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Neuropsychiatric symptoms in patients with possible vascular cognitive impairment, does sex matter?

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ABSTRACT

Background: Neuropsychiatric symptoms (NPS) are common in patients with vascular cognitive impairment (VCI). We aimed to establish sex differences in the manifestation of NPS in memory clinic patients with possible VCI and identify which NPS are determinants of clinical progression in women and men separately.

Methods: We included 718 memory clinic patients (age 68 ± 8; 45% women) with cognitive complaints and vascular brain lesions on MRI (i.e. possible VCI). NPS were measured using the 12-item Neuropsychiatric Inventory. Clinical progression after two years (women 18%, men 14%) was defined as increase in CDR ≥1 or institutionalization (available $n = 589$ without advanced dementia at baseline). The association between NPS and clinical progression was assessed with Cox proportional hazard models stratified by sex, adjusted for age and clinical diagnosis and in a second model additionally for manifestations of vascular brain lesions.

Results: Men more often presented with agitation (29% versus 17%, $p<.05$) and irritability (58% versus 45%, $p<.05$), the other 10 NPS (delusions, hallucinations, depression, anxiety, euphoria, apathy, disinhibition, aberrant motor behavior, nighttime disturbances and appetite & eating abnormalities) did not differ between sexes. In women the presence of apathy (HR 2.1[1.1;4.3]) was associated with higher risk of clinical progression. In men the presence of depression (HR 2.7[1.4;5.1]) and aberrant motor behavior (HR 2.1[1.1;3.8]) were associated with increased risk of clinical progression.

Conclusion: Manifestations of NPS in patients with possible VCI differ by sex. Different NPS are associated with future clinical progression in men and women. Management strategies of NPS could benefit from sex-specific approaches.

1. Introduction

Neuropsychiatric symptoms (NPS) are increasingly recognized as important and disruptive clinical features in patients at a memory clinic [1]. They include behaviors such as apathy, irritability, anxiety and nighttime disturbances. NPS are prevalent across the clinical severity spectrum [2]. The presence of NPS have a large impact on the quality of life of both patients and their caregivers [3]. NPS are more closely related to caregiver burden than other symptoms, such as deteriorated cognitive function or limitations in the activities of daily-living [4,5]. Furthermore, the presence of NPS in patients with Alzheimer's Disease (AD) is associated with worse prognosis including more rapid progression of cognitive and functional decline [6,7] and earlier institutionalization[8], leading to higher costs of care [9].

NPS are also common in patients with Vascular Cognitive Impairment (VCI) (review [10]). Different manifestations of vascular brain lesions on MRI are associated with different NPS in patients attending a memory clinic [11–13]. Recently, we showed that female and male patients with possible VCI have different manifestations of vascular brain lesions. Women had a larger white matter hyperintensity (WMH) volume, while men more often showed (lacunar) infarcts [14]. Sex differences in manifestations and predictive value of NPS in VCI are largely unknown. Only one study in a population of patients with vascular dementia (VaD) reported on sex differences in NPS [15]. Female patients

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were more likely to exhibit delusions, hallucinations, and depression and male patients were more likely to exhibit apathy.

Studies have consistently shown that active management of NPS can improve quality of life for both patients and their caregivers [5]. Current dementia strategies have not explicitly considered sex and gender differences in the management of dementia to ensure equitable care [16]. This a consequence of a lack of research on sex- and gender-based differences in dementia. Which in turn has led to an absence of policy and guidelines designed to best answer to the specific respective needs of women and men. We aimed first to establish sex differences in the manifestation of NPS in memory clinic patients with vascular brain lesions and second identify which NPS are determinants of clinical progression in women and men separately.

