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ORIGINAL ARTICLE

ADAMTS13 and von Willebrand Factor in relation to vascular cognitive impairment and cerebral small vessel disease: the heart-brain connection study

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Abstract

Background: Reduced activity of a disintegrin-like and metalloprotease with thrombospondin type 1 repeats 13 (ADAMTS13) is associated with an increased risk of dementia, independent of Von Willebrand factor (VWF) levels. Pathways underlying this association remain poorly understood.

Objectives: Investigate the associations of VWF levels and ADAMTS13 activity with vascular cognitive impairment (VCI) and cerebral small vessel disease (CSVD).

Methods: In this cross-sectional study, we included 147 participants with VCI and 120 reference subjects (mean age: 67.5 years, 41% women). Using multivariable logistic regression, we determined the cross-sectional association of ADAMTS13 activity and

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VWF levels in plasma with VCI. Additionally, across cases and reference subjects combined, we determined the cross-sectional association of VWF and ADAMTS13 with markers of CSVD on 3T brain magnetic resonance imaging (MRI) scan.

Results: Participants with lower ADAMTS13 activity had a higher odds of VCI (odds ratio [OR] per 1-SD decrease: 1.46 [95% CI, 1.04-2.04]), whereas participants with higher VWF levels did not (OR per 1-SD increase: 1.15 [95% CI, 0.85-1.56]). Overall, lower ADAMTS13 and higher VWF levels were similarly associated with higher white matter hyperintensity volume (mean difference per 1-SD change in ADAMTS13: 0.12 [95% CI, -0.01 to 0.25] and for VWF: 0.13 [95% CI, 0.01-0.26]). For microbleeds, lacunes, and microinfarcts, low ADAMTS13 and high VWF showed ORs of around 2 for the uppermost quartiles, which were statistically significant only for VWF and lacunes. We found no evidence of synergistic effects of ADAMTS13 and VWF.

Conclusions: Low ADAMTS13 activity is associated with VCI, independent of concurrently measured VWF. Low ADAMTS13 activity and high VWF levels are associated with markers of CSVD.

KEYWORDS

ADAMTS13 protein, Von Willebrand factor, vascular cognitive impairment, dementia, cerebral small vessel diseases

1 | BACKGROUND

Vascular brain injury is a key contributor to dementia, present in more than half of all dementia cases [1,2]. Growing evidence implicates endothelial dysfunction and coagulation pathways in the development of vascular cognitive impairment (VCI) [3,4]. Against this backdrop, a disintegrin-like and metalloprotease with thrombospondin type I repeats 13 (ADAMTS13) gained particular interest in the onset of stroke as well as dementia [5-7]. ADAMTS13 is a metalloprotease primarily produced by hepatic stellate cells and known for limiting platelet adhesion through cleavage of ultra-large Von Willebrand factor (VWF) multimers into smaller, less prothrombotic forms [8]. Severe ADAMTS13 deficiency (< 10%), as seen in thrombotic thrombocytopenic purpura, leads to the formation of microthrombi in small vessels, resulting in neurological symptoms such as stroke and confusion in about 60% of cases [9]. Lower levels of ADAMTS13 in the general population (< 70%-80%) are associated with a higher risk of coronary heart disease, ischemic stroke, and dementia [6,7,10]. This suggests that low activity of ADAMTS13—even within the normal range—can contribute to a prothrombotic state, vascular brain injury, and potentially cognitive impairment. While the association between lower ADAMTS13 activity and increased cardiovascular disease risk is fairly well-established [11], only 1 previous study reported on and found an association with dementia [7]. Moreover, the increased risk of ischemic stroke was highest in those with elevated VWF levels [6], but the observed association with dementia appeared independent of VWF levels [7].

This calls for further study exploring the underlying pathways above and beyond those related to VWF.

Beyond its hemostatic function, exploratory analyses have found associations between ADAMTS13 as well as VWF and dementia-related pathways such as inflammation, extracellular matrix degradation, and vascular remodeling [7,12-14]. These mechanisms also play a part in the etiology of cerebral small vessel disease [15,16], an important risk factor of dementia [17-20]. Indeed, the 1 study to date ($n = 296$) on the association between ADAMTS13 and small vessel disease found lower ADAMTS13 activity to be cross-sectionally associated with increased cerebral small vessel disease [21]. As such, combining clinical and subclinical phenotyping within the same population may help disentangle the role of ADAMTS13 in neurodegenerative disease.

