

RESEARCH ARTICLE

Sex differences in memory clinic patients with possible vascular cognitive impairment

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Abstract

Introduction: We aimed to establish sex differences in vascular brain damage of memory clinic patients with possible vascular cognitive impairment (VCI).

Methods: A total of 860 memory clinic patients (aged 67.7 ± 8.5 ; 46% female) with cognitive complaints and vascular brain damage (ie, possible VCI) from the prospective TRACE-VCI (Utrecht-Amsterdam Clinical Features and Prognosis in Vascular Cognitive Impairment) cohort study with 2-year follow-up were included. Age-adjusted female-to-male differences were calculated with general linear models, for demographic variables, vascular risk factors, clinical diagnosis, cognitive performance, and brain magnetic resonance imaging markers.

Results: We found no difference in age nor distribution of clinical diagnoses between females and males. Females performed worse on the MMSE (Mini-Mental State Examination) and CAMCOG (Cognitive and Self-Contained Part of the Cambridge Examination for Mental Disorders of the Elderly). Females had a larger white matter hyperintensity volume, while males more often showed (lacunar) infarcts. There was no difference in microbleed prevalence. Males had smaller normalized total brain and gray

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matter volumes. During follow-up, occurrence of cognitive decline and institutionalization was comparable, but mortality was higher in males.

Discussion: Our results suggest that susceptibility and underlying etiology of VCI might differ by sex. Males seem to have more large vessel brain damage compared to females that have more small vessel brain damage.

KEYWORDS

CAMCOG, infarcts, microbleeds, MMSE, mortality, sex differences, vascular cognitive impairment, white matter hyperintensities

1 | INTRODUCTION

Dementia disproportionately affects females. The lifetime risk of dementia is 19% in males versus 31% in females.¹ Vascular pathology occurs in the majority of dementia cases, including patients with a clinical diagnosis of Alzheimer's disease (AD). This vascular burden in dementia is referred to as vascular cognitive impairment (VCI).² The influence of sex on the incidence and prevalence of VCI is unknown. Only in post-stroke dementia the influence of sex has been studied—with conflicting results.³ Worldwide stroke prevalence, however, whether ischemic or hemorrhagic, is 44% higher in males than females.⁴

For cardiovascular disease, there is accumulating evidence indicating sex-specific patterns of disease manifestation, risk factors, and prognosis. For instance, males who are diagnosed with myocardial infarction often (60%) have visible coronary obstructions at angiography, while this is only seen in a minority of females (20%).⁵ It is suggested that this represents a greater role of microvascular disease in the pathophysiology of cardiac events among females.⁶ Hypertensive females have an estimated three-fold higher risk of developing heart failure or stroke compared to males.⁵ Females have a worse outcome after stroke, in contrast to heart failure, from which females have a more favorable outcome compared to males.⁷

To date, there are very little existing data regarding potential modulating effects of sex in VCI. While a better appreciation of sex differences in manifestation, risk factors and prognosis are crucial to advance clinical care of VCI.⁸ We therefore aim to establish sex differences in the vascular brain damage and prognosis of memory clinic patients with possible VCI.

2 | METHODS

2.1 | Study population

Patients were included from the TRACE-VCI (Utrecht-Amsterdam Clinical Features and Prognosis in Vascular Cognitive Impairment) study population, a prospective multicenter cohort study on memory clinic patients with possible VCI (n = 860) in the Netherlands. The rationale and design of the TRACE-VCI study has been

published previously.⁹ In short, the cohort consists of consecutive patients attending the memory clinics of the Amsterdam University Medical Center, location VUMC and from two outpatient memory clinics of the University Medical Center Utrecht (UMCU) between September 2009 and December 2013. Patients were not primarily selected for a particular clinical diagnosis and included regardless of severity of their cognitive deficit, including patients with no objective cognitive impairment (NOCI), mild cognitive impairment (MCI), and dementia. All patients showed evidence of vascular brain damage on magnetic resonance imaging (MRI), which was operationalized as the presence of at least one of the following neuro-imaging markers: (1) mild white matter hyperintensities (WMH; Fazekas scale grade 1¹⁰) and an increased vascular risk defined as the presence of ≥ 2 vascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus, obesity, current smoking, or a reported history of a vascular event other than stroke), (2) moderate to severe WMH (Fazekas scale grade ≥ 2), (3) ≥ 1 lacunar infarct(s), (4) ≥ 1 non-lacunar (large vessel) infarct(s), (5) ≥ 1 cerebral microbleed(s), (6) ≥ 1 intracerebral hemorrhage(s) (ICH)/macrobleed(s). The presence of co-occurring etiologies, in addition to vascular damage, such as neurodegenerative pathology or depression, was accepted, in line with earlier proposed VCI criteria.² Patients with a presumed primary etiology other than vascular brain damage or neurodegeneration (eg, brain tumors, hydrocephalus, and excessive alcohol consumption) were excluded.