2. Methods

2.1. Study population

The TRACE-VCI study is a prospective multicenter cohort study on memory clinic patients ($n = 860$) in the Netherlands [17]. Patients were recruited through the Amsterdam Dementia Cohort of the VU University Medical center (VUMC) ($N = 665$) and the outpatient memory clinic and VCI cohort of the University Medical center Utrecht (UMCU) ($N = 196$). These tertiary referral clinics receive referrals from specialists from other memory clinics (e.g., for a second opinion) but also direct referrals from general practitioners. In short, included are consecutive patients (between 2009 and 2013) with cognitive complaints and evidence of at least one of the following manifestations of vascular brain lesions on MRI (i.e. with possible VCI): moderate to severe WMH rated on Fazekas scale ≥ 2, ≥ 1 lacunar infarct(s), ≥ 1 non-lacunar (large vessel) infarct (s), ≥ 1 cerebral microbleed(s), ≥ 1 intracerebral hemorrhage(s) (ICH) /macrobleed(s) and/or mild WMH (Fazekas 1) 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).

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. The presence of co-occurring etiologies, in addition to vascular lesions, such as neurodegenerative pathology or depression was accepted, in line with earlier proposed VCI criteria [18]. Patients with a presumed primary etiology other than vascular brain lesions or neurodegeneration (e.g. brain tumors, hydrocephalus, and excessive alcohol consumption) were excluded.

We included 718 patients with a complete Neuropsychiatric Inventory (NPI). The 139 patients with missing or incomplete NPI were younger and were less cognitively impaired compared to patients with a complete NPI (Supplementary Table 1). Fig. 1 depicts the flowchart of the cohort.

Patient data collection and storage was 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. Procedure

Each patient underwent a standardized extensive one-day memory clinic evaluation including an interview, physical and cognitive neurological examination, laboratory testing, extensive neuropsychological testing and MRI of the brain. Patients were asked to bring a relative or good friend for an informant interview. During a multidisciplinary meeting, a clinical diagnosis (NOCI, MCI, dementia) for each patient was established based on the whole baseline evaluation and international criteria [17].

Follow-up investigation was performed around two years after the baseline evaluation at the memory clinic. Follow-up data were collected

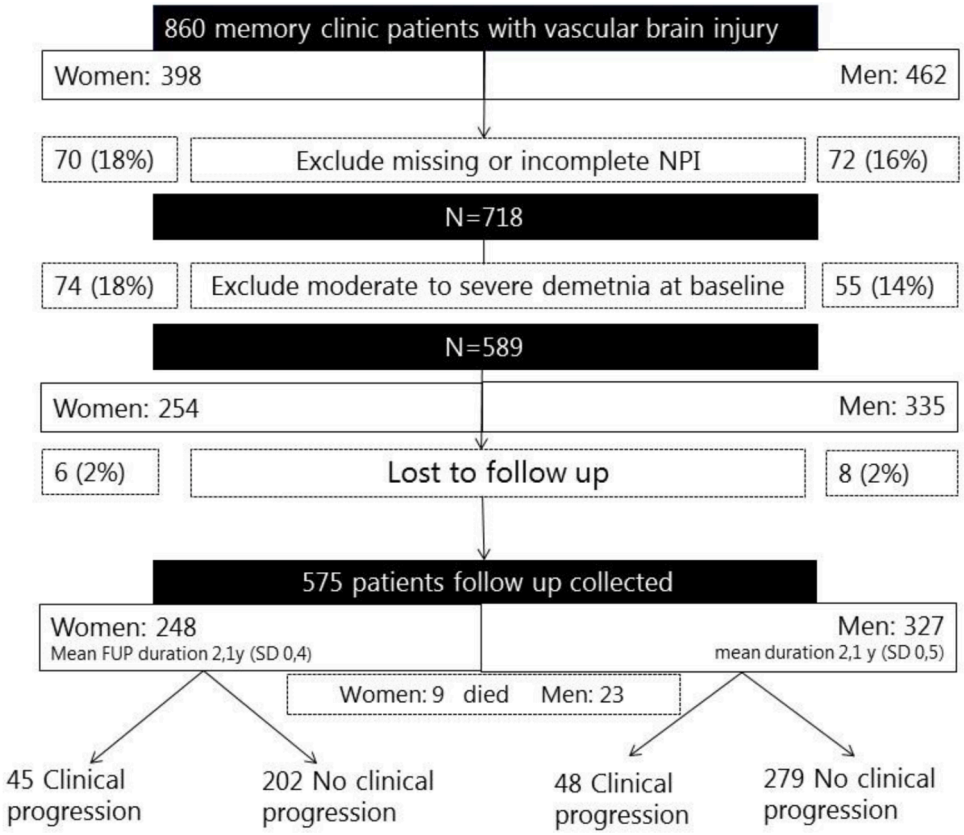

Fig. 1. Flowchart of cohort.

