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The Role of Vascular Risk Factors in Biomarker-Based AT(N) Groups: A German-Dutch Memory Clinic Study

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Abstract.
Background: The relation between vascular risk factors (VRFs) and Alzheimer's disease (AD) is important due to possible pathophysiological association.
Objective: To assess the prevalence of VRFs in biomarker-based AT(N) groups and the associations between VRFs, AD cerebrospinal fluid (CSF) biomarkers, brain magnetic resonance imaging (MRI), and cognition in clinical context.
Methods: We included patients from two memory clinics in University Hospital Aachen (Germany) and Maastricht University Medical Centre (The Netherlands). Subjects were older than 45 years and had available data on demographics, VRFs, CSF AD biomarkers, and MRI. We categorized individuals in normal AD biomarkers, non-AD change, and AD-continuum groups based on amyloid (A), tau (T), and neurodegeneration (N) status in CSF and MRI. Regression models were corrected for age, sex, and site.
Results: We included 838 participants (mean age 68.7, 53.2% male, mean MMSE 24.9). The most common VRFs were smoking (60.9%), hypertension (54.6%), and dyslipidemia (37.8%). Alcohol abuse and smoking were most frequent in the non-AD-change group, and coronary heart disease and carotid artery stenosis in the AD continuum group. Higher rates of depression were found in the normal AD biomarkers group. Parietal atrophy and cortical microbleeds were specific for the AD continuum group. Carotid artery stenosis was associated with pathological $A\beta_{42}$ and T-tau values, and diabetes and alcohol abuse were associated with worse medial temporal atrophy and atrial fibrillation, with worse cognition.
Conclusion: VRFs are common in memory clinic patients, showing differences across the AT(N) biomarker groups. This is important for prevention and individualized treatment of dementia.

Keywords: Alzheimer's disease, ambulatory care facilities, biomarkers, classification, risk factors, vascular diseases

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INTRODUCTION

Cognitive decline and dementia pose a great challenge for healthcare systems worldwide, with the global number of individuals living with dementia having doubled in the last three decades [1], contributing to the increased disease burden [2]. Understanding the relationship between dementia pathophysiology and vascular risk factors (VRFs) is especially important not only due to their possible association, but also due to the availability of modification and prevention strategies. However, study results have often been inconsistent. Despite showing that vascular disease in elderly persons is common, the relationship between VRFs and Alzheimer's disease (AD) pathophysiology, as well as AD-related cognitive decline, remain unclear.

Studies investigating the association between vascular comorbidities, AD pathophysiological changes, and cognitive decline are scarce and mostly focused on population-based data. Such approaches have shown that VRFs such as hypertension [3, 4], diabetes [3, 4], stroke [5], and atrial fibrillation [6] are associated with an increased risk of future cognitive impairment. Nevertheless, in clinical-based studies, the association between VRFs and future cognitive decline could not be found in patients with mild cognitive impairment (MCI) [7] or AD [8]. A clinical-based study in a memory clinic showed that hypertension and lower body mass index, in combination with pathological AD biomarkers in cerebrospinal fluid (CSF), were associated with a higher risk of progression to dementia in patients with a MCI [9]. Also, having a combination of pathological amyloid levels in CSF and cerebrovascular disease in brain MRI has been found to be associated with higher medial temporal atrophy scores, which is one of the hallmarks of AD [10]. However, a clear relationship between VRFs and typical AD specific biomarker changes in CSF has not yet been shown [11, 12].

So far, the association of VRFs and the newly proposed biomarker classification system for AD by Jack et al. [13] remains unknown. In 2018, the NIA-AA Research Framework presented a biomarker classification system, based on the presence of amyloid-pathology (A), tauopathy (T), and neurodegeneration (N), aiming for a more precise definition and understanding of AD pathophysiology. The AT(N) is a descriptive binary system for categorizing multidomain biomarker findings and could be paired with any other staging system. Having said this, the AT(N) classification does not yet include an important aspect of dementia pathophysiology—vascular burden (V) [14, 15]. Studies suggest that (V) may serve as a comorbidity next to the amyloid-pathology, tauopathy, and neurodegeneration while promoting cognitive decline [16, 17].