Each patient underwent a standardized extensive one-day memory clinic evaluation including an interview, physical and cognitive neurological examination, laboratory testing including cerebrospinal fluid (CSF) examination, extensive neuropsychological testing, and a MRI scan of the brain. Male or female sex was determined based on the information on the medical chart. Patient data collection and storage were performed in accordance with national and international regulations, with approval by the local ethics committees, and with informed consent of the patients, where applicable.

2.2 | Interview and physical examination

Patients received a standardized diagnostic assessment performed by a neurologist or geriatrician including an interview on cognitive

complaints and medical history, medication use (verified through current pharmacy listings), educational level (defined according to a 7-point rating scale¹¹), smoking, alcohol and drug abuse, family medical history, and social status. Patients were asked to bring a relative or good friend for an informant interview. Physical examination included blood pressure measurement, height (centimeters), and weight (kilograms). Depressive symptoms were evaluated by the 15-item Geriatric Depression Scale (GDS).¹²

2.3 | Cognitive assessment

We used the Dutch version of the Mini-Mental State Examination (MMSE; maximum score of 30) as a cognitive screening test.¹³ The severity of cognitive symptoms was assessed using the Clinical Dementia Rating (CDR; 0-3) global score.¹⁴ Furthermore, the cognitive and self-contained part of the Cambridge Examination for Mental Disorders of the Elderly (CAMCOG; maximum score of 107) was performed.¹⁵

All participants underwent a neuropsychological examination, with some variation between centers and over time. Harmonization of the test battery had been established through a Dutch multicenter university memory clinic research program on diagnosis and prognosis of cognitive impairment and dementia.¹⁶ Tasks that were available for the majority of patients (>70%) were included. The domain memory was assessed by the Dutch version of the Rey Auditory Verbal Learning Test (RAVLT)¹⁷ and the Visual Association Test (VAT) part A.¹⁸ The domain attention and executive functioning was assessed using the ratio of the Trail-Making Test part B and A (TMT-B and TMT-A),¹⁹ the Stroop Color Word Test card III,²⁰ and the category naming tasks (animal naming, one minute) and lexical fluency tasks (1 minute per letter).²¹ The domain information processing speed was assessed by the TMT-A, the Stroop Color Word Test card I and II, and the Digit Symbol-Coding Test (DSCT) of the WAIS-III or the Letter Digit Substitution Test (LDST).^{22,23} The cognitive domain perception and construction was assessed using the Fragmented Letters and Dot Counting subtests of the Visual Object and Space Perception Battery (VOSP).²⁴ The domain working memory was assessed by the Digit Span of the Wechsler Adult Intelligence Scale—3rd edition (WAIS-III).²² The availability per task is presented in Table S1 in supporting information. Z-scores based on the total study population were created for each individual test (inverted Z-scores for the TMT and Stroop Color Word Test, so that higher scores imply a better performance). The available test Z-scores were averaged to create Z-scores per domain.

2.4 | Laboratory testing

In 84% (724/860) of patients, apolipoprotein E (APOE) genotyping was performed. Subjects were classified as APOE ϵ 4 carriers if they had one or two ϵ 4 alleles and as non-carriers if they had none.⁹ CSF concentration of amyloid beta ($A\beta$), tau and/or tau phosphorylated at threonine-181 were measured in 63% (541/860) of patients, at a central

RESEARCH IN CONTEXT

- 1. Systematic review:** With a PubMed search we did not identify papers reporting on sex differences in VCI in a memory clinic setting. Sex differences have been reported in population based cohorts and *post mortem* studies.
- 2. Interpretation:** We show that patterns of brain tissue damage, history of vascular disease, and mortality rate differed by sex, suggesting different underlying etiologies. Males were more highly educated and more often brought their spouse as informant; this can influence the diagnostic process. Clinical diagnosis did not markedly differ; however, female patients perform worse on MMSE (Mini-Mental State Examination) and CAMCOG (Cognitive and Self-Contained Part of the Cambridge Examination for Mental Disorders of the Elderly), suggesting that females are more severely affected at presentation. Overall, stratification by sex revealed potentially relevant differences in clinical presentation of VCI.
- 3. Future directions:** Corroboration of our results is needed, to confirm relevant sex differences in VCI. Future studies on VCI should stratify rather than adjust for sex.