only from patients with a MMSE score of ≥20 and/or a Clinical Dementia Rating Scale (CDR) score of ≤1 at baseline visit (i.e. those who did not already have moderate to severe dementia at baseline) and were not institutionalized ($n = 589$). Patients returned to the memory clinic for a follow-up investigation, including CDR and inquiry of the living situation (i.e. institutionalization and cause). At the baseline visit, the patient and doctor decided if a follow-up visit would be planned. Patients who did not visit the clinic after approximately 2 years were contacted by phone. A close relative or friend was also contacted to complement the information. If patients were unreachable or did not give permission to be contacted, we contacted the patients' general practitioner or doctor of the nursing home if permitted by informed consent at baseline [17,19]. There was no follow-up information from 14 (2%) patients (9 were lost to follow-up and 5 did not provide permission at baseline), resulting in 575 patients included in the longitudinal analyses. Women had on average 2.1 years ((±0.4) and men 2.1 (±0.5) years follow-up. In 149 (59%) women and 204 (61%) men CSF was available to evaluate biomarker CSF AD profile.

2.3. Patient characteristics

During the baseline visit several patient characteristics were collected. Male or female sex was determined based on the information on the medical chart. Level of education is expressed by the Verhage scale, which ranges from Level 1 (less than primary school) to 7 (university degree). The presence of vascular risk factors is based on medical history and medication use. Cognitive functioning at baseline, is evaluated with MMSE and Clinical Dementia Rating Scale (CDR).

2.5. Brain MRI

Brain MRI scans were performed on 3.0 Tesla (682 (95%)) or 1.5 Tesla MRI scanners (36 patients (5%)). The MRI scan protocol included the following sequences: 3D T1-weighted, T2-weighted, T2*-weighted/susceptibility-weighted imaging (SWI) and fluid-attenuated inversion recovery (FLAIR) sequences. Further details of the MRI sequence parameters were described in the design article of the TRACE-VCI-study [17]. WMH were rated using the Fazekas scale (WMH grade 0–3: none or a single punctate lesion, multiple punctate lesions (mild WMH), beginning confluency of lesions (moderate WMH), large confluent lesions (severe WMH)) on FLAIR images [20]. Non-lacunar and lacunar infarct(s), microbleed(s) and ICH/macrobleed(s) were all rated in line with the STRIVE (standards for reporting vascular changes on neuroimaging) criteria [21]. Ratings were performed by or under the supervision of a neuroradiologist (in training).

2.5. Cerebrospinal fluid

CSF concentrations of amyloid-β42 (Aβ42), tau and/or total tau phosphorylated at threonine 181 (p-tau) were measured at a central laboratory for clinics at the Department of Clinical Chemistry of the VUMC [23]. CSF samples were stored at – 20 °C until biomarker analysis (within 2 months). Aβ42, total tau, and p-tau were measured with commercially available ELISAs (Innotest β-amyloid(1 - 42), Innotest hTAU-Ag and Innotest Phosphotau(181ρ), respectively; Innogenetics, Ghent, Belgium) on a routine basis [23]. Patients with a ratio of total tau to amyloid-β42 of more than 0.52 were classified as having a positive CSF biomarker AD profile [22].

2.6. Neuropsychiatric symptoms

During the baseline visit, the 12-item NPI, an informant-based structured interview, was used to evaluate the presence, frequency and severity of NPS including delusions, hallucinations, agitation/aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, sleep/nighttime disturbances and appetite & eating abnormalities [23,24]. For the current study, we defined presence of NPS as a score of ≥1 per item. When a symptom was present, caregivers were asked to rate their experienced distress in relation to this symptom. Due to high rates of missing data on this item, particularly on the most prevalent symptoms like apathy and irritability, we did not use these (experienced distress) scores in the analyses.

