

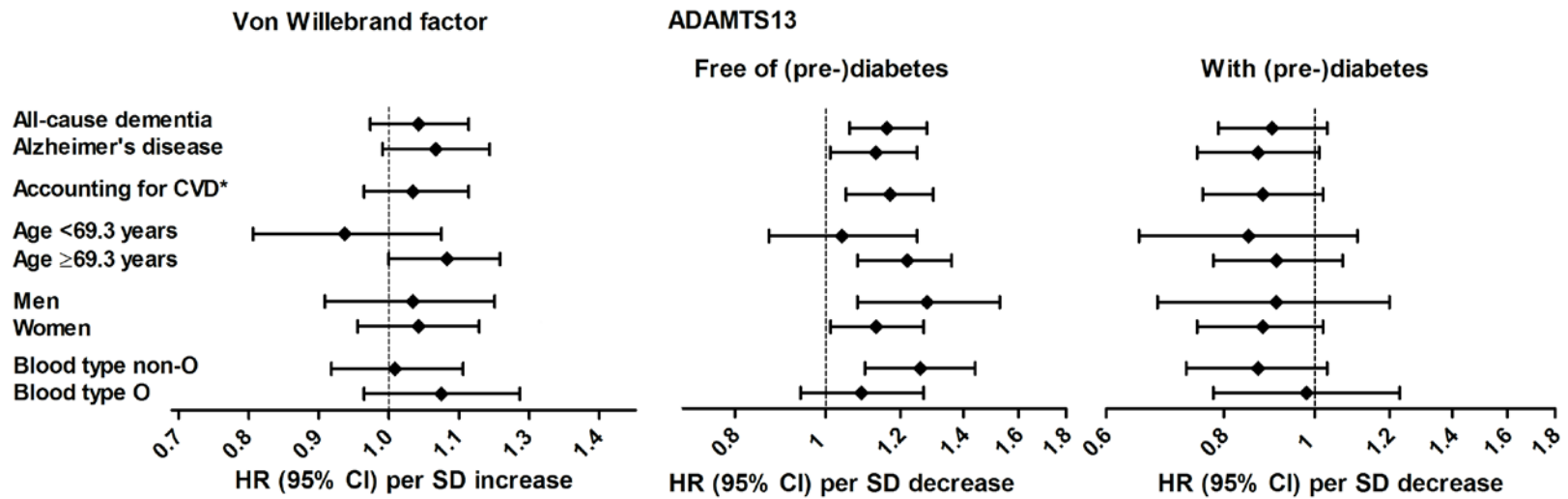
Supplementary material with the article

Von Willebrand factor and ADAMTS13 activity in relation to risk of dementia: a population-based study

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Supplementary Figure S1. Associations of Von Willebrand factor (VWF) and ADAMTS13 with risk of dementia for several subgroups of interest.



Legend: HR=hazard ratio from fully adjusted model; CI=confidence interval; SD=standard deviation
Age stratification was done by the median age of the study population.

Supplementary Table S1

Von Willebrand factor (VWF) and ADAMTS13 at baseline in relation to the prevalence of Alzheimer's disease, and all-cause dementia excluding participants with cardiovascular disease at baseline.

	Alzheimer's disease			All-cause dementia excluding cardiovascular disease		
	No (n=5970)	Yes (n=68)	P-value	No (n=5674)	Yes (n=72)	P-value
VWF:Ag						
Geometric mean (95% CI)	1.22 (1.20-1.23)	1.31 (1.19-1.44)	0.119	1.21 (1.20-1.22)	1.37 (1.25-1.50)	0.011
OR (95% CI) per SD increase	1.22 (0.95-1.56)		0.122	1.34 (1.06-1.69)		0.016
ADAMTS13 activity						
Mean (95% CI)	91.2 (90.7-91.6)	85.0 (80.9-89.0)	0.003	91.2 (90.8-91.7)	86.0 (82.1-89.9)	0.009
OR (95% CI) per SD increase	1.36 (1.03-1.78)		0.029	1.30 (1.00-1.70)		0.052
ADAMTS13:VWF ratio						
Geometric mean (95% CI)	73.5 (72.6-74.3)	62.4 (56.1-69.5)	0.003	73.8 (73.0-74.8)	61.1 (55.0-67.8)	0.0004
OR (95% CI) per SD decrease	1.35 (1.06-1.72)		0.016	1.43 (1.13-1.80)		0.003

n=number of participants; se=standard error; SD=standard deviation; OR=odds ratio; CI=confidence interval;
Model adjusted for age, sex, study subcohort

