on hippocampal calcifications (3–5). The prevalence of hippocampal calcifications in our study was 19.1%, which is comparable to the 21.7% observed in an Australian university hospital study of 217 randomly selected CT scans of patients older than 50 years, although another study observed a higher prevalence of 38.8% in 67 patients visiting a memory clinic and a prevalence of 13.4% in the control group (4,5). Both studies also used multiplanar CT scans (4,5). All studies showed a strong association between hippocampal calcifications and older age. The results of our study are consistent with this finding. One previous study assessed the association of vascular risk factors with hippocampal calcifications (4). There was no significant difference in the number of vascular risk factors in patients with hippocampal calcifications or those without hippocampal calcifications. However, in this previous study, the sample of 47 patients with hippocampal calcifications compared with 253 patients without hippocampal calcifications was too small to draw any firm conclusions (4). In our study, we showed an association of hippocampal calcifications with DM and smoking, but not with other vascular risk factors. Therefore, hippocampal calcifications could be a marker of a vascular abnormality. Wegiel et al (3) performed a pathology study and described a nonarteriosclerotic process of vasculopathy with fibrosis and calcifications. The lack of association with hypertension and dyslipidemia may support nonatherosclerotic arterial calcifications, although this remains speculative until further verification with histologic assessment is performed. Our findings support that these calcifications may be of vascular origin. Currently, if radiologists decide to report hippocampal calcifications in a radiology report, we suggest reporting the presence of hippocampal calcifications as mild, moderate, or severe (vascular) calcifications in the hippocampus on the right or left side, with the remark that this is an incidental finding of currently unknown clinical relevance.

Given the location of hippocampal calcifications in the hippocampal tail and the association with some vascular risk factors, we hypothesized that hippocampal calcifications could be associated with cognitive decline. In a pilot study of patients visiting a memory clinic (5), hippocampal calcifications were three times more common in these patients than in control subjects and were associated with lower MMSE scores. In our study, however, we did not find a significantly lower score on any of the cognitive tests in patients with hippocampal calcifications, including

Table 4: Association between Hippocampal Calcifications and Cognition

	Univariable Analysis (Model 1)			Age- and Sex-adjusted Analysis (Model 2)			Multivariable Analysis (Model 3)		
Parameter and Cognitive Test	β	95% CI	*P* Value	β	95% CI	*P* Value	β	95% CI	*P* Value
HC presence									
CAMCOG	0.18	0.00, 0.35	.05	−0.00	−0.16 to 0.16	.99	−0.05	−0.20 to 0.10	.48
MMSE	0.05	−0.05 to 0.16	.33	−0.06	−0.16 to 0.05	.28	−0.08	−0.18 to 0.01	.09
HC severity									
CAMCOG	0.05	−0.05 to 0.15	.32	−0.02	−0.11 to 0.08	.72	−0.04	−0.13 to 0.05	.37
MMSE	0.00	−0.06 to 0.07	.93	−0.04	−0.10 to 0.02	.17	−0.05	−0.11 to 0.00	.07

Note.—Data were analyzed with linear regression. Multivariable analysis was adjusted for age, sex, and education level. CAMCOG = Cambridge Cognitive Examination, CI = confidence interval, HC = hippocampal calcifications, MMSE = Mini-Mental State Examination.

the MMSE. A possible explanation for this discrepancy is the correction for age, sex, and education level in our study; the pilot study did not correct for these potential confounding factors. Hippocampal calcifications do not seem to be associated with cognitive decline. Further population-based cohort studies are needed to confirm our findings.