Overall, there is a need to deepen the knowledge about the complex associations between VRFs, pathophysiological AD biomarkers, and clinical characteristics in patients with suspected cognitive impairment. The aims of this study were to investigate the prevalence of VRFs with regard to the AT(N) classification in a memory clinic setting, as well as to assess in more detail the association between VRFs, AD CSF biomarkers, imaging, and clinical characteristics.

METHODS

Participants

We included consecutive patients from the Department of Neurology, University Hospital Aachen (Germany) and the Maastricht University Medical Centre (The Netherlands) memory clinics, referred for diagnostic evaluation of cognitive complaints, between 2008–2019 (Aachen) and 2009–2019 (Maastricht). Available data included information on demographics (age, sex, marital status, education level, history of dementia in first-degree family members), medical history, VRFs, medication, cognitive assessment, CSF neurodegeneration biomarkers, and brain MRI. All data in Maastricht and Aachen were collected according to common standards and concepts as part of clinical routine at both memory clinics. Data was anonymized and harmonized to enable the analysis of both databases simultaneously. We selected patients who were older than 45 years and had CSF and MRI data available to allow for AT(N) classification. We chose this age group in order to keep the sample as representative as possible, as restricting the cohort to only middle-aged and old patients would have led to a loss of an important part of memory clinic patients. We excluded patients, who were younger or equal than 45 years, did not have CSF or MRI data available and/or had a cognitive impairment due to other causes rather than probable neurodegenerative and/or cerebrovascular disease (e.g., post-traumatic, post-infectious, chronic-inflammatory). We did not exclude patients with depression, as it is known to be an important

risk factor and possible prodromal symptom of mild cognitive impairment and dementia [18, 19].

Clinical measures

The information about the history of following VRFs was collected from medical documentation and questionnaires: arterial hypertension, diabetes mellitus (types 1 and 2), dyslipidemia (including elevated cholesterol, triglycerides and low density lipoprotein levels, and also reduced levels of high-density lipoproteins), relevant carotid artery stenosis, atrial fibrillation, coronary heart disease, myocardial infarction, history of cardiovascular surgery (coronary stent, bypass operation or both), history of cerebral ischemic event (stroke or transitory ischemic attack), history of alcohol abuse (present or past), history of smoking (present or past). The diagnoses of VRFs were made by clinicians according to common guidelines. Obesity was defined as body mass index $\geq 30\,kg/m^2$. Although not a VrF per se, history of depression was also included, as it is an important risk factor for cognitive decline. Additionally, information on medication was gathered for antihypertensives, diuretics, antithrombotic agents (antiplatelet agents, anticoagulants or both), statins, benzodiazepines, neuroleptics, antidepressants, anticonvulsants, antiparkinsonian drugs, anticholinergic drugs, narcotic analgesics, nonsteroidal anti-inflammatory drugs, vitamins, thyroid supplements, hormone replacement therapy, diabetes medication and steroids, as well as dementia specific medication (cholinesterase inhibitors and/or memantine).

Global cognition and neuropsychiatric measures

All subjects underwent the Mini-Mental State Examination (MMSE) [20] and/or Montreal Cognitive Assessment (MoCA) [21] tests to screen for global cognitive impairment. In cases where only MoCA was available, its score was converted to a MMSE score according to previously published conversion scores [22]. The Clinical Dementia Rating (CDR) [23] score was also measured.

MRI atrophy and vascular measures

MRI scans from clinical routine exams usually included T1-weighted, T2-weighted, T2*, and FLAIR sequences. In Maastricht, all MRIs were acquired with a 3 Tesla scanner, in Aachen 55% of MRIs were acquired with 1.5 Tesla, 31% with 3 Tesla, and for 14% this information was missing. All scans were rated using the following atrophy visual rating scales: medial temporal lobe atrophy for left and right hemispheres (MTA, scale 0–4) [24], Koedam score for posterior atrophy (scale 0–3) [25], and global cortical atrophy (GCA, scale 0–3) [26]. Vascular pathology in MRI was also assessed using the Fazekas visual rating score for white matter hyperintensities (WMH, scale 0–3) [27]. Subcortical and cortical cerebral microbleeds were counted. Ischemic infarcts and macrohemorrhages were evaluated visually and also coded according to the neuroradiological reports. Ischemic infarcts were divided into strategic (middle cerebral artery, posterior cerebral artery, watershed and lacunar bilateral thalamic infarctions) and non-strategic [28]. All MRI scans were rated by two independent raters, blinded to clinical data. Discrepancies, defined as greater than 1 point for each of the rating scales, were solved by consensus. Average scores of both raters were used for statistical analyses.