Therefore, we investigated associations of ADAMTS13 activity and VWF quantity with VCI and separate MRI scan markers of cerebral small vessel disease.

2 | METHODS

2.1 | Study population

This study was part of the heart-brain connection (HBC) study (a multicenter study that recruited patients aged 50 years and older with VCI, heart failure, and carotid occlusive disease between 2014 and 2017 across 4 university medical centers in the Netherlands:

Leiden University Medical Centre, Maastricht University Medical Centre, University Medical Centre Utrecht, and Amsterdam University Medical Centre. Recruitment and methods of the HBC study have been described in detail previously [22]. We included patients with VCI who were older than 50 years and able to undergo a magnetic resonance imaging (MRI) scan and cognitive testing. Inclusion criteria for VCI were cognitive complaints in the absence of moderate and severe dementia (Clinical Dementia Rating score ≤ 1 and a Mini-Mental State Examination score ≥ 20), combined with either moderate vascular brain injury on MRI scan (operationalized as moderate to severe white matter hyperintensities (Fazekas 2 or 3) and/or lacunes and/or cerebral microbleeds) or mild vascular brain injury (Fazekas = 1) in the presence of at least 2 vascular risk factors (ie, hypertension, hypercholesterolemia, diabetes mellitus, obesity, smoking, or clinically manifest vascular disease). Exclusion criteria included clinical evidence of a neurodegenerative disease other than VCI or Alzheimer's disease, a psychiatric diagnosis that affected cognitive functioning, and atrial fibrillation at the time of inclusion. As part of the HBC study, reference participants were recruited via advertisements and among the spouses of participants. Reference participants were eligible if they did not have all 3 diagnoses (ie, VCI, heart failure, and carotid occlusive disease). For the current study, we included all 166 participants with VCI and all 129 recruited reference subjects.

2.2 | Ethical approval and data availability

The Medical Ethics Review Committee of the Leiden University Medical Centre performed central approval of the HBC study (number P.14.002). Subsequently, local boards of the other university medical centers approved the local performance of the study. The HBC study is performed in accordance with the Declaration of Helsinki (version 2013) and the Medical Research Involving Human Subjects Act. Reasonable requests for use of the data underlying this study can be sent to the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

2.3 | Assessment of ADAMTS13 and VWF

Participants provided nonfasting venous blood samples, which were centrifuged and stored at -80°C within 4 hours. VWF levels were quantified using a multiplex proximity extension immunoassay [23] from the OLINK Cardiovascular III panel (OLINK Proteomics) [24]. Results were reported as Normalized Protein eXpression (NPX) values, a relative unit on a log2 scale, with higher NPX indicating higher protein concentration. Because NPX provides relative quantification within this specific cohort, these values cannot be directly converted into the absolute clinical units (eg, IU/dL or mg/L) typically used in traditional VWF assays. ADAMTS13 activity was measured in citrated plasma using a kinetic FRET-VWF73 assay [25], which detects cleavage of a VWF-derived peptide substrate (Peptide

Institute). Activity was quantified against a reference curve using serial dilutions of standard human plasma (Siemens, calibrated against the National Institute for Biological Standards and Control international standard) with high and low controls (VisuN, Affinity Biologicals) for quality control. The intra-assay coefficient of variation was 4.1%, and the interassay coefficient of variation was 12.2%.

2.4 | Clinical characteristics and other variables

Smoking status, alcohol status, use of antihypertensive medication, and lipid-lowering medication were determined by interview. Body mass index was calculated from measurements of height and weight. Systolic blood pressure was measured twice using an automatic blood pressure monitor, and the average of 2 readings was used for analysis. Low-density lipoprotein (LDL) cholesterol and creatinine were measured in nonfasting blood samples.

2.5 | MRI scan acquisition and processing

A brain MRI scan was acquired on Philips Ingenia, Achieva, and Gemini 3T MRI scanners. The brain imaging protocol included a 3-dimensional T1-weighted image (resolution = $1.0 \times 1.0 \times 1.0 \text{ mm}^3$; TR = 8.2 ms; TE = 4.5 ms; and inversion delay = 990 ms), a fluid-attenuated inversion recovery image (resolution = $1.11 \times 1.11 \times 1.11 \text{ mm}^3$; TR = 4.8 ms; TE = 313 ms; and TI = 1.65 ms), and a 3-dimensional susceptibility-weighted image (resolution $0.8 \times 0.8 \times 0.8 \text{ mm}^3$; TR = 45 ms; and TE = 31 ms). The white matter hyperintensities volume, corrected for total brain volume, was calculated with an automated pipeline (Quantib Brain) after manual segmentation of infarcts and other focal pathologies [26]. The presence of lacunes (3–15 mm lesions) and microbleeds (small homogeneous round foci at any anatomical location) was visually rated by an experienced neuroradiologist in accordance with the Standards for Reporting Vascular Changes on Neuroimaging criteria [27]. Cortical cerebral microinfarcts were rated separately according to the Standards for Reporting Vascular Changes on Neuroimaging-2 criteria [28]. Representative imaging examples have previously been published [29].