Supplementary Table S2 Baseline levels of Von Willebrand factor antigen and risk of dementia, depicted per increasing year of follow-up

	All-cause dementia n/N	Odds ratio/ Hazard ratios (95% confidence interval) Per standard deviation increase
Cross-sectional	85/6055	1.37 (1.06-1.77)
Longitudinal		
≤2 years	61/5970	1.32 (1.02-1.72)
≤3 years	111/5970	1.21 (1.00-1.48)
≤4 years	125/5970	1.15 (0.96-1.39)
≤5 years	204/5970	1.07 (0.93-1.24)
≤6 years	263/5970	1.08 (0.95-1.23)
≤7 years	322/5970	1.06 (0.95-1.19)
≤8 years	360/5970	1.08 (0.97-1.20)
≤9 years	399/5970	1.05 (0.95-1.17)
≤10 years	455/5970	1.07 (0.97-1.19)

n=number of dementia cases; N=sample at risk. Model adjusted for age, sex, study subcohort, smoking, systolic and diastolic blood pressure, antihypertensive medication, diabetes, serum cholesterol, high-density lipoprotein and triglycerides, lipid-lowering medication, creatinine, antithrombotic medication, fibrinogen, C-reactive protein, ABO blood type, and *APOE* genotype

Supplementary Table S3

Von Willebrand factor in relation to cognitive performance at baseline and during follow-up.

Cognitive test	Cross-sectional	Up till 2 nd examination	Up till 3 rd examination	Up till 4 th examination
		(4.4 years)	(10.8 years)	(15.4 years)
Letter-digit substitution – per SD	-0.026 (-0.051;-0.003)	-0.016 (-0.061;0.029)	0.012 (-0.016;0.039)	-0.001 (-0.022;0.021)
Q2 (vs. Q1)	-0.015 (-0.079; 0.048)	-0.013 (-0.133 ;0.107)	0.017 (-0.054; 0.088)	0.017 (-0.037; 0.071)
Q3 (vs. Q1)	-0.005 (-0.071; 0.061)	0.012 (-0.110; -0.134)	0.012 (-0.060; 0.084)	-0.012 (-0.067; 0.044)
Q4 (vs. Q1)	-0.081 (-0.151; -0.011)	-0.066 (-0.192; 0.060)	0.045 (-0.031; 0.122)	0.007 (-0.052; 0.066)
Verbal fluency – per SD	-0.050 (-0.076;-0.024)	-0.037 (-0.096;0.022)	0.020 (-0.010;0.050)	0.006 (-0.017;0.029)
Q2 (vs. Q1)	-0.061 (-0.127; 0.005)	-0.032 (-0.190; 0.125)	0.003 (-0.075; 0.081)	0.022 (-0.036; 0.081)
Q3 (vs. Q1)	-0.031 (-0.100; 0.037)	-0.145 (-0.305; 0.016)	-0.021 (-0.100; 0.059)	-0.036 (-0.097; 0.024)
Q4 (vs. Q1)	-0.157 (-0.230; -0.085)	-0.069 (-0.233; 0.096)	0.059 (-0.025; 0.143)	0.021 (-0.044; 0.086)
Stroop test – per SD	-0.031 (-0.057;-0.005)	-0.049 (-0.110;0.012)	-0.015 (-0.046;0.017)	-0.027 (-0.053;-0.0004)
Q2 (vs. Q1)	-0.028 (-0.094; 0.037)	-0.024 (-0.185; 0.136)	0.032 (-0.050; 0.113)	0.008 (-0.059; 0.074)
Q3 (vs. Q1)	-0.044 (-0.112; 0.024)	-0.009 (-0.172; 0.154)	0.024 (-0.059; 0.107)	-0.027 (-0.095; 0.041)
Q4 (vs. Q1)	-0.103 (-0.175; -0.030)	-0.093 (-0.263; 0.076)	-0.007 (-0.095; 0.081)	-0.049 (-0.122; 0.023)
G-factor – per SD	-0.047 (-0.072;-0.021)	-0.057 (-0.103;-0.010)	-0.005 (-0.030;0.019)	-0.013 (-0.034;0.007)
Q2 (vs. Q1)	-0.050 (-0.113; 0.014)	-0.021 (-0.144; 0.103)	0.025 (-0.038; 0.089)	0.024 (-0.028; 0.075)
Q3 (vs. Q1)	-0.039 (-0.105; 0.027)	-0.089 (-0.214; 0.036)	-0.001 (-0.066; 0.064)	-0.033 (-0.086; 0.020)
Q4 (vs. Q1)	-0.156 (-0.227; -0.086)	-0.123 (-0.252; 0.007)	0.004 (-0.065; 0.073)	-0.024 (-0.081; 0.033)