CSF measures

CSF parameters were obtained from the Neurochemical Laboratory at the University Medical Center Göttingen in Germany for Aachen (including amyloid-β_{42} ($A\beta_{42}$), $A\beta_{40}$, Aβ ratio ($[A\beta_{42}/A\beta_{40}]$x10), total tau (T-tau) protein, phosphorylated tau protein 181p (P-tau)) or from Radboud University in Nijmegen in the Netherlands for Maastricht (including $A\beta_{42}$, T-tau, and P-tau). The analyses were conducted using commercially available assays (IBL highly sensitive $A\beta_{40}$ ELISA and Fujirebio Innotest for $A\beta_{42}$, T-tau, and P-tau). For harmonizing purposes, CSF markers were dichotomized into normal and abnormal based on each of the assay's specific cut-off scores for each center. The cut-off values for pathological results in Maastricht were: $A\beta_{42} < 500$ pg/ml, T-tau > 350 pg/ml, P-tau > 85 pg/ml; in Aachen: for $A\beta_{42}$ until May $2011 < 500$ pg/ml, after May $2011 < 450$ pg/ml; $A\beta_{42}/A\beta_{40} < 0.5$; T-tau until May $2011 > 500$ pg/ml, after May $2011 > 450$ pg/ml; P-tau > 61 pg/ml.

AT(N) biomarker classification

Each individual was assigned an AT(N) profile according to Jack et al. [13], depending on CSF

and MRI results, with "A" referring to amyloid-pathology (pathological CSF $A\beta_{42}$/ $A\beta_{40}$ ratio or, if not available – CSF $A\beta_{42}$ value), "T" to tauopathy (pathological CSF P-tau values), and "N" representing neurodegeneration (pathological CSF T-tau values and/or average MTA score ≥ 2). In this manner, every subject gained an individual A (+/–) T (+/–) N (+/–) profile. Subsequently, participants were grouped into three groups depending to their AT(N) profile: normal AD biomarkers (A-T-N-), non-AD pathological change (A-T+N-, A-T-N+, A-T+N+), and AD continuum (A + T-N-, A + T+N-, A + T-N+, A + T+N+).

Statistical analysis

Statistical analysis was carried out with SPSS Statistics software, version 26. The normality of variables was assessed using Kolmogorov-Smirnov test. To investigate the differences between the AT(N) groups, Kruskal–Wallis test was used for continuous variables and Pearson χ^2 for nominal and ordinal variables. When applicable, *post-hoc* analyses were done with correction for multiple comparisons. Correction for multiple comparisons was done using SPSS program for linear variables (Bonferroni and Games-Howell tests). For nominal variables, we used squared adjusted Z-values for every variable to calculate new, corrected p-values using SPSS. The associations between risk factors, CSF biomarkers, MRI data, and cognitive scores were investigated using linear regression analyses (continuous outcomes) or logistic regression analyses (dichotomous outcomes), corrected for age at baseline, sex, and study center (Aachen or Maastricht). For cognitive scores, additional correction for years of education was applied. For regression analyses, risk factors, infarctions, macrohaemorrhages, subcortical, and cortical microbleeds were dichotomized (0 – absent/normal, 1 – present/pathological). The remaining MRI and cognitive scores (MTA, GCA, Koedam score, white matter hyperintensities (Fazekas) score, MMSE) were considered continuous. The significance level was set at 0.05. The calculated Cohen *d* effect sizes were classified as follows: 0.2–0.4 – small effect, 0.5–0.7 – intermediate effect, > 0.8: large effect.

Ethics

The study was approved by the local ethics committees (EK 018-19 for Aachen, METC 09-3-037, METC 09-3-038, and METC 15-4-100 for Maastricht) and conducted according to The Code of Ethics of the World Medical Association (Declaration of Helsinki).