2.6 | Statistical analysis

We computed z-scores for ADAMTS13 and VWF. White matter hyperintensity volume was log-transformed to obtain a roughly normal distribution of the data and subsequently standardized. Missing data for covariables ($< 5\%$ for all covariables) were computed using 5-fold multiple imputation.

We determined the odds of prevalent VCI per SD increase in VWF and per SD decrease in ADAMTS13, using logistic regression. We fitted 2 models, one adjusted for age and sex (model I) and a second model additionally adjusting for diabetes, smoking, body mass

index, alcohol use, systolic blood pressure, use of antihypertensive medication, LDL cholesterol level, use of lipid-lowering medication, and creatinine level (model II). Estimates were expressed per SD change and per quartile of ADAMTS13 activity and VWF level.

Next, across both participants with VCI and reference subjects, we determined the association of VWF and ADAMTS13 with volume of white matter hyperintensities, presence of lacunes, cerebral microbleeds, and cortical microinfarcts using linear and logistic regression, adjusting for the same variables as above in models I and II.

We assessed the interaction between VWF and ADAMTS13 on VCI status and imaging outcomes, stratifying at the median value of VWF level. In light of previous findings [7], we also examined the interactive effects of ADAMTS13 and diabetes by performing sensitivity analyses for ADAMTS13 in which we excluded participants with diabetes. Finally, we performed a sensitivity analysis in which we analyzed ADAMTS13 and imaging outcomes in reference subjects only in order to differentiate effects driven by the definition of VCI.

All analyses were performed using R statistical software 4.4.1 (packages: 'tableone' 0.13.2, 'mice' 3.17.0, 'ggplot2' 3.5.1, and 'interactionR' 0.1.7). The alpha level was set at 0.05.

3 | RESULTS

3.1 | Participant characteristics

Among 166 participants with VCI and 129 reference subjects, we were unable to measure either ADAMTS13 or VWF in 28 participants due to insufficient sample volume (19 VCIs and 9 references), leaving 267 participants for analysis, comprising 147 participants with VCI and 120 reference subjects. A comparison of baseline characteristics between measured and unmeasured participants is presented in [Supplementary Table S1](#).

The mean age was 67.5 years, and 110 (41.2%) participants were female. Participants with VCI were significantly older, had a higher prevalence of diabetes, and more often used antihypertensive and lipid-lowering medication. Among all participants, cerebral microbleeds were present in 65 (26%) participants, lacunes in 77 (31%) participants, and cortical microinfarcts in 24 (10%) participants ([Table 1](#)).

Regarding ADAMTS13 measurements, 2 participants had activity levels below the lower limit of quantification (< 3% activity), and 6 exceeded the upper limit of quantification (> 155%). Sensitivity analyses excluding these observations did not significantly change the results. Additionally, we were unable to determine white matter hyperintensity volume in 11, cerebral microbleeds in 21, microinfarcts in 27, and lacunes in 19 participants. Characteristics of the included participants are presented in [Table 1](#).

3.2 | Association of VWF and ADAMTS13 with VCI

ADAMTS13 activity was associated with a lower prevalence of VCI (mean $\pm$ SD, 104.5% $\pm$ 29.9% versus 113.7% $\pm$ 3 0.8%; odds ratio [OR] per 1-SD decrease: 1.46 [95% CI, 1.04-2.04]; [Table 2](#)). When analyzed in quartiles, participants in the lowest 2 quartiles of ADAMTS13 had the highest prevalence of VCI compared with the highest reference quartile ([Table 2](#)). Results were similar after excluding participants with diabetes (OR per 1-SD decrease: 1.44 [95% CI, 1.02-2.03]). Levels of VWF were slightly higher in participants with VCI than in reference subjects (6.8 $\pm$ 0.9 NPX versus 6.7 $\pm$ 0.7 NPX), but this difference was not statistically significant in the fully adjusted models (OR per 1-SD increase: 1.15 [95% CI, 0.85-1.56]; [Table 2](#)). There was no significant additive or multiplicative interaction effect between ADAMTS13 and VWF ([Table 3](#)).