SD=standard deviation. Results reflect the betas per standard deviation increase for baseline VWF and the VWF*follow-up time interaction (expressed per 10 years follow-up) from a fully adjusted linear mixed model including all four examinations, and restricting analyses to the first two or three assessments, respectively. Lower scores reflect worse performance for all tests.

Supplementary Table S4

Baseline ADAMTS13 in relation to the risk of dementia in the overall population: comparison of model I with model II, and stratifying between pre-diabetes and diabetes at baseline

	Overall study population		Free of (pre-)diabetes		Pre-diabetes		Diabetes	
	$n_{\text{dem}}/N_{\text{tot}}$	HR (95% CI)	$n_{\text{dem}}/N_{\text{tot}}$	HR (95% CI)	$n_{\text{dem}}/N_{\text{tot}}$	HR (95% CI)	$n_{\text{dem}}/N_{\text{tot}}$	HR (95% CI)
Model I								
Per quartile								
Q1 <80.6%	239/1492	1.09 (0.89-1.33)	190/1081	1.38 (1.07-1.77)	28/238	0.57 (0.33-0.98)	21/163	0.77 (0.44-1.35)
Q2 80.6-91.2%	210/1493	0.93 (0.76-1.14)	158/1088	1.10 (0.86-1.41)	31/235	0.67 (0.41-1.12)	20/154	0.75 (0.44-1.30)
Q3 91.2-101.9%	191/1493	0.83 (0.67-1.02)	133/1095	0.90 (0.69-1.16)	31/223	0.77 (0.46-1.28)	27/168	0.79 (0.48-1.29)
Q4 >101.9%	181/1492	REFERENCE	106/995	REFERENCE	31/223	REFERENCE	43/259	REFERENCE
Q1 versus Q2-4		1.19 (1.02-1.39)		1.38 (1.15-1.65)		0.73 (0.47-1.13)		0.91 (0.56-1.49)
Per SD decrease	821/5970	1.04 (0.96-1.12)	587/4259	1.13 (1.03-1.24)	121/919	0.87 (0.73-1.04)	111/744	0.97 (0.81-1.16)
Model II								
Per quartile								
Q1 <80.6%	239/1492	1.16 (0.94-1.43)	190/1081	1.51 (1.16-1.95)	28/238	0.52 (0.29-0.91)	21/163	0.87 (0.48-1.55)
Q2 80.6-91.2%	210/1493	1.00 (0.82-1.23)	158/1088	1.22 (0.94-1.57)	31/235	0.65 (0.38-1.11)	20/154	0.79 (0.44-1.41)
Q3 91.2-101.9%	191/1493	0.85 (0.69-1.04)	133/1095	0.90 (0.69-1.17)	31/223	0.75 (0.44-1.26)	27/168	0.84 (0.50-1.41)
Q4 >101.9%	181/1492	REFERENCE	106/995	REFERENCE	31/223	REFERENCE	43/259	REFERENCE
Q1 versus Q2-4		1.23 (1.05-1.44)		1.44 (1.20-1.73)		0.69 (0.44-1.07)		0.98 (0.59-1.64)
Per SD decrease	821/5970	1.06 (0.98-1.15)	587/4259	1.16 (1.06-1.28)	121/919	0.83 (0.68-1.01)	111/744	1.04 (0.85-1.27)

HR=hazard ratio; CI=confidence interval; n_{dem} =number of dementia cases and N_{tot} =number of individuals in group, presented for non-imputed data (missing diabetes status, n=48)

Model I: adjusted for age, sex, and study subcohort

Model II: as model I with additional adjustment for smoking, systolic and diastolic blood pressure, antihypertensive medication, serum cholesterol, HDL and triglycerides, lipid-lowering medication, body mass index, (pre-)diabetes (if applicable), creatinine, antithrombotic medication, CRP, fibrinogen, ABO blood type, and APOE genotype

Supplementary Table S5

Baseline ADAMTS13:VWF ratio and risk of dementia.