laboratory for clinics at the Department of Clinical Chemistry of Amsterdam UMC.²⁵

2.5 | MRI assessment

Brain MRI scans were performed on 3.0 tesla (809 out of 860 patients [94%]) or 1.5 tesla MRI scanners (51 patients [6%]). Most scans were performed on a General Electric (GE) (619 patients [72%]) or Philips (239 patients [28%]) MRI scanner. The MRI scan protocol included, among others, the following sequences: near-isotropic 3D T1-weighted, T2-weighted, T2*-weighted/susceptibility-weighted imaging (SWI), and fluid-attenuated inversion recovery (FLAIR) sequences. The vast majority of patients (849 [99%]) were scanned using all of these sequences. In 11 patients (1%) a 2D T1-weighted sequence was acquired instead of a 3D T1-weighted sequence and/or no FLAIR sequence was available. Further details of the MRI sequence parameters were described in the design article of the TRACE-VCI-study.⁹

2.5.1 | Visual MRI ratings

WMH were rated on FLAIR images using the Fazekas scale (WMH grade 0 to 3: none or a single punctate lesion, multiple punctate lesions [mild WMH], beginning confluent lesions [moderate WMH], large or confluent lesions [severe WMH]).¹⁰ Non-lacunar and lacunar

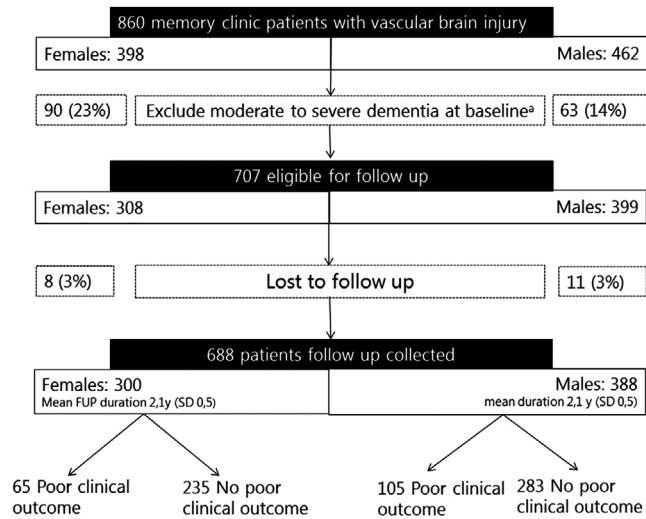


FIGURE 1 Flowchart of patients eligible for follow-up and primary outcome measures. *Mini-Mental State Examination (MMSE) score of <20 and/or a Clinical Dementia Rating (CDR) of >1 at baseline visit

infarct(s), microbleed(s), and ICH/macroblood(s) were rated in line with the STRIVE (standards for reporting vascular changes on neuroimaging) criteria.²⁶ Ratings were performed by or under the supervision of a neuroradiologist.

2.5.2 | Image processing

A stepwise semi-automated processing pipeline was used to obtain WMH and brain volumes as reported previously.²⁷ In short, WMHs were automatically segmented using k-nearest neighbor classification with tissue type priors.²⁸ Next, WMH lesion-filled 3D T1 images were automatically segmented using the Computational Anatomical Toolbox—CAT12.²⁹ Quality assessment was performed visually on all segmentations. No manual editing was found to be needed. Gray matter volumes, white matter volumes, and CSF volumes were obtained from the probabilistic segmentations using MeVisLab (MeVis Medical Solutions AG, Bremen, Germany).³⁰ The automated segmentations for total brain, white/gray matter, and WMH volumes were subsequently corrected for manually created segmentations of infarcts or hemorrhages and incidental findings (eg, meningioma). A total of 823 (95.7%) scans passed quality control and were evaluated through the pipeline.²⁷

2.6 | Follow-up investigation

Follow-up data were collected around 2 years from baseline only from patients with a MMSE score of ≥ 20 and/or a CDR of ≤ 1 at baseline visit (ie, those who did not already have moderate to severe dementia at baseline were eligible) either during a (return) visit at the out-patient clinic, or by phone. To complement the information a close relative or friend also was contacted. Figure 1 shows a flowchart of eligibility and

availability for follow-up and primary outcome measures. Among 707 (82%) patients with follow-up, there were more males (399/462) than females (308/398). Out of the 707 patients with follow-up, at least one outcome measure was available from 688 (97.3%); female: 97.4%, male: 97.2%. Fourteen patients (six females, eight males) were lost to follow-up and five (two females and three males) gave no permission to collect follow-up data. Mean follow-up duration was 2.1 years (range 0.2 to 3.0) and this did not differ between the sexes.