3.3 | Association of VWF and ADAMTS13 with vascular neuroimaging markers

Across all participants with VCI and reference subjects, lower activity of ADAMTS13 was associated with higher volume of white matter hyperintensities, although this association was not statistically significant (mean difference per 1-SD decrease: 0.12 [95% CI, -0.01 to 0.25]; [Table 4](#)). Comparing the lowest 2 quartiles to the highest reference quartile, point estimates showed a roughly 2-fold increase in the odds of cerebral microbleeds and cortical microinfarcts with lower ADAMTS13, but these differences were not statistically significant ([Table 4](#)). No significant associations were observed between ADAMTS13 activity and the presence of lacunes. Results were broadly similar after excluding participants with diabetes (eg, for white matter hyperintensities: mean difference: 0.12 [95% CI, -0.02 to 0.26]).

Higher levels of VWF were significantly associated with increased volume of white matter hyperintensities and presence of lacunes (mean difference per 1-SD decrease: 0.13 [95% CI, -0.01 to 0.26]; [Table 4](#)). We observed no significant association of VWF with cerebral microbleeds or cortical microinfarcts, although confidence intervals were wide around the ORs of 2 to 3 for the upper quartile of VWF ([Table 4](#)).

Regarding joint effects of ADAMTS13 and VWF, we observed stronger associations of ADAMTS13 with volume of white matter hyperintensities and presence of lacunes and microbleeds in participants with low levels of VWF, although formal tests for statistical interaction were only significant for lacunes ([Figure A](#); [Supplementary Table S2](#)). In sensitivity analyses among reference subjects only, effect estimates for the association of ADAMTS13 and VWF with cerebral small vessel disease markers were generally stronger than in the overall analyses, except for a nonsignificant opposite effect of VWF on the presence of lacunes ([Supplementary Table S3](#)).

TABLE 1 Characteristics of the study population.

Characteristic	Overall (N = 267)	Vascular cognitive impairment (N = 147)	Reference subjects (N = 120)
Female sex, n (%)	110 (41.2)	56 (38.1)	54 (45.0)
Age, mean ($\pm$ SD), y	67.5 (8.1)	68.7 (8.7)	66.0 (7.0)
Smoking, n (%)			
Never	89 (33.3)	38 (25.9)	51 (42.5)
Current	33 (12.4)	25 (17.0)	8 (6.7)
Former	145 (54.3)	84 (57.1)	61 (50.8)
Alcohol use, n (%)			
None	60 (22.5)	42 (28.6)	18 (15.0)
1-14 IE/wk	176 (66.4)	85 (57.8)	91 (75.8)
>15 IE/wk	31 (11.6)	20 (13.6)	11 (9.2)
Body mass index, mean ($\pm$ SD), kg/m ²	26.4 (4.2)	26.6 (4.6)	26.0 (3.8)
Systolic blood pressure, mean ($\pm$ SD), mm Hg	142.8 (20.9)	142.4 (22.1)	143.2 (19.4)
Use of antihypertensive medication, n (%)	127 (49.8)	98 (70.5)	29 (25.0)
LDL cholesterol, mean ($\pm$ SD), mmol/L	2.9 (1.0)	2.6 (0.9)	3.3 (0.9)
Statin use, n (%)	121 (47.5)	94 (66.7)	27 (23.7)
Diabetes, n (%)	20 (7.5)	17 (11.6)	3 (2.5)
Creatinine, median (IQR), μ mol/L	79.0 (69.0-91.0)	82.0 (73.0-95.0)	76.0 (65.5-85.0)
Von Willebrand Factor, mean ($\pm$ SD), NPX	6.8 (0.8)	6.8 (0.9)	6.70 (0.7)
ADAMTS13, mean ($\pm$ SD), %	108.6 (30.6)	104.5 (29.9)	113.67 (30.8)
Cerebral microbleeds, n (%; N = 244)			
0	181 (73.6)	84 (63.2)	97 (85.8)
1	26 (10.6)	15 (11.3)	11 (9.7)
≥ 2	39 (15.9)	34 (25.6)	5 (4.4)
Lacunes, n (%; N = 246)			
0	171 (69.0)	65 (49.6)	106 (90.6)
1	23 (9.3)	18 (13.7)	5 (4.3)
≥ 2	54 (21.8)	48 (36.6)	6 (5.1)
Cortical microinfarcts, n (%; N = 239)			
0	216 (90.0)	108 (86.4)	108 (93.9)
1	16 (6.7)	11 (8.8)	5 (4.3)
≥ 2	8 (3.3)	6 (4.8)	2 (1.7)
white matter hyperintensities volume, median (IQR, N = 254), mL	2.3 (0.5-9.2)	6.8 (2.1-20.4)	0.6 (0.2-2.1)

Data are presented as mean ($\pm$ SD) for continuous variables with a normal distribution, median (IQR) for continuous variables with a skewed distribution, or n (%) for categorical variables.

IE, international units; LDL, low-density lipoprotein; NPX, normalized protein expression; VWF, Von Willebrand factor.

4 | DISCUSSION

In this study, embedded within the HBC study, we found that low ADAMTS13 activity was associated with the prevalence of VCI and increased white matter hyperintensity volume, apparently independent of concurrent levels of VWF. Levels of VWF were not

significantly associated with the prevalence of VCI, but they were significantly associated with higher white matter hyperintensity volume and with the presence of lacunes.

The lower activity of ADAMTS13 in patients with VCI aligns with results from the only prior study on ADAMTS13 in relation to cognition in humans. In this population-based study, lower

TABLE 2 ADAMTS13 and Von Willebrand factor (VWF) in relation to vascular cognitive impairment (VCI).

Determinant	VCI (model I) OR (95% CI)	VCI (model II) OR (95% CI)
ADAMTS13 activity		
Q4 > 127.8%	REF	REF _e
Q3 108.8%-127.8%	1.23 (0.61-2.47)	2.25 (0.89-5.71)
Q2 89.8%-108.8%	2.00 (1.06-4.43)	4.01 (1.51-10.60)
Q1 < 89.8%	2.99 (0.98-4.10)	3.50 (1.32-9.25)
Per 1-SD decrease	1.27 (0.98-1.66)	1.46 (1.04-2.04)
VWF (NPX)		
Q1	REF	REF
Q2	1.19 (0.60-2.39)	1.21 (0.49-2.98)
Q3	1.44 (0.72-2.91)	1.35 (0.55-3.33)
Q4	1.37 (0.78-2.75)	1.72 (0.69-4.33)
Per 1-SD increase	1.12 (0.87-1.45)	1.15 (0.85-1.56)

Model I: adjusted for age and sex.

Model II additionally adjusted for diabetes, smoking, body mass index (BMI), alcohol use, systolic blood pressure, use of antihypertensive medication, low-density lipoprotein (LDL) cholesterol level, use of lipid-lowering medication, and creatinine level. Results are shown for three approaches: per SD decrease in ADAMTS13 and per SD increase in VWF; by quartiles (VWF: $p_{\text{trend}} = .24$; ADAMTS13: $p_{\text{trend}} = .007$); and for the most extreme quartile compared with all others.

ADAMTS13, activity of a disintegrin-like and metalloprotease with thrombospondin type 1 repeats 13; NPX, normalized protein expression; OR, odds ratio; Q, quartile; REF, reference quartile; VWF, Von Willebrand factor.

ADAMTS13 activity was associated with increased dementia risk and accelerated cognitive decline during 15 years of follow-up [7]. Adding the assessment of MRI scan markers of cerebral small vessel disease, our current study provided insight into potential pathways underlying the associations with clinical outcome. We observed a nonlinear association with the prevalence of VCI, with the highest risk estimates for the lowest 2 quartiles of ADAMTS13 activity. Similarly, effect estimates for all markers of cerebral small vessel disease,

except for lacunes, were highest for the lowest 2 quartiles. These observations suggest a threshold effect of ADAMTS13, as was previously observed [7,21]. A threshold may reflect a critical activity of ADAMTS13 needed to fulfill its biological function. However, the precise threshold seems to differ in our study. The distribution of ADAMTS13 activity varied, with around 60% of individuals in the current study falling in the highest quartile of ADAMTS13 in the distribution of previous studies [7,21]. Possible explanations for this discrepancy include differences in population characteristics, as the current study has a higher prevalence of cardiovascular disease, or differences in methods, as both previous studies did not use the international standard for ADAMTS13 standardization. In post hoc analysis, we found no statistically significant effect of sample storage duration on ADAMTS13 activity levels.

We found no evidence of additive or multiplicative interaction between ADAMTS13 activity and VWF levels on VCI, although the limited sample size may have limited our ability to detect such effects. However, this concurs with the aforementioned report from the Rotterdam Study, in which ADAMTS13 activity showed a stronger association with dementia risk than the ADAMTS13:VWF ratio or VWF levels separately [7]. Among previous studies on ischemic stroke, cardiovascular disease, and mortality, only those on ischemic stroke showed increased risk with combined exposures, although statistical interaction was not significant [10,30]. The previous study reporting on cerebral small vessel disease did model ADAMTS13 and the ADAMTS13:VWF ratio; however, the use of different scales precludes comparison of their effect sizes or inference about interaction [21]. Interestingly, evidence from in vitro and animal studies suggests that ADAMTS13 only exerts its effects in the presence of VWF. For example, in a study comparing APOE, VWF, and ADAMTS13 knockout mice to APOE and ADAMTS13 knockout mice, it was found that the effect of ADAMTS13 deficiency on atherosclerosis is absent in VWF-deficient mice [31,32]. This highlights that cleavage of VWF remains the only established pathway through which ADAMTS13 exerts these effects. However, the absence of clear interaction effects in humans suggests that physiological levels of VWF are abundant for decreased activity of ADAMTS13 to take effect. This could also reflect that the multimer size of VWF plays a

TABLE 3 Interaction of activity of a disintegrin-like and metalloprotease with thrombospondin type 1 repeats 13 (ADAMTS13) and Von Willebrand factor (VWF) on the occurrence of vascular cognitive impairment (VCI).

	High ADAMTS13 OR (95% CI)	Low ADAMTS13 OR (95% CI)	Effect of ADAMTS13 within the strata of VWF OR (95% CI)
Low VWF	1 (Reference)	1.97 (0.77-5.05)	1.97 (0.77-5.05)
High VWF	1.21 (0.5-2.93)	3.34 (1.30- 8.62)	2.77 (1.13-6.80)
Effect of VWF within the strata of ADAMTS13 OR (95% CI)	1.21 (0.5-2.93)	1.70 (0.68-4.23)	

VWF and ADAMTS13 were dichotomized at the sample median (low: $\leq$ median; high: $>$ median); results shown are derived from model II: adjusted for age and sex, diabetes, smoking, body mass index (BMI), alcohol use, systolic blood pressure, use of anti-hypertensive medication, low-density lipoprotein (LDL) cholesterol level, use of lipid lowering medication, and creatinine level. Measures of interaction: multiplicative interaction: 1.41 (95% CI, 0.40-4.99); Relative excess risk due to interaction (RERI): 1.17 (95% CI, -2.26 to 5.64); Attributable Proportion (AP): 0.35 (95% CI, -0.78 to 0.79); synergy index (SI): 1.99 (95% CI, 0.35-11.44).

OR, odds ratio.

TABLE 4 Activity of a disintegrin-like and metalloprotease with thrombospondin type 1 repeats 13 (ADAMTS13) and VWF in relation to magnetic resonance imaging (MRI) scan markers of cerebral small vessel disease.

Determinant	White matter hyperintensities (Mean difference, 95% CI)	Cerebral microbleeds (OR, 95% CI)	Lacunes (OR, 95% CI)	Cortical microinfarcts (OR, 95% CI)
ADAMTS13 activity				
Q4 > 127.84%	Reference	Reference	Reference	Reference
Q3 108.85%-127.84%	0.19 (-0.16 to 0.53)	0.80 (0.29-2.21)	1.40 (0.58-3.36)	0.76 (0.15-3.82)
Q2 90.15%-108.85%	0.44 (0.09-0.80)	2.03 (0.79-5.23)	1.26 (0.51-3.07)	2.67 (0.70-10.2)
Q1 < 90.15%	0.32 (-0.04 to 0.68)	1.79 (0.71-4.50)	1.45 (0.59-3.58)	1.74 (0.42-7.18)
Per 1-SD decrease	0.12 (-0.01 to 0.25)	1.20 (0.85-1.68)	0.99 (0.72-1.37)	1.10 (0.67-1.82)
VWF (NPX)				
Q1	Reference	Reference	Reference	Reference
Q2	0.07 (-0.27 to 0.41)	1.32 (0.53-3.28)	1.50 (0.61-3.69)	0.73 (0.15-3.62)
Q3	0.16 (-0.19 to 0.51)	0.57 (0.20-1.57)	1.35 (0.54-3.34)	2.37 (0.61-9.26)
Q4	0.39 (0.04-0.74)	2.14 (0.86-5.32)	2.72 (1.10-6.76)	3.28 (0.87-12.4)
Per 1-SD decrease	0.13 (0.01-0.26)	1.16 (0.84-1.62)	1.44 (1.03-2.01)	1.44 (0.89-2.32)

Results shown are derived from model II: adjusted for age and sex, diabetes, smoking, body mass index (BMI), alcohol use, systolic blood pressure, use of antihypertensive medication, low-density lipoprotein (LDL) cholesterol level, use of lipid-lowering medication, and creatinine level.

CMB, cerebral microbleeds; CMI, cortical microinfarcts; LAC, lacunes; NPX, normalized protein expression; OR, odds ratio; VWF, Von Willebrand factor; WMH, white matter hyperintensities (corrected for intracranial volume).

more important role than VWF levels; however, since ADAMTS13 activity was within the normal range for almost all participants, any functional shifts would be small, making it unlikely that multimer

sizes differed substantially. Since systemic functional shifts are likely minimal, the cleavage of VWF multimers by ADAMTS13 might be particularly important in local microvascular environments where

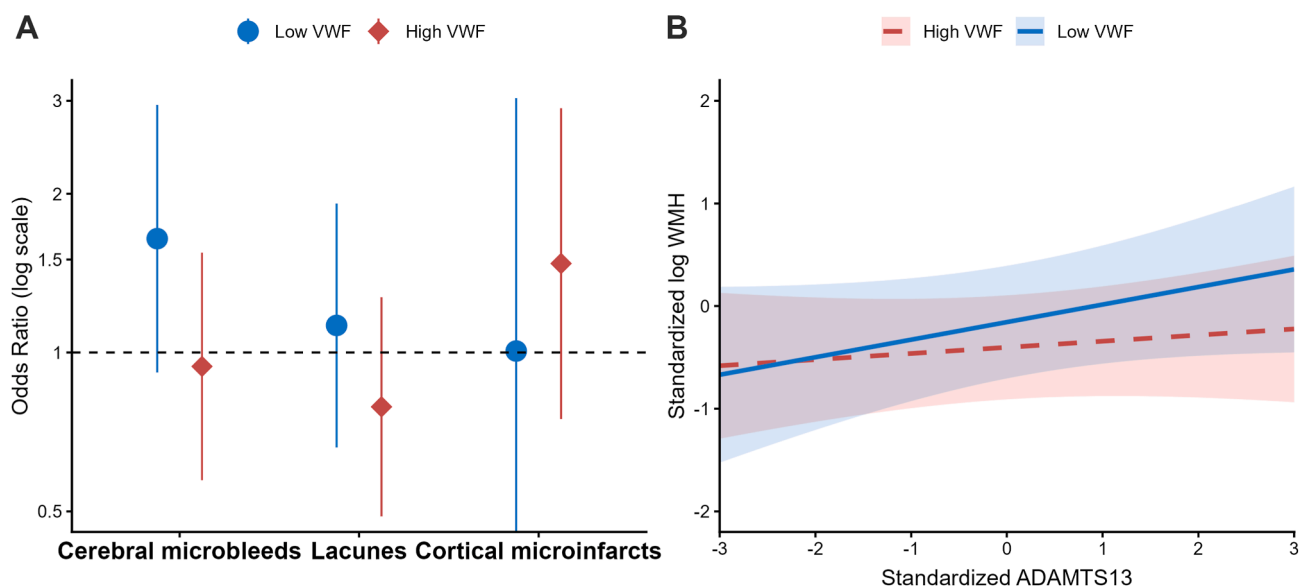


FIGURE Impact of concurrent VWF on the association between ADAMTS13 activity and markers of cerebral small vessel disease. (A) Odds ratios (ORs) and 95% CIs for the association between ADAMTS13 activity (per SD decrease) and the presence of cerebral microbleeds ($p_{\text{interaction}} = .08$), lacunes ($p_{\text{interaction}} = .06$), and cortical microinfarcts ($p_{\text{interaction}} = .7$). Estimates are based on fully adjusted logistic regression models using multiply imputed data and stratified by VWF levels ($\leq$ median versus $>$ median). ORs are shown on a logarithmic scale. (B) Association between standardized ADAMTS13 activity and standardized log-transformed white matter hyperintensity (WMH) volume ($p_{\text{interaction}} = .3$), estimated using fully adjusted linear regression models on multiply imputed data. Lines represent predicted values, and shaded areas indicate 95% CIs. Results are stratified by VWF levels ($\leq$ median versus $>$ median) ADAMTS13, activity of a disintegrin-like and metalloprotease with thrombospondin type 1 repeats 13; VWF, Von Willebrand factor.

shear stress is high [33,34]. Future research using human organoids could improve our understanding of local VWF regulation by ADAMTS13. Alternatively, it remains possible that ADAMTS13 influences vascular brain pathology through mechanisms that are entirely independent of VWF. Pathways such as blood-brain barrier permeability, extracellular matrix degradation, and vascular remodeling have been linked to ADAMTS13 in exploratory analyses; however, VWF is also implicated in these pathways [7,14]. Moreover, ADAMTS13 has been associated with incident diabetes—an association that cannot be explained by its role in VWF cleavage [35]. Finally, it is possible that the observed associations of ADAMTS13 with these outcomes are explained by the fact that, as a liver-produced protein, ADAMTS13 is a negative acute-phase reactant. Fibrinogen, another acute-phase reactant, has indeed also been associated with dementia [36].

As a strongly glycosylated protein, ADAMTS13 function may be affected by diabetes. However, we did not replicate previously observed differential effects in those with and without impaired fasting glucose and diabetes [7], possibly due to the low prevalence of diabetes in our sample. Further investigation of ADAMTS13 in metabolic diseases, including diabetes, may provide further clues to its biological function. Since therapies targeting ADAMTS13 are increasingly emerging [37], understanding the underlying pathways could significantly impact preventive and therapeutic strategies for cerebrovascular diseases.

Levels of VWF in our study were associated with an increased volume of white matter hyperintensities and with the presence of lacunes. A prior systematic review found conflicting results for the association of VWF with white matter hyperintensities and lacunes [38], and more recent cross-sectional studies have similarly reported inconsistent associations with white matter hyperintensities [21,39]. Our findings fit the acknowledged role of VWF levels as a marker of endothelial cell injury. Whether VWF levels also contribute causally to cerebral small vessel disease and VCI remains uncertain, as evidenced by the inconsistency in earlier findings. We did not observe a significant association between VWF and VCI, in line with the absence of a long-term association of VWF with cognitive decline and dementia in the population-based Rotterdam study [7]. Cross-sectional and short-term associations of VWF levels with cognition [7,40,41] may therefore primarily reflect endothelial dysfunction rather than a direct causal role of arterial thrombosis in these associations [5].

Strengths of the current study include the deep phenotyping of patients with VCI and reference subjects, including the joint measurement of ADAMTS13 and VWF. Several limitations should also be taken into account. First, the definition of VCI relies partly on features of cerebral small vessel disease on MRI scans, and the observed association of ADAMTS13 with imaging markers of cerebral small vessel disease may therefore also reflect alternative pathways leading to VCI, independent of these cerebral small vessel disease markers. However, effect estimates were consistent among the reference subjects only, in whom this does not play a part. Second, our sample was too small to account for the location of cerebral microbleeds, which could have shed further light on the

underlying pathology [42]. Third, our study population consisted mostly of White participants, potentially hampering generalizability to other ancestries. Finally, measuring VWF activity or multimer size instead of just VWF levels could have provided more mechanistic insight into the relationship with ADAMTS13. However, because ADAMTS13 activity was within the normal range for almost all participants, any functional shifts are likely minor, making it unlikely that VWF multimer sizes differed substantially enough to alter our conclusions.

In conclusion, low ADAMTS13 activity is associated with VCI and white matter hyperintensities, above and beyond its measured effects on VWF levels. These findings suggest that ADAMTS13 activity and VWF levels may contribute to cerebral small vessel disease and cognitive impairment, in part through separate mechanisms. Future research is warranted on the biological pathways underlying these associations.

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AUTHOR CONTRIBUTIONS

A.C.P. performed the statistical analyses and drafted the manuscript. M.T.R. and F.J.W. supervised the data analysis and the interpretation of the results. M.P.M.M. led the laboratory measurements of ADAMTS13 activity and VWF levels and assisted in the interpretation of the results. All other authors contributed to the study design and provided a critical review of the manuscript for important intellectual content. F.J.W. served as the primary senior supervisor and oversaw the study in its entirety. All authors have read and approved the final version of the manuscript.

DECLARATION OF COMPETING INTERESTS

None

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SUPPLEMENTARY MATERIAL

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