		Overall analysis (n=5970)		Free of (pre-)diabetes (n=4259)		With (pre-)diabetes (n=1663)	
		Model I	Model II	Model I	Model II	Model I	Model II
ADAMTS13:VWF ratio	n _{dem} /N _{tot}	HR, 95% CI	HR, 95% CI	HR, 95% CI	HR, 95% CI	HR, 95% CI	HR, 95% CI
Per quartile							
Q1	239/1492	1.12 (0.92-1.38)	1.20, 0.96-1.49	1.30 (1.01-1.66)	1.40 (1.10-1.82)	0.80 (0.56-1.15)	0.81 (0.54-1.22)
Q2	210/1493	0.97 (0.79-1.19)	0.98, 0.79-1.21	1.08 (0.84-1.38)	1.07 (0.83-1.39)	0.76 (0.53-1.10)	0.77 (0.52-1.13)
Q3	191/1493	1.16 (0.94-1.43)	1.21, 0.98-1.49	1.34 (1.05-1.72)	1.41 (1.10-1.82)	0.79 (0.54-1.17)	0.82 (0.55-1.22)
Q4	181/1492	REFERENCE	REFERENCE	REFERENCE	REFERENCE	REFERENCE	REFERENCE
Per SD decrease	821/5970	1.05 (0.98-1.13)	1.08 (1.00-1.17)	1.08 (0.99-1.18)	1.11 (1.01-1.23)	0.99 (0.86-1.13)	0.99 (0.86-1.17)

Model adjusted for age, sex, study subcohort, smoking, systolic and diastolic blood pressure, antihypertensive medication, diabetes, serum cholesterol, HDL and triglycerides, lipid-lowering medication, body mass index, diabetes, creatinine, antithrombotic medication, CRP, fibrinogen, and *APOE* genotype

Supplementary Table S6

Quartiles of ADAMTS13 activity in relation to change in cognitive test scores during four consecutive rounds

ADAMTS13	Free of (pre-)diabetes (n=4259)	Impaired fasting glucose (n=919)	Diabetes (n=744)
	β , 95% CI	β , 95% CI	β , 95% CI
G-factor			
Q1	-0.051 (-0.117; 0.015)	-0.088 (-0.233; 0.057)	0.046 (-0.147; 0.238)
Q2	0.006 (-0.054; 0.066)	-0.021 (-0.155; 0.114)	0.002 (-0.190; 0.194)
Q3	0.009 (-0.049; 0.067)	0.057 (-0.079; 0.193)	-0.015 (-0.189; 0.158)
Q4	REFERENCE	REFERENCE	REFERENCE
Q1 versus Q2-4	-0.056 (-0.113; 0.001)	-0.098 (-0.223; 0.026)	0.050 (-0.122; 0.222)
Letter-digit substitution			
Q1	-0.044 (-0.114; 0.025)	0.001 (-0.144; 0.147)	0.078 (-0.118; 0.275)
Q2	0.005 (-0.059; 0.068)	-0.007 (-0.143; 0.129)	-0.075 (-0.272; 0.123)
Q3	-0.001 (-0.063; 0.060)	0.128 (-0.010; 0.265)	-0.049 (-0.228; 0.131)
Q4	REFERENCE	REFERENCE	REFERENCE
Q1 versus Q2-4	-0.046 (-0.106; 0.014)	-0.036 (-0.160; 0.088)	0.113 (-0.063; 0.288)
Verbal fluency			
Q1	-0.014 (-0.089; 0.062)	-0.073 (-0.254; 0.108)	0.001 (-0.195; 0.197)
Q2	0.059 (-0.010; 0.127)	0.016 (-0.151; 0.183)	-0.020 (-0.213; 0.174)
Q3	0.005 (-0.062; 0.071)	0.161 (-0.007; 0.329)	0.037 (-0.143; 0.216)
Q4	REFERENCE	REFERENCE	REFERENCE
Q1 versus Q2-4	-0.034 (-0.099; 0.031)	-0.129 (-0.284; 0.026)	-0.007 (-0.181; 0.167)
Stroop test			
Q1	-0.060 (-0.141; 0.021)	-0.252 (-0.476; -0.028)	0.100 (-0.164; 0.363)
Q2	-0.009 (-0.083; 0.064)	-0.130 (-0.340; 0.080)	0.047 (-0.216; 0.310)
Q3	0.004 (-0.067; 0.075)	-0.118 (-0.329; 0.092)	-0.065 (-0.306; 0.177)
Q4	REFERENCE	REFERENCE	REFERENCE
Q1 versus Q2-4	-0.059 (-0.129; 0.011)	-0.170 (-0.359; 0.019)	0.108 (-0.127; 0.343)

Model adjusted for age, sex, study subcohort, smoking, systolic and diastolic blood pressure, antihypertensive medication, serum cholesterol, HDL and triglycerides, lipid-lowering medication, body mass index, creatinine, antithrombotic medication, CRP, fibrinogen, ABO blood type, and *APOE* genotype.