There are limitations of our study that must be taken into account when interpreting the data. First, there was a referral bias because all patients were referred to a memory clinic. Although some patients did not have cognitive impairment at examination, they did have memory complaints for which they had been referred. We did not have a control group of persons without memory complaints, which might have led to an underestimation of the association between hippocampal calcifications and cognition. Thin-section reconstructions of the CT scans were unavailable, which could have led to an underestimation of the presence of hippocampal calcifications if subtle calcifications were missed. However, if hippocampal calcifications had an effect on cognitive function, we would expect to find this with the more severe calcifications and not with the subtle calcifications we might have missed. Another limitation is the measurement of cardiovascular risk factors. The presence of cardiovascular risk factors was based on history taking. This may have led to misclassification, especially in patients with memory complaints, because some patients classified as not having a cardiovascular risk factor actually did have the risk factor as determined with laboratory tests or the use of medication. This might have led to an underestimation of the associations that were found between the risk factors and the presence of hippocampal calcifications. In addition, the smoking classification was arbitrary because nonsmokers may have stopped smoking recently. This could have led to an overestimation of the risk of smoking.

In conclusion, older age, DM, and smoking appear to be associated with an increased risk of hippocampal calcifications on CT images, which suggests that these calcifications may be of vascular origin. The findings from our study do not support hippocampal calcifications as a marker of cognitive impairment in patients visiting a memory clinic, although further confirmation is needed.

Author contributions: Guarantors of integrity of entire study, E.J.M.d.B., J.J.C., P.A.d.J., H.L.K.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, E.J.M.d.B., W.P.T.M.M., J.H., P.A.d.J.; clinical studies, E.J.M.d.B., R.K., J.J.C., T.E.F.J., W.P.T.M.M., P.A.d.J., H.L.K.; statistical analysis, E.J.M.d.B., R.K., H.L.K.; and manuscript editing, all authors

Disclosures of Conflicts of Interest: **E.J.M.d.B.** disclosed no relevant relationships. **R.K.** disclosed no relevant relationships. **J.J.C.** disclosed no relevant relationships. **A.d.J.** disclosed no relevant relationships. **M.I.G.** disclosed no relevant relationships. **T.E.F.J.** disclosed no relevant relationships. **W.P.T.M.M.** disclosed no relevant relationships. **J.H.** disclosed no relevant relationships. **P.A.d.J.** disclosed no relevant relationships. **H.L.K.** disclosed no relevant relationships.

References

1. Prince M, Wimo A, Guerchet M, Ali GC, Wu YT, Prina M. World Alzheimer report 2015: the global impact of dementia—an analysis of prevalence, incidence, cost and trends. London, England: Alzheimer's Disease International, 2015.
2. Fotuhi M, Hachinski V, Whitehouse PJ. Changing perspectives regarding late-life dementia. Nat Rev Neurol 2009;5(12):649–658.
3. Wegiel J, Kuchna I, Wisniewski T, et al. Vascular fibrosis and calcification in the hippocampus in aging, Alzheimer disease, and Down syndrome. Acta Neuropathol (Berl) 2002;103(4):333–343.
4. Chew AP, Gupta G, Alatakis S, Schneider-Kolsky M, Stuckey SL. Hippocampal calcification prevalence at CT: a retrospective review. Radiology 2012;265(2):504–510.
5. Kockelkoren R, De Vis JB, Mali WP, et al. Hippocampal calcification on computed tomography in relation to cognitive decline in memory clinic patients: a case-control study. PLoS One 2016;11(11):e0167444.
6. Claus JJ, Staekenborg SS, Roorda JJ, et al. Low prevalence of mixed dementia in a cohort of 2,000 elderly patients in a memory clinic setting. J Alzheimers Dis 2016;50(3):797–806.
7. Verhage F. Intelligentie en leeftijd bij volwassenen en bejaarden. Assen, the Netherlands: Van Gorcum, 1964.
8. Huppert FA, Brayne C, Gill C, Paykel ES, Beardsall L. CAMCOG—a concise neuropsychological test to assist dementia diagnosis: socio-demographic determinants in an elderly population sample. Br J Clin Psychol 1995;34(Pt 4):529–541.
9. Roth M, Tym E, Mountjoy CQ, et al. CAMDEX: a standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. Br J Psychiatry 1986;149(6):698–709.
10. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56(3):303–308.
11. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7(3):263–269.
12. Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993;43(2):250–260.