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HEALTH PROFESSIONALS

Thursdays Webinars

Von Willebrand factor and von Willebrand disease in ageing: mechanisms, evolving phenotypes, and clinical implications

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12 March 2026

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THE LANCET
Haematology

Review