The primary outcome measure in the TRACE-VCI study was poor clinical outcome, defined as (1) marked cognitive decline (2) occurrence of a major vascular event, and/or (3) death. Marked cognitive decline was defined as a change in CDR of ≥ 1 and/or institutionalization due to cognitive dysfunction during the follow-up period.³¹ Occurrence of a major vascular event during follow-up was defined as a stroke, myocardial infarction, or clinical manifestations of arterial disease requiring surgical or endovascular intervention.

2.7 | Statistical analysis

Demographic variables, vascular risk factors, measures of global cognitive status, and distribution of clinical diagnoses were compared between male and female patients using independent samples t-tests for parametric data, Mann-Whitney *U* tests for non-parametric data, and χ^2 tests for proportions. Next, general linear models were used to obtain female-to-male differences and 95% confidence intervals (CI). All analyses were adjusted for age. In a second model, we adjusted analyses on cognitive screening test results and the cognitive domains for clinical diagnosis (NOCI, MCI, and dementia) and level of education. In a third model, the MRI markers were adjusted for age and type of scanner. Finally, in the subgroup with available APOE status (84%), we evaluated a putative interaction with APOE by adding APOE $\epsilon 4$ carrier and the interaction APOE*sex to models two and three. Sensitivity analyses on brain MRI features were performed in (1) subjects with objective cognitive impairment (excluding NOCI) and (2) subjects without known AD pathology, based on CSF biomarker profile. AD-CSF biomarker was defined as CSF ratio tau/A β > 0.52.³²

Follow-up data were analyzed using Cox proportional hazard models, to assess the risk of males (in reference to females) on the time-to-event for the combined poor clinical outcome and each separate outcome. Cox proportional hazard models were adjusted for age and additionally also for clinical diagnosis and medical history of vascular events.

All analyses were done with the use of SPSS (version 21; SPSS, Chicago, IL, USA), and associations were judged to be significant with *P*-value < .05. We took multiple comparisons in account by controlling the false discovery rate.³³

3 | RESULTS

Sociodemographic characteristics and vascular risk factors are shown in Table 1. Of the 860 patients with possible VCI, 54% were male and

TABLE 1 Demographic characteristics and vascular risk factors at baseline

	Female n = 398	Male n = 462	Female-to-male difference (95% CI)
Age	67.3 ± 8.7	68.0 ± 8.3	-0.7 (-1.9:0.4)
Education ^a			
Low	65 (16%)	54 (12%)	4% (-0.2:9)
Middle	213 (54%)	205 (45%)	9% (2:16)
High	119 (30%)	199 (43%)	-13% (-20:-7)
Marital status			
Married	236 (59%)	389 (84%)	-26% (-31:-20)
Separated	53 (13%)	23 (5%)	8% (4:12)
Widow(er)	67 (17%)	23 (5%)	13% (9:16)
Cohabiting	12 (3%)	10 (2%)	1% (-1:3)
Single	29 (7%)	14 (3%)	4% (1:7)
Caregiver present at visit			
Partner	199 (50%)	358 (78%)	-30% (-36:-24)
Relative	135 (34%)	52 (11%)	24% (19:29)
Different	21 (5%)	12 (3%)	3% (-0:5)
Non	29 (7%)	18 (4%)	3% (0.1:6)
APOE ε4 carrier (n = 724)	186 (54%)	192 (50%)	4% (-4%:11%)
Vascular risk factors			
Number of risk factors (0-7)	2 (1-3)	2 (1-4)	
Hypertension ^b	337 (85%)	392 (85%)	0% (-5:5)
Hypercholesterolemia ^c	161 (41%)	225 (49%)	-8% (-15:-1)
Diabetes mellitus ^d	63 (16%)	96 (21%)	-5 (-10:0.4)
Current smoker	74 (19%)	99 (21%)	-4% (-9:2)
Obesity ^e	99 (25%)	77 (17%)	8% (3:14)
History of			
Atrial fibrillation ^f	8 (2%)	25 (5%)	-3 (-6:-0.7)
Reported stroke	26 (7%)	52 (11%)	-5% (-9:-1)
Reported vascular event other than stroke ^g	16 (4%)	70 (15%)	-11% (-15:-7)
Ischemic heart disease ^h	11 (3%)	46 (11%)	
Carotid artery stenting	3 (1%)	1 (0.2%)	
Peripheral arterial disease ⁱ	7 (2%)	24 (5%)	
Clinical diagnosis			
No objective cognitive impairment	94 (23.6%)	104 (22.5%)	0% (-5:5)
MCI	89 (22.4%)	124 (26.8%)	-4% (-10:2)
Dementia			4% (-3:11)