2.7. Clinical progression

Clinical progression was defined as an increase in CDR score at follow-up of ≥1.0 ($CDR_{Difference} = CDR_{Follow\text{-}up} - CDR_{Baseline}$) or institutionalization due to cognitive performance. We used the Dutch version of the CDR to determine the severity of cognitive impairment and associated functional deficits, ranging from no dementia (0) to severe dementia (3) [25]. When follow-up information was collected by telephone, we used the modified CDR, which can be completed based on information from the caregiver [26].

2.8. Statistical analysis

Demographic variables, measures of global cognitive status, vascular risk factors, brain MRI measures and the 12 NPS, were compared between male and female patients using independent samples t-tests for parametric data, Mann-Whitney U tests for non-parametric data and $\chi 2$ tests for proportions. Post-hoc, the comparison by sex of the 12 NPS was adjusted for manifestation of vascular brain lesions (i.e. separate variables for the presence of WMH, lacune(s), cortical infarct(s) and microbleed(s)) with regression analyses, The rational for this is the observed sex differences in manifestations of vascular brain lesions and previous studies [11–13] have shown that different manifestations of vascular brain lesions are related to the presence of different NPS.

Follow up data were analyzed using Cox proportional hazard models, to assess the associations between the twelve NPS and the occurrence of clinical progression at two year follow-up, for women and men separately. Cox proportional hazard models were adjusted for age and clinical diagnosis (NOCI, MCI, dementia). In a second model additional adjustment for manifestations of vascular brain injury (i.e. separate variables for WMH, lacune(s), cortical infarct(s) and microbleed(s)) were made. In addition stratified models by biomarker CSF AD profile were made.

All analyses were done with the use of SPSS (version 27; SPSS, Chicago, IL, USA), and associations were judged to be significant with P-value <0.05.

3. Results

Baseline characteristics of the study population are summarized in Table 1. Of the 718 patients with possible VCI, 46% was women and 54% men. There was no difference in age between women (68 ± 9) and men (68 ± 8). Men more often had their partner as caregiver present at the visit (80%) compared to women (51%). Women had on average lower scores on the MMSE (23 ± 5) compared to men (25 ± 5). In both sexes almost half of the patients was diagnosed with dementia, one third with mild cognitive impairment and one fifth with no objective cognitive impairment. Women more often had moderate to severe WMH, while men more often had lacune(s) and cortical infarct(s).

At baseline, 89% of women and 91% of men showed at least one symptom on the NPI. The prevalence of the 12 NPS in women and men are presented in Fig. 2. The three most common NPS in women were apathy (58%), irritability (45%) and depression (35%) and in men apathy (61%), irritability (58%) and nighttime disturbances (33%). In men agitation (29%) and irritability (58%) were more common than in women (17%, $p<.001$; 45%, $p=.001$). None of the symptoms was significantly more common in women. Additional adjustments for MRI manifestations of vascular brain lesions, did not change these results (agitation $p<.001$; irritability $p=.001$). There was no association

Table 1
Demographic characteristics and vascular risk factors at baseline.