RESULTS

Patient characteristics

There were 897 subjects in the initial dataset. Of the 838 subjects included into the final analysis after exclusion (see Supplementary Figure 1), 446 (53.2%) were men. Classification into the 3 AT(N) groups yielded: 315 (37.6%) subjects in the normal AD biomarkers, 255 (30.4%) in the non-AD change, and 268 (32.0%) in the AD continuum group (see Table 1 for patient characteristics). Age ranged from 46 to 92 years with a mean age of 68.7 ± 9.7 years. The three groups differed in age, with both non-AD change and the AD continuum groups being significantly older than the normal AD biomarkers group. Marital status and education level did not differ between the groups. Within the AD continuum group, more patients had a positive history of dementia in first-degree family members. The average symptom duration at the first visit in the memory clinic was 3.0 ± 2.8 years.

According to the CDR score, 5.2% of the subjects had subjective cognitive impairment (CDR 0), 60.3% MCI (CDR 0.5), 27.9% mild dementia (CDR 1), 6.2% moderate dementia (CDR 2), and 0.4% severe dementia (CDR 3). The average MMSE score was 24.9 ± 4.5, being worse in both non-AD change and AD continuum groups compared to the normal AD biomarkers group (see Supplementary Figure 2). The average MoCA score was 19.0 ± 5.5 and differed only between the normal AD biomarkers group and AD continuum group.

Considering the etiological diagnoses from the medical documentation, the majority of patients were diagnosed with AD (36.5%), vascular dementia (16.9%), major depression (8.4%), and mixed dementia (4.9%). Other etiological diagnoses included frontotemporal dementia (4.3%), Parkinson's dementia (1.6%), Lewy body dementia (1.4%), normal pressure hydrocephalus (1.4%), progressive supranuclear palsy (0.5%), and corticobasal degeneration (0.4%). In 8.5% of the cases, the etiological diagnosis was unclear and for 15.3% subjects this information was missing (only syndromic diagnosis was available). For further data on etiological diagnoses see Supplementary Table 1.

Table 1
Demographic and clinical characteristics

	Data available (N)	Total group	Normal AD biomarkers	Non-AD change	AD continuum	Effect size	Test statistic	*p*
N		838	315	255	268			
Age, M (SD)	838	68.7 (± 9.7, min. 46, max. 91)	64.3 (± 10.0) †,††	70.4 (± 8.6) †	72.4 (± 8.2) ††	0.56	62.71	*< 0.001*
Sex, n men (%)	838	446 (53.2%)	176 (55.9%)	130 (51.0%)	140 (52.2%)	0.04	1.51	*0.477*
Education, y, M (SD)	800	11.6 (± 3.3, min. 0, max. 25)	11.6 (± 3.2)	11.4 (± 3.2)	11.8 (± 3.5)	0.04	1.68	*0.431*
Married, N (%)	827	648 (77.3%)	243 (78.9%)	193 (76.3%)	212 (79.7%)	0.03	0.98	*0.614*
Positive family history of dementia, N (%)	663	262 (31.3%)	92 (35.8%)	71 (36.0%)	99 (47.4%) §	0.11	7.87	*0.020*
Symptom duration at the first visit, y, M (SD)	804	3.0 (± 2.8, min. 0, max. 38)	3.4 (± 3.8)	2.7 (± 1.9)	2.7 (± 2.0)	0.06	2.80	*0.247*
CDR	807					0.18	52.00	*< 0.001*
0		42 (5.2%)	28 (9.2%)	8 (3.3%)	6 (2.3%)			
0.5		487 (60.3%)	208 (68.4%)	148 (60.7%)	131 (50.6%)			
1		225 (27.9%)	54 (17.8%)	66 (27.0%)	105 (40.5%)			
2		50 (6.2%)	13 (4.3%)	21 (8.6%)	16 (6.2%)			
3		3 (0.4%)	1 (0.3%)	1 (0.4%)	1 (0.4%)			
MMSE, M (SD)	792	24.9 (± 4.5, min. 1, max. 30)	26.2 (± 4.2) †,††	24.5 (± 4.4) †,¶	23.6 (± 4.6) ††,¶	0.53	52.99	*< 0.001*
MoCA, M (SD)	573	19.0 (± 5.5, min. 1, max. 30)	20.3 (± 5.8) ††	18.5 (± 5.5)	18.3 (± 4.9) ††	0.26	11.15	*0.004*

Post hoc significance $p < 0.05$: † normal/non-AD, †† normal/AD, ¶ non-AD/AD, chi square. AD, Alzheimer's disease; CDR, Clinical Dementia Rating, M, mean, max., maximum; min., minimum; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; SD, standard deviation. Normal AD biomarkers: A-T-N-; non-AD pathological change: A-T+N-, A-T-N+, A-T+N+; AD continuum: A + T-N-, A + T+N-, A + T-N+, A + T+N+.

Prevalence of risk factors

The most common VRFs in the total group were smoking (60.9%), arterial hypertension (54.6%), and dyslipidemia (37.8%). From the total of 274 smoking participants, 105 were current and 169 were past smokers. In the subgroup of subjects with arterial hypertension, 359 (79,4%) were taking antihypertensive medication. The least common comorbidities in the whole cohort were atrial fibrillation (5.3%), myocardial infarction (5.7%), and history of cardiovascular surgery (8%).

Both alcohol abuse and smoking were the most prevalent in the non-AD-change group (smoking: Pearson $\chi^2 = 7.871$, $p = 0.020$, alcohol abuse: Pearson $\chi^2 = 7.501$, $p = 0.024$). A higher prevalence in the AD continuum group than in normal and non-AD-change groups was found for coronary heart disease (Pearson $\chi^2 = 9.788$, $p = 0.007$) and carotid artery stenosis (Pearson $\chi^2 = 22.326$, $p < 0.001$). An additional analysis on depression showed that it was more frequent in the normal AD biomarkers group than in non-AD-change and AD continuum groups (Pearson $\chi^2 = 12.930$, $p = 0.002$). No differences between the groups were observed for the remaining risk factors (see Table 2 for the prevalence of VRFs).

Moreover, the overall usage of medication was analyzed. The most commonly used medication was antihypertensive drugs (51.2% of the total cohort), antithrombotic agents (37.7%), and statins (32.9%). The usage of antidepressants was also fairly prevalent (24.1% in the total cohort), with a significant higher percentage in the normal AD biomarkers group (27.0%). The number of persons taking dementia medication was highest in the AD continuum group (32.2% versus 10.3% in the normal AD biomarkers group and 20.4% in the non-AD change group, Pearson $\chi^2 = 40.113$, $p < 0.001$) (for data on medication see Supplementary Table 2).

MRI findings

For the whole group median visual ratings for GCA and Koedam scales corresponded to mild atrophy scores. Also, the median WMH (Fazekas) score in the full cohort was 1.00, reflecting mild vascular changes (see Table 3 for full MRI results). Compared to the normal AD biomarkers group, higher scores for GCA were observed in both non-AD change and AD continuum groups. The Koedam score was higher in the non-AD change group than in the normal AD biomarkers group, and the highest in the AD

Table 2
Vascular risk factors per AT(N) biomarker category

Risk factors	Data available (N)	Total positive	Normal AD biomarkers	Non-AD change	AD continuum	Effect size	Test statistic	*p*
Smoking, N (%)	450	274 (60.9%)	120 (60.3%)	93 (69.4%)	61 (52.1%)	0.13	7.87	*0.020*
Arterial hypertension, N (%)	830	453 (54.6%)	154 (49.5%)	144 (57.4%)	155 (57.8%)	0.08	5.15	*0.076*
Dyslipidemia, N (%)	830	314 (37.8%)	101 (32.4%)	100 (39.8%)	113 (42.3%)	0.09	6.67	*0.036*
Carotid artery stenosis, N (%)	830	174 (21.0) %	49 (15.8%)	43 (17.1%)	82 (30.6%)	0.16	22.33	*<0.001*
Obesity, N (%)	252	43 (17.1%)	21 (19.1%)	14 (18.2%)	8 (12.3%)	0.08	1.43	*0.490*
Alcohol abuse, N (%)	300	48 (16.0%)	18 (15.0%)	22 (23.9%)	8 (9.1%)	0.16	7.50	*0.024*
Diabetes mellitus, N (%)	824	128 (15.5%)	48 (15.5%)	48 (19.3%)	32 (12.1%)	0.08	5.08	*0.079*
Ischemic event, N (%)	829	112 (13.5%)	43 (13.9%)	32 (12.7%)	37 (13.8%)	0.02	0.18	*0.926*
Coronary heart disease, N (%)	830	71 (8.6%)	15 (4.8%)	24 (9.6%)	32 (11.9%)	0.11	9.79	*0.007*
Cardiovascular surgery, N (%)	830	66 (8.0%)	17 (5.5%)	22 (8.8%)	27 (10.1%)	0.07	4.50	*0.105*
Myocardial infarction, N (%)	830	47 (5.7%)	16 (5.1%)	12 (4.8%)	19 (7.1%)	0.04	1.54	*0.462*
Atrial fibrillation, N (%)	677	36 (5.3%)	11 (4.8%)	10 (4.9%)	15 (6.1%)	0.03	0.50	*0.781*

Post hoc significance $p < 0.05$: chi square. Normal AD biomarkers: A-T-N-; non-AD pathological change: A-T+N-, A-T-N+, A-T+N+; AD continuum: A + T-N-, A + T+N-, A + T-N+, A + T+N+.

continuum group. WMH were significantly more pronounced in both non-AD change and AD continuum groups than in the normal AD biomarkers group (see Supplementary Figure 3 for MRI scores). Considering microbleeds, a difference between the groups was seen only for cortical microbleeds, as they were most often found in the AD continuum group (Pearson $\chi^2 = 9.441, p = 0.009$). The frequency of ischemic infarctions and macrohaemorrhages in MRIs was in general quite scarce and no differences between the groups were observed.

Association between the risk factors and CSF biomarkers

The association between the VRFs and CSF biomarkers was assessed using logistic regression models. After corrections for age, sex, and study center, carotid artery stenosis was found to be associated with pathologic $A\beta_{42}$ (Odds Ratio (OR) 1.76 (95% Confidence Interval (CI) 1.22–2.59), $p = 0.003$) as well as pathologic T-tau (OR 1.67 (95% CI 1.16–2.40), $p = 0.006$). Some associations showed risk factors leading to better outcomes in CSF biomarkers. Ischemic event (OR = 0.59 (95% CI 0.36–0.97), $p = 0.036$) and smoking (OR 0.56 (95% CI 0.35–0.89), $p = 0.015$) were negatively associated with $A\beta_{42}$ pathology. Also, persons with diabetes mellitus were less prone to having a pathological $A\beta_{42}/A\beta_{40}$ ratio (OR 0.60 (95% CI 0.37–0.97), $p = 0.036$). No other significant associations were observed.

Association between risk factors and MRI atrophy scores

We also investigated the association between VRFs and MRI atrophy scores. More severe MTA scores were associated with diabetes mellitus ($\beta = 0.067$, $p = 0.025$) and alcohol abuse ($\beta = 0.120$, $p = 0.022$). Some reverse effects were also observed. For MTA, coronary heart disease was associated with lower atrophy scores ($\beta = -0.074$, $p = 0.014$) and for Koedam score, cardiovascular surgery ($\beta = -0.105$, $p = 0.002$) and dyslipidemia ($\beta = -0.110$, $p = 0.002$) were associated with lower scores.

AT(N) subgroup analyses revealed some additional insights. In the non-AD change group, atrial fibrillation was associated with more severe scores for both GCA ($\beta = 0.179$, $p = 0.010$) and Koedam score ($\beta = 0.253$, $p < 0.001$). In the AD continuum group, carotid artery stenosis was associated to worse GCA

Table 3
MRI chrematistics per AT(N) biomarker category

MRI data	Data available (N)	Total group	Normal AD biomarkers	Non-AD change	AD continuum	Effect size	Test value	*p*
GCA, median (IQR)	810	1.00 (± 1.00, min. 0, max. 3)	0.50 (± 0.50) †,††	1.00 (± 1.00) †	1.00 (± 1.00) ††	0.44	39.98	*< 0.001*
Koedam score, median (IQR)	808	0.50 (± 1.00, min. 0, max. 3)	0.50 (± 0.50) †,††	0.50 (± 1.00) †,¶	1.00 (± 1.00) ††,¶	0.62	71.82	*< 0.001*
WMH, median (IQR)	806	1.00 (± 1.00, min. 0, max. 3)	1.00 (± 1.00) †,††	1.00 (± 0.50) †	1.00 (± 0.50) ††	0.23	12.14	*0.002*
Strategic infarction, N (%)	810	33 (4.1%)	14 (4.7%)	12 (4.8%)	7 (2.7%)	0.05	1.76	*0.415*
Non-strategic infarction, N (%)	810	38 (4.7%)	11 (3.7%)	14 (5.6%)	13 (5.1%)	0.04	1.22	0.543
cMB, N (%)	727	127 (17.5 %)	38 (14.5 %)	34 (14.5 %)	55 (23.8 %)	0.11	9.44	*0.009*
sMB, N (%)	727	72 (9.9 %)	20 (7.6 %)	22 (9.4 %)	30 (13.0 %)	0.08	4.04	*0.133*
Macrohaemorrhages, N (%)	810	16 (2.0 %)	5 (1.7 %)	6 (2.4 %)	5 (1.9 %)	0.02	0.45	*0.820*

Post hoc significance $p < 0.05$: † normal/non-AD, †† normal/AD, ¶ non-AD/AD, chi square. MTA, medial temporal atrophy (range 0–4); IQR, interquartile range; GCA, global cortical atrophy (range 0–3); WMH, white matter hyperintensities (Fazekas score) (range 0–3), Koedam score (parietal atrophy) (range 0–3); cMB, cortical microbleeds; sMB, subcortical microbleeds; min., minimum; max., maximum. MTA score represents averaged ratings for both hemispheres. Normal AD biomarkers: A-T-N-; non-AD pathological change: A-T+N-, A-T+N+; AD continuum: A + T-N-, A + T+N-, A + T-N+, A + T+N+.

scores (β = 0.160, $p = 0.008$). However, some reverse effects were also observed: in the non-AD change group, carotid artery stenosis (β = –0.127, $p = 0.018$) and obesity (β = –0.242, $p = 0.013$) were associated with lower MTA scores, and carotid artery stenosis predicted less severe GCA scores (β = –0.135, $p = 0.029$). Additionally, in the AD continuum group, depression was associated with lower Koedam scores (β = –0.153, $p = 0.013$).

Association between vascular risk factors and cognitive scores

The association between the VRFs and MMSE scores was assessed. Atrial fibrillation was a significant predictor for lower MMSE scores (β = –0.067, $p = 0.047$), whereas ischemic event (β = 0.067, $p = 0.046$) and smoking (β = 0.073, $p = 0.039$) were associated with higher MMSE scores. Other VRFs were not associated with MMSE scores. No additional associations were found in the subgroup analysis.

DISCUSSION

Our study showed that VRFs are common in patients from a memory clinic setting. The highest prevalence was found for smoking, arterial hypertension and dyslipidemia. Furthermore, prevalence rates of risk factors differed between the AT(N) groups: smoking and alcohol abuse were most often found in the non-AD change group and coronary heart disease and carotid artery stenosis were most frequent in the AD continuum group. We also found higher rates of depression in the normal AD biomarkers group than in other groups. Considering the MRI results, only Koedam score and cortical microbleeds seemed to be specific for the AD continuum group, whereas GCA and WMH were frequently more severe in both non-AD change and AD continuum groups than in the normal AD biomarkers group. We found diabetes mellitus and alcohol abuse to be associated with worse MTA atrophy scores. In the AT(N) subgroup analysis, several other risk factors emerged: atrial fibrillation was associated with worse atrophy scores in the non-AD change group and carotid artery stenosis, to higher atrophy scores in AD continuum group. We also found an association between having carotid artery stenosis and pathological $A\beta_{42}$ and T-tau values. Lastly, we observed an association between atrial fibrillation and worse MMSE score.

Our results on the prevalence of risk factors in a memory clinic cohort are mainly in line with those from other studies [9, 11]. Our study is, to the best of our knowledge, the first study to approach the prevalence of VRFs in regard to the biological-based AT(N) classification in a memory clinic setting, therefore adding new insights about possible associations between AT(N) biomarkers, VRFs, and clinical characteristics.

In our data, carotid artery stenosis was associated with pathological $A\beta_{42}$ and T-tau values. Previous studies have shown, that midlife VRFs are associated with elevated brain amyloid levels in positron emission tomography [29], although the particular association between carotid artery stenosis and amyloid-pathology was not found in another study [30]. On the other hand, the same study found [30] intracranial artery stenosis to be related to amyloid-independent neurodegeneration, which is in line with our findings on the association with T-tau pathology. Our results suggest, that macroangiopathy, leading to chronic hypoxia, might be a relevant risk factor for both amyloid-independent and amyloid-related brain pathology.

Furthermore, we found that diabetes mellitus and alcohol abuse were associated with worse MTA scores in the total cohort. Additionally, atrial fibrillation was related with worse atrophy scores in the non-AD change group and carotid artery stenosis, with higher atrophy scores in AD continuum group. In previous studies, various VRFs, such as diabetes mellitus [31] and arterial hypertension [32] have been found to be associated with lower medial temporal lobe volume. Our results, showing different associations between VRFs and atrophy scores depending on the AT(N) group, suggest the importance of considering both AD biomarkers as well as VRFs, when assessing the clinical and neuroimaging characteristics of patients in memory clinic.

During the data analysis, we have also investigated, whether there was a difference in the association of VRFs, biomarkers, and cognition in subjects with treated versus untreated arterial hypertension, diabetes, atrial fibrillation, and dyslipidemia. We did not find any difference in treated and untreated subjects for these outcomes.

When analyzing the MRI measures, we found that parietal atrophy was an important parameter in distinguishing AD continuum subjects from normal and non-AD change AT(N) groups. This emphasizes the importance of considering not only the medial temporal lobe atrophy, but also other brain areas, especially the parietal region, as well as microbleeds when considering the AD diagnosis. We also found more cortical microbleeds in AD continuum than in any other AT(N) group. As the neuropathological intersection between AD and cerebral amyloid angiopathy is widely known [33], it is likely, that in subjects with microbleeds, positive amyloid biomarkers, and cognitive decline both pathologies are present simultaneously.

Our results on the impact of atrial fibrillation on MMSE are in line with previous studies, which found a link between dementia and atrial fibrillation independently from stroke history [6]. Other studies also found VRFs, such as hypertension, smoking, and diabetes to be associated with an increased risk of cognitive impairment and dementia [34]; however, we did not observe this link with any other risk factor. This unexpected result might be explained by the cross-sectional, rather than longitudinal nature of our study. Another limitation is that in our study we mainly analyze the late life risk factors in a "real world" memory clinic setting. Including a younger population and investigating midlife VRFs might reveal additional insights on this association as well. Although analysis involving the clinical severity of the cognitive decline (e.g., CDR score) did not reveal additional associations in our study, one could expect that with increasing level of cognitive impairment, more or stronger associations between VRFs and AD biomarkers might emerge. Future studies should consider this, when exploring the association between the vascular and AD pathologies in cognitive decline.

The strengths of this study are the relatively large memory clinic-based dataset of 838 subjects with available CSF and neuroimaging markers, allowing the AT(N) classification. The limitations are mostly due to the heterogeneity of the sample and patient differences between Maastricht and Aachen. We therefore have used standardized protocols when harmonizing the data as well as corrected analysis for study center when calculating multivariate models. The clinical setting of the study has made the harmonization of the data and clear definition of risk factors rather difficult and led to some variables with high amounts of missing data (e.g., pack-years for smoking was not available in most of the cases) or underreporting, which is often seen in such type of studies. Another possible limitation of the study stems clinical nature of the study: as our data were obtained from a clinical setting, the first etiological assessment (or etiological diagnosis) was often based on anamnestic and clinical evaluation, before the full

diagnostics, including biomarkers, have been completed. That is why these are rather clinical, and not biomarker-based diagnoses.

Although vascular burden is clearly an important aspect of dementia pathophysiology, adding the (V) factor to the AT(N) classification remains a challenging task because of the complex and heterogeneous association between VRFs, AD biomarkers, clinical and neuroimaging characteristics. Additionally, the difficulty to find clear and strong associations between V and AT(N) suggests at least a partial independence between those two pillars of the pathophysiology of cognitive decline. In our study we suggest the associations of VRFs, AD biomarkers, and cognition, but do not intend to build a V factor, as our results do not allow it.

In summary, we found that VRFs are very common in memory clinic patients, showing distinct differences between different AT(N) biomarker profiles. VRFs show an association with biomarkers, neuroimaging and clinical characteristics, emphasizing the importance of their therapeutic control in memory clinic patients, in order to improve the prevention and treatment of dementia. Furthermore, well controlled studies in clinical settings, investigating the coexistence of vascular burden and AD pathology are needed to gain a better understanding of this highly complex relationship.

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SUPPLEMENTARY MATERIAL

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