(Continues)

TABLE 1 (Continued)

	Female n = 398	Male n = 462	Female-to-male difference (95% CI)
Alzheimer's disease	155 (38.9%)	149 (32.3%)	
Vascular dementia	17 (4.3%)	20 (4.3%)	
Dementia other ^j	30 (7.5%)	51 (11.0%)	
Unknown etiology ^k	13 (3.3%)	14 (3.0%)	
Clinical Dementia Rating	0.5 (0-1)	0.5 (0-1)	0.05 (-0.02:0.12)
Geriatric Depression Scale ≥5	121 (33%)	130 (29%)	3% (-4:9)

Abbreviations: CI, confidence interval; MCI, mild cognitive impairment.

Data are presented as n (%) or means ± SD.

Sex difference calculated as female-to-male adjusted for age. Significant differences are in bold ($P < .05$).^aAccording to Verhage, Level 1-7, divided in three categories 1-3, 4-5, and 6-7 (five missing data).^bBased on a self-reported medical history, use of antihypertensive drugs, or a newly diagnosed hypertension defined as a systolic pressure ≥140 mmHg or a diastolic pressure ≥90 mmHg.^cBased on medical history or medication use.^dBased on medical history or medication use. Glucose or HbA1c levels were available from 96.9% (834/861) of patients. Patients were classified as newly diagnosed diabetes mellitus if they had a non-fasting glucose of ≥11.1 mmol/L or an HbA1c ≥48 mmol/mol (or ≥6.5%).^eDefined as a baseline body mass index ≥30, calculated as weight in kilograms divided by height in meters squared.^fBased on a history of paroxysmal and permanent atrial fibrillation.^gDefined as a myocardial infarction, surgery, or endovascular treatment for coronary artery disease, any arterial occlusion or surgical intervention of a peripheral artery (such as an abdominal or leg artery) or carotid artery intervention (stenting or endarterectomy).^hMyocardial infarction, surgery, or endovascular treatment for coronary artery.ⁱAny arterial occlusion or surgical intervention of a peripheral artery (eg, abdominal or leg artery).^jFrontotemporal dementia, Lewy body dementia, and others such as Primary Progressive Aphasia, Cortical Basal Syndrome, and Progressive Supranuclear Palsy.^kDementia of unknown origin; further examination needed to state diagnosis.^{*}Remained significant after correction for multiple testing.

46% female. The average age was 67.7 (standard deviation [SD] 8.5) and age was comparable between sexes. The proportion of males with a high level of education was higher than females (high school or higher 43% vs 30%; $P < .001$). Females more often lived alone (37% were widows, separated, or single) compared to males (13%). Accordingly, males more often (78%) brought their partner as informant compared to females (50%). The total number and type of vascular risk factors differed by sex. Males more often had hypercholesterolemia (49% vs 41%; $P = .02$), atrial fibrillation (5% vs 2%; $P = .01$), and a history of a vascular event including stroke (26% vs 11%; $P < .001$). By contrast, females more often had obesity compared to males (25% vs 17%, $P = .002$) and 3% of females were underweight (body mass index [BMI] ≤18) while

TABLE 2 Cognitive functioning assessment at presentation

	Female n = 398	Male n = 462	Female-to-male difference (95% CI)
Measures of global cognitive status			
MMSE	25 (17-29)	26 (18-29)	-0.9 (-1.4:-0.3)[*]
CAMCOG (n = 697) ^a	79 (66-90)	85 (74-92)	-2.7 (-4.3:-1.0)[*]
Poor performance			
MMSE < 21	98 (25%)	67 (15%)	9% (4%:13%)[*]
CAMCOG ^b	197 (61%)	172 (47%)	12% (6%:17%)[*]
Cognitive domains (z-scores)			
Working memory	-0.05 ± 0.8	0.04 ± 0.9	-0.04 (-0.15:0.07)
Memory	-0.04 ± 0.9	-0.04 ± 0.8	0.04 (-0.06:0.13)
Attention and executive functioning	-0.13 ± 0.8	-0.09 ± 0.8	0.01 (-0.09:0.09)
Information processing speed	-0.09 ± 1.0	-0.09 ± 1.0	0.04 (-0.09:0.16)
Perception and construction	-0.05 ± 1.0	-0.01 ± 0.8	-0.01 (-0.13:0.13)

Abbreviations: CAMCOG, Cognitive and Self-Contained Part of the Cambridge Examination for Mental Disorders of the Elderly; CI, confidence intervals; IQR, interquartile range; MMSE, Mini-Mental State Examination; VCI, vascular cognitive impairment.