	Women*n* = *328*	Men*n* = *390*
Age, years	68 ± 9	68 ± 8
Education[†]		
Low	59 (18)	44 (11)*
Middle	175 (53)	175 (45)*
High	93 (28)	167 (43)*
Caregiver present at visit	308 (94)	364 (93)
Partner	168 (51)	315 (80)*
APOE e4 carrier (*n* = 279/*n* = 324)	155 (56)	170 (53)
Cognitive functioning at baseline		
MMSE	23 ± 5	25 ± 5*
CDR	0.5 [0.5–1]	0.5 [0.5–1]
Level of cognitive impairment		
No objective cognitive impairment	56 (22)	74 (21)
MCI	80 (31)	112 (33)
Dementia	192 (47)	207 (46)
Vascular risk factors		
Hypertension[‡]	282 (86)	337 (86)
Hypercholesterolemia[§]	135 (41)	197 (51)*
Diabetes Mellitus[¶]	52 (16)	80 (21)
Current smoker	62 (19)	80 (21)
Obesity[#]	78 (24)	58 (15)*
Atrium fibrillation**	8 (2)	21 (5)*
History of stroke	20 (6)	38 (10)*
History of vascular event other than stroke [††]	14 (4)	60 (15)*
MRI manifestions		
Fazekas ≥ 2	172 (52)	165 (42)*
≥ 1 Lacune(s)	60 (18)	99 (25)*
≥ 1 Cortical Infarct(s)	27 (8)	50 (13)*
≥ 1 Microbleed(s)*	133 (41)	178 (46)
≥ 1Intracerebral hemorrhage(s)	6 (2)	7 (2)

Data are presented as n (%), means ± SD or median [IQR].

* Significant difference $p<.05$, tested with chi-square, student *t*-test or Mann-Whitney U.

† According to Verhage, Level 1 (less than primary school) to 7 (university degree) divided in 3 categories 1–3, 4–5 and 6–7 (5 missing data).

‡ Based on a self-reported medical history, use of antihypertensive drugs, or a newly diagnosed hypertension defined as a systolic pressure ≥ 140 mm Hg or a diastolic pressure ≥ 90 mm Hg.

§ Based on medical history or medication use.

¶ Based 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 nonfasting glucose of ≥11.1 mmol/l or an HbA1c ≥48 mmol/mol (or ≥6.5%).

Defined as a baseline body mass index ≥30, calculated as weight in kilograms divided by height in meters squared.

** Based on a history of paroxysmal and permanent atrial fibrillation.

†† Defined 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).

between the burden of NPS and the vascular brain lesion burden in either women (p=.34) and men (p=.39.

In the subgroup of patients with biomarker CSF AD positive profile, men more often had agitation (25%) and hallucinations (7%) compared to women (13% and 1%). Women more often had depression (35%) compared to men (18%). In the subgroup with biomarker CSF AD negative profile, men more often had agitation (31%) and irritability (68%) compared to women. In this subgroup none of the symptoms was significantly more common in women. Data are shown in supplementary Table 2.

Follow-up data was obtained in 575 (98%) of eligible patients, with a mean follow-up of 2.1 ± 0.5 years. The duration of follow-up was similar between women and men. During follow-up, 9 women and 23 men died. After two years follow-up, 45 women and 48 men showed clinical progression (Fig. 1). The results of the Cox proportional hazard models for women and men on the association between the different NPS and clinical progression are shown in Fig. 3. In women only apathy was associated with an increased risk of clinical progression (Hazard Ratio [HR]: 2.1, 95% CI [1.1;4.3], p=.03). In men depressive symptoms (HR 2.7 [1.4;5.1], p=.003) and aberrant motor behavior (HR 2.1 [1.1;3.8]) were associated with increased risk of clinical progression. The adjustments for manifestations of vascular brain lesions (Fig. 3), did not markedly change the results.

4. Discussion

In both women and men with vascular brain lesions visiting a memory clinic, NPS are common at the first presentation. Most NPS have a comparable occurrence in women and men, but agitation and irritability were more common in men than in women. Our main finding is that different NPS are associated with clinical progression in men and women with possible VCI, also when known sex-differences in manifestations of vascular brain lesions are taken into account. In women the presence of apathy was associated with an increased risk of clinical progression. While in men depression and aberrant motor behavior were associated with an increased risk of clinical progression. This implies that women and men might benefit from different management strategies of NPS in VCI.