Estimates represent change in cognitive performance per 10 years of follow-up, relative to the highest quartile(s).

Supplementary Table S7

ADAMTS13:VWF ratio and change in cognitive test scores during the 15-year follow-up period.

	β , 95% CI
G-factor	
Q1	-0.084 (-0.142; -0.026)
Q2	0.003 (-0.050; 0.056)
Q3	-0.005 (-0.055; 0.045)
Q4	REFERENCE
Letter-digit substitution	
Q1	-0.013 (-0.074; 0.048)
Q2	-0.004 (-0.060; 0.051)
Q3	-0.003 (-0.056; 0.050)
Q4	REFERENCE
Verbal fluency	
Q1	-0.009 (-0.076; 0.058)
Q2	0.003 (-0.058; 0.064)
Q3	-0.025 (-0.083; 0.033)
Q4	REFERENCE
Stroop test	
Q1	-0.113 (-0.188; -0.038)
Q2	0.012 (-0.056; 0.080)
Q3	0.033 (-0.032; 0.098)
Q4	REFERENCE

Model adjusted for age, sex, study subcohort, smoking, systolic and diastolic blood pressure, antihypertensive medication, serum cholesterol, HDL and triglycerides, lipid-lowering medication, BMI, diabetes, creatinine, antithrombotic medication, CRP, fibrinogen, ABO blood type, and *APOE* genotype. Estimates represent change in cognitive performance per 10 years of follow-up, relative to the highest quartile.

Supplementary Table S8

ADAMTS13 activity and cognitive change, excluding participants who developed dementia during follow-up

	Overall population (n=5970) β, 95% CI	Excluding incident dementia (n=5149) β, 95% CI
G-factor		
Q1	-0.044 (-0.102; 0.014)	-0.055 (-0.107; -0.003)
Q2	0.009 (-0.044; 0.061)	-0.002 (-0.050; 0.046)
Q3	0.020 (-0.031; 0.071)	0.017 (-0.029; 0.063)
Q4	REFERENCE	REFERENCE
Q1 versus Q2-4	-0.053 (-0.103; -0.004)	-0.061 (-0.106; -0.015)
Letter-digit substitution		
Q1	-0.021 (-0.081; 0.039)	-0.030 (-0.076; 0.017)
Q2	-0.0002 (-0.056; 0.055)	-0.034 (-0.077; 0.009)
Q3	0.016 (-0.037; 0.070)	0.002 (-0.039; 0.044)
Q4	REFERENCE	REFERENCE
Q1 versus Q2-4	-0.027 (-0.079; 0.025)	-0.020 (-0.060; 0.020)
Verbal fluency		
Q1	-0.019 (-0.084; 0.047)	-0.036 (-0.099; 0.027)
Q2	0.052 (-0.008; 0.113)	0.046 (-0.012; 0.103)
Q3	0.034 (-0.025; 0.092)	0.010 (-0.046; 0.066)
Q4	REFERENCE	REFERENCE
Q1 versus Q2-4	-0.047 (-0.104; 0.010)	-0.054 (-0.108; 0.001)
Stroop test		
Q1	-0.074 (-0.148; 0.0001)	-0.071 (-0.137; -0.006)
Q2	-0.019 (-0.087; 0.050)	-0.028 (-0.089; 0.033)
Q3	-0.012 (-0.078; 0.054)	0.007 (-0.051; 0.065)
Q4	REFERENCE	REFERENCE
Q1 versus Q2-4	-0.064 (-0.128; -0.0002)	-0.065 (-0.122; -0.008)

Model adjusted for age, sex, study subcohort, smoking, systolic and diastolic blood pressure, antihypertensive medication, serum cholesterol, HDL and triglycerides, lipid-lowering medication, BMI, diabetes, creatinine, antithrombotic medication, CRP, fibrinogen, ABO blood type, and *APOE* genotype.