Notes: Data are presented as n (%) or median (IQR).

Sex difference calculated as female-male adjusted for age, level of education and clinical diagnosis. Significant differences are in bold ($P < .05$).

^aThe outpatient memory clinic of the UMCU did not perform the CAMCOG, and the VCI outpatient clinic of the UMCU introduced it at a later stage; therefore, 163 (18.9%) were missing, females n = 325, males n = 368

^bReference values of the CAMCOG score depend on education level and age; this analysis is therefore only adjusted for clinical diagnosis.

^{*}Remained significant after correction for multiple testing.

TABLE 3 Brain magnetic resonance imaging (MRI) features at baseline

	Female N = 398	Male n = 462	Female-to-male difference (95% CI)
Intracranial volume (ICV) ^a	1367 mL ± 109	1528 mL ± 135	
Cerebrovascular lesions			
Non-lacunar (sub)cortical infarcts	34 (9%)	62 (13%)	-5% (-9%:-0.4%)
Lacunar infarcts	72 (18%)	116 (25%)	-6% (-12%:-0.7%)
Intracerebral hemorrhages	7 (2%)	9 (2%)	-0.2% (-2:2%)
Microbleeds (all locations) ^b	160 (40%)	208 (45%)	-4% (-11%:2%)
WMH volume (% of ICV)	0.97% ± 1.2	0.77% ± 1.0	0.22% (0.08:0.36)[*]
Cerebral volumes			
Total brain volume as % of ICV	71.3% ± 4.1	70.4% ± 4.2	0.70% (0.24:1.2)[*]
Total gray matter volume as % of ICV	38.8% ± 3.2	37.9% ± 3.0	0.85% (0.52:1.2)[*]
Total white matter volume as % of ICV	32.4% ± 2.1	32.4% ± 2.3	-0.14% (-0.41:0.14)

Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation; WMH, white matter hyperintensities.

Notes: Data presented as mean ± SD or n (%).

Sex difference calculated as female-male adjusted for age and scanner type. Significant differences are in bold ($P < .05$).

^aAutomated segmentation brain volumes were available for 823 (96%); females 15 missing and males 22 missing).

^bMicrobleed(s) ratings were available for 848 (99%) patients (females 4 missing, males 8 missing).

^{*}Remained significant after correction for multiple testing.

none of the males was underweight. The presence of hypertension, diabetes mellitus, and current smoking did not significantly differ between females and males. Symptoms of depression (GDS ≥ 5) were equally common among females (33%) and males (29%).

There were no between-sex differences in syndrome diagnosis (NOCI, MCI, or dementia), nor in dementia subtypes (AD, vascular dementia [VaD], other). Also, CDR scores did not differ by sex. Table 2 shows baseline cognitive functioning of males and females.

TABLE 4 Follow-up measurements

	Female n = 300	Male n = 388	HR (95% CI) [†]
Poor clinical outcome	65 (22%)	105 (27%)	1.25 (0.91-1.70)
Based on first event:			
Cognitive decline	45 (15%)	55 (14%)	0.94 (0.63-1.40)
Change in CDR \geq 1	26 (9%)	38 (10%)	
Institutionalization due to cognitive dysfunction	19 (6%)	17 (4%)	
MACE	6 (2%)	14 (4%)	1.77 (0.68-4.61)
Fatal stroke ^a	1	4	
Non-fatal stroke ^a	5	10	
Non-fatal myocardial infarction	-	1	
Death	10 (3%)	27 (7%)	2.1 (1.02-4.35)

Abbreviations: CDR, clinical dementia rating; CI, confidence interval; HR, hazard ratio; IQR, interquartile rating; MACE, major adverse cardiovascular event. Nots: Data presented as n (%), median (IQR).

^aStroke is defined as ischemic stroke and intracerebral hemorrhage.

[†]Analyses adjusted for age, female sex is the reference. Significant differences are in bold ($P < .05$).

Females performed worse on MMSE (25% females vs 15% males had a MMSE < 21; $P < .001$) and CAMCOG (below age and educational level cutoff in 61% females and 47% males; $P < .001$). However, performance in the five cognitive domains—working memory, memory; attention; executive functioning; information processing speed and perception; and construction—did not differ between sexes. There was no interaction between sex and APOE ϵ 4 carrier. The individual neuropsychological test scores that comprise the cognitive domains are shown in Table S1. Females performed better on the RAVLT immediate recall (30.2 ± 11.9 vs 27.9 ± 11.1 ; $P < .001$), TMT ratio (3.2 ± 1.5 vs 3.0 ± 1.3 ; $P = .04$), and letter fluency tasks (27.9 ± 13.4 vs 26.0 ± 13.0 ; $P = .001$), while males performed better on the VAT (9.5 ± 3.4 vs 8.3 ± 4.1 ; $P < .001$).

Brain MRI features at baseline are shown in Table 3. Females had a larger mean (\pm SD) WMH volume (as % of intracranial volume [ICV]: 0.96 ± 1.2 vs 0.77 ± 1.0 ; $P = .002$). Males more often had infarcts (13% vs 9%; $P = .04$) and lacunes (25% vs 18%; $P = .03$) compared to females. The frequency of intracerebral hemorrhages and microbleeds was comparable between the sexes. When adjusting for vascular risk factors only the analyses of infarcts lost statistical significance (female–male difference of -4% [95% CI -8% : 0.4%]; $P = .08$) but the effect size did not markedly change. Males had smaller total brain volume (as % of ICV: 70.4 ± 4.2 vs 71.3 ± 4.1 ; $P = .003$) and gray matter volume (as % of ICV 37.9 ± 3.0 vs 38.8 ± 3.2 ; $P < .001$) than females. When we ran an additional model to assess putative interactions between sex and APOE ϵ 4 carrier, there was only a significant interaction for lacunes. After stratification for APOE ϵ 4 status, a sex-effect in ϵ 4 carriers was found (adjusted female-to-male difference of -9% lacunes [95% CI -16% , -2%]) and not in the ϵ 4 non-carriers (3% [95% CI: -6% , 12%]). There was no difference in total white matter volume (as % of ICV: 32.4 ± 2.1 vs 32.4 ± 2.3 ; $P = .34$). In subjects with objective cognitive impairment ($n = 662$ 46% female; data shown in Table S2 in supporting information) or subjects without known AD-CSF profile ($n = 560$ 43% female;

data shown in Table S3 in supporting information) the results were comparable.

Follow-up outcomes are shown in Table 4. Overall, males tended to more often (27%) meet the primary outcome of overall poor clinical outcome compared to females (22%), but this was not statistically significant. Female and male patients did not differ in substantial cognitive decline (defined as a change of CDR \geq 1 or institutionalization due to cognitive dysfunction), or risk of major adverse cardiovascular events. By contrast, males had a higher mortality rate (hazard ratio [HR] 2.1, 95% CI 1.02-4.35) compared to females; this effect seemed only partially mediated by medical history of vascular events (HR 1.99 95% CI 0.96-4.14).

4 | DISCUSSION

Our main finding is that in memory clinic patients with VCI, the type of vascular damage and mortality rate differ by sex. Male patients more often had lacunar and cortical infarcts, while female patients had more pronounced WMH. In addition, we found that the distribution of vascular risk factors and social characteristics differ by sex.

There are several difficulties in comparing our findings with the current body of literature. Most studies do not report their findings by sex,^{8,34} but solely adjust for sex. In addition, most studies on vascular brain damage do not select for cognitive complaints but are population based, or patients are selected on the presence of a certain form of vascular brain damage.³⁵

Post mortem studies show similar sex differences. In the Religious Orders Study and the Rush Memory and Aging Project, females were more likely to have more severe arteriosclerosis (odds ratio [OR] = 1.28, 95% CI: 1.04 to 1.58, $P = .018$), and less likely to have gross infarcts (OR = 0.78, 95% CI 0.61 to 0.98, $P = .037$).³⁶ The association with gross infarcts was attenuated after controlling for

vascular risk factors. In our study, too, the sex difference in cortical infarcts lost significance after controlling for vascular risk factors. Our male patients had more vascular risk factors and more often had a history of cardiovascular events. However, risk factors are not likely to completely explain the reported sex differences in infarcts, because adjusting for vascular risk factors did not markedly change their effect size. Likewise, adjusting for vascular risk factors did not change the results for lacunar infarcts and WMH. Our findings on sex differences in vascular brain-imaging markers are in line with large-scale population-based studies (Rotterdam study $n > 5000$ ³⁷ and Framingham study $n > 4000$ ³⁸). Those studies show that elderly female subjects have more pronounced WMH,^{37,38} also in cognitively normal participants,³⁹ compared to elderly male subjects. Furthermore, elderly male subjects had a higher prevalence of lacunar and cortical infarcts than female subjects. They did not find a significant difference in the prevalence of microbleeds between male and female subjects.³⁷ Like in our cohort, these population-based studies showed that elderly males have smaller volumes of gray matter (expressed as percentage of intra-cranial volume) compared to elderly females.^{37,38,40} Our study extends those findings, by showing that also in subjects presenting with cognitive complaints at a memory clinic, microvascular disease is more common in females, in contrast to large vessel disease in males.

During neuropsychological testing females performed better on the immediate recall of the RAVLT and letter fluency, while males had higher scores on the VAT. This is in line with known sex differences in the performance on neuropsychological tests. The most consistent cross-sectional difference at all ages is that females perform better on verbal memory tasks⁴¹ and males perform better on visuospatial tasks.⁴² This is also seen in memory clinic cohorts studying AD.^{43,44} In our study, the domain memory comprised of verbal memory (RAVLT) and visual memory (VAT), canceling out sex differences. Indeed, there were no differences by sex in the domain score memory. Previous work in the Alzheimer's Disease Neuroimaging Initiative showed that sex differences in verbal memory persisted despite similar levels of pathology (eg, hippocampal volume).⁴⁴ This suggests a cognitive benefit for females with MCI. Although this advantage may benefit females by delaying verbal memory impairment until more advanced pathology, it may also delay diagnosis of MCI and treatment intervention.⁴³ In our cohort there was no difference in the distribution of severity of the clinical diagnosis (eg, NOCI, MCI, dementia) and the female and male participants were of comparable age at presentation. Female patients, however, performed worse on cognitive screening tools (also after adjustments for level of education), suggesting that they were more severely affected at presentation. It is noteworthy that in contradiction to neuropsychological tests, performance on cognitive screening tests like MMSE are influenced by level of education, but not by sex.⁴⁵

In recent years, there has been a growing awareness of the importance to distinguish between sex, a biological construct, and gender, a social construct. In practice, it is often not possible to rigorously delineate effects of sex and gender.⁴⁶ Sex (or gender) differences in social characteristics, such as level of education and living situation, can influence the memory clinic work-up. Low education has repeatedly

been associated with a higher prevalence and incidence of dementia.⁴² In the past century, men have had more opportunities for higher educational attainment than women.⁴² In line with previous memory clinic studies, our male patients more often attained higher education than female patients. All analyses on cognitive performance were therefore adjusted for level of education. In our cohort male patients more often (78%) came with their partner as informant, compared to female patients (50%). An Australian study has shown that females seek help on behalf of someone else that has early signs of dementia, while males are more likely to delay help seeking.⁴⁷ It is imaginable that female patients present later at a memory clinic because of a delay by their male spouse. This is in line with our finding that females are more severely affected at presentation. In that case the difference would be caused by different gender roles; however, a possible sex-based biological mechanism for faster decline in females cannot be excluded yet.

A strength of this study is the memory clinic setting. Additional strengths of the study include the relatively large sample size, the longitudinal design, and the standardized and detailed recording of imaging markers and cognitive performance. A limitation of our study is that the TRACE VCI cohort was not designed to study sex differences. We defined sex based on the information in the medical chart. There is no information on gender identity or gender role. Another limitation is the absence of information on sex-specific risk factors for both dementia^{8,48} and cerebrovascular disease,⁴⁹ such as preeclampsia, menarche, menopause, and erectile problems. These shared sex-specific risk factors could potentially explain part of the found differences. Specifically, hormone status has been shown to be related to both dementia and stroke risk.⁵⁰

In conclusion, we found sex differences in the phenotype of patients with possible VCI presenting at a memory clinic. Males were more likely to have lacunar infarcts, cortical infarcts, and smaller brain volumes, while females had more pronounced WMH and were cognitively more severely affected at presentation. Males more often died in the 2 years after presentation, potentially due to cardiovascular events. Our results suggest that susceptibility and underlying etiology of VCI might differ by sex. Males seem to have more large vessel brain damage compared to females that have more small vessel brain damage. This could direct different treatment strategies.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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