Our findings on the prevalence and pattern of NPS in patients with possible VCI are in line with previous studies concerning NPS in VCI [10]. A review showed that apathy, irritability and depressed mood were the most common symptoms in VCI [10], as did we. Sex differences in the presentation of NPS however are hardly studied. Only one previous study in patients with VaD reported on sex differences. Female patients with VaD are more likely to exhibit delusions (16% versus 7%), hallucinations (10% versus 3%), and depression (43% versus 27%) than male patients. Male patients with VaD are more likely to exhibit apathy (51% versus 35%) than female patients [15]. These findings differ from the current findings. Probably because the cohorts markedly differ. They specifically included patients with a clinical diagnosis of VaD, with focal signs on neurological examination and CDR ≥1, whereas we have a much broader inclusion criteria. We included patients with vascular brain lesions irrespective of the level of cognitive impairment (also individuals with NOCI and MCI). Moreover, the presence of focal signs on neurological examination results in a rather specific patient population in the previous cohort. Our findings highlight that the manifestations of NPS in memory clinic patients with vascular brain lesions are common in both women and men, yet the prevalence and pattern of the different NPS differs by sex.

Different NPS were associated with clinical progression in women and men with VCI. We did not find previous studies on sex differences in the prognostic value of NPS for clinical progression. Several studies have reported that in a memory clinic population, worse NPS at presentation are associated with faster progression of cognitive impairment [7, 27–29] and a higher risk of institutionalization [30]. Also, in the context of VCI, worse NPS are a predictor of poor clinical outcome in memory clinic patients [19]. These previous studies adjust for sex, but do not report the results stratified by sex. To the best of our knowledge, we are the first to show that the predictive value of NPS differs by sex in memory clinic patients with vascular brain lesions.

Several explanations for the reported sex differences in the prevalence, pattern and predictive value of NPS in patients with VCI can be considered. Previously, different manifestations of vascular brain lesions have been associated with different NPS in patients attending a memory clinic. In patients with VaD, apathy and aberrant motor behavior are more prevalent in small-vessel VaD compared with large-vessel VaD. Conversely, euphoria is more prevalent in patients with large-vessel VaD [11]. A meta-analysis on the association of NPS and cerebral small vessel disease suggests that worse WMH severity is associated with apathy [12]. They found insufficient evidence to confirm or refute associations with other NPS or other manifestations of cerebral small vessel disease due to heterogenic study designs. None of the 13 studies included in this meta-analysis report on the potential modifying effect of sex. In our

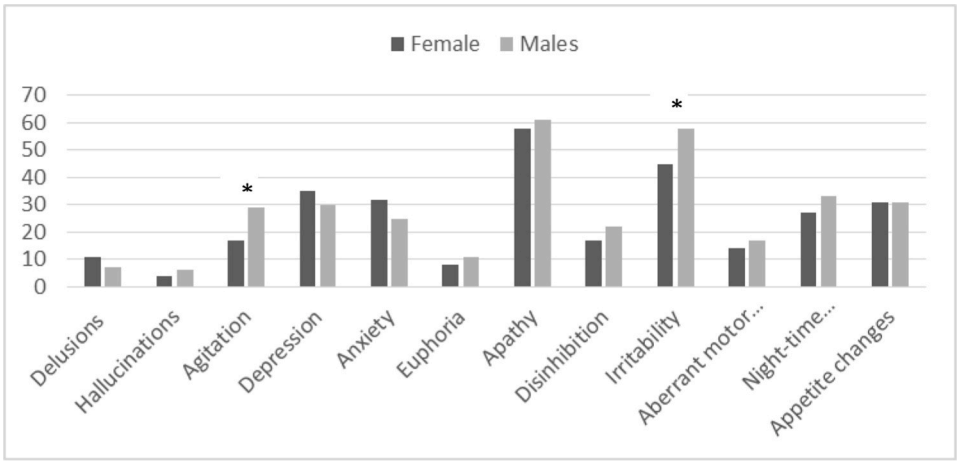

Fig. 2. Percentage of neuropsychiatric symptom at presentation for women and men.
* significant difference $p < 0.05$
Additional adjustments for vascular brain lesions did not change the results.

Model 1 (square) is adjusted for age and clinical diagnosis at baseline

Model 2 (diamond) is additionally adjusted for manifestations of vascular brain lesions

Fig. 3. HR for clinical progression per neuropsychiatric symptom for women and men separate.
Model 1 (square) is adjusted for age and clinical diagnosis at baseline
Model 2 (diamond) is additionally adjusted for manifestations of vascular brain lesions.

population, women were more likely to have worse WMH severity, while men were more likely to have lacunar and cortical infarcts. Adjustments for manifestations of vascular brain lesions, did not markedly change our results on both the prevalence and predictive value. Suggesting, that the reported sex differences in NPS are not likely explained by the differences in vascular brain lesions. In addition, the results are comparable with the subgroup of patients with a negative biomarker AD profile. Indication that our results are not driven by AD pathology. Alternative explanations may include the location and burden of cerebral vascular lesions [31,32]. Furthermore, sex hormone levels can influence the occurrence of NPS. Estradiol and testosterone levels are positively associated with apathy and anxiety in female, but not male patients with VaD [33]. Cognitive reserve may also impact the risk, expression and outcome of NPS [34]. Many of the contributors to cognitive reserve are highly gendered, including education, occupation, physical activity, and social support [35]. In the current study more men had higher levels of educational attainment and more often their partner present as caregiver. Moreover, coping strategies have been shown to differently affect the levels of neuropsychiatric symptoms in women and men. For instance, women with more self-blame, have higher anxiety levels, although a similar effect was not seen in men [36].

The presence of NPS is based on a structured interview with an informant. In the current study, 51% of the female patients and in 80% of male patients the informant was the partner. It can be argued that the sex differences we found could have been related to the perception of the reporting caregiver. Spouses experience a higher degree of burden than non-spouses, which might be explained by the fact that daily contact with a patient suffering from dementia can be stressful [37]. It is reasonable to think that when caregivers are asked to evaluate symptoms that are closely related to burden, such as the patient's neuropsychiatric symptoms, the patients' sleep, or depression, spouses overreport the level of impairment [4,37]. In contrast, when caregivers are asked to evaluate factors related to everyday functioning, the slow and gradual decline, disease denial, or psychological aspects of not wanting to expose the patient might make spouses more prone to underreport, and non-spouses more prone to overreport, the level of impairment [4]. Furthermore, there is an abundance of research on sex differences in emotion recognition, showing women are superior in decoding emotions compared to men [38]. In addition, women in general are more likely to seek medical help compared to men [39]. An Australian study has shown that women seek help on behalf of someone else that has early signs of dementia, while men are more likely to delay help seeking [40]. In the context of reporting NPS, Ott et al. [41], found that sex of the patient rather than of the informant is the stronger predictor of sex differences in behavior in AD. This last study makes it less likely that the current sex differences we found are only related to gender of the reporting caregiver. However, the gender of the caregiver and the and type of relationship with the patient likely influences the reporting of NPS.

Strengths of this study are the relatively large cohort of memory

clinic patients with possible VCI. A high follow-up rate was achieved 2 years from baseline. 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. Also sex and gender of the caregiver is unknown. Another possible limitation of our study is the unrestricted inclusion criteria for possible VCI. By contrast, most diagnostic criteria for VCI state that this construct only applies to patients with MCI or dementia [18,42]. The rationale of the approach of the TRACE VCI cohort is that some patients with cognitive decline as result of vascular brain injury may not present with cognitive deficits that are severe enough to be classified as MCI [17]. Lastly, clinical progression was based on increase in CDR rather than cognitive testing. Nonetheless, the CDR provides information about cognition and clinically meaningful functioning [25]. Furthermore, the use of CDR maximizes our follow-up rate as we could provide clinically relevant information from patients who were not able to visit the clinic for follow-up measurements.

Treatment of NPS can be effective [43] and is recommended, also in early stages of cognitive impairment [44]. Our study highlights that sex differences exist in manifestations and predictive value of NPS in memory clinic patients with vascular brain lesions. Management strategies of NPS may benefit from sex-specific approaches. Since non-pharmacological treatment depends on caregivers. Integrating the gender of the caregiver might improve efficacy and relieve care burden. Future studies aimed at further characterizing the nature of sex differences in NPS among patients with VCI will be valuable in suggesting future targets for treatment.

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Supplementary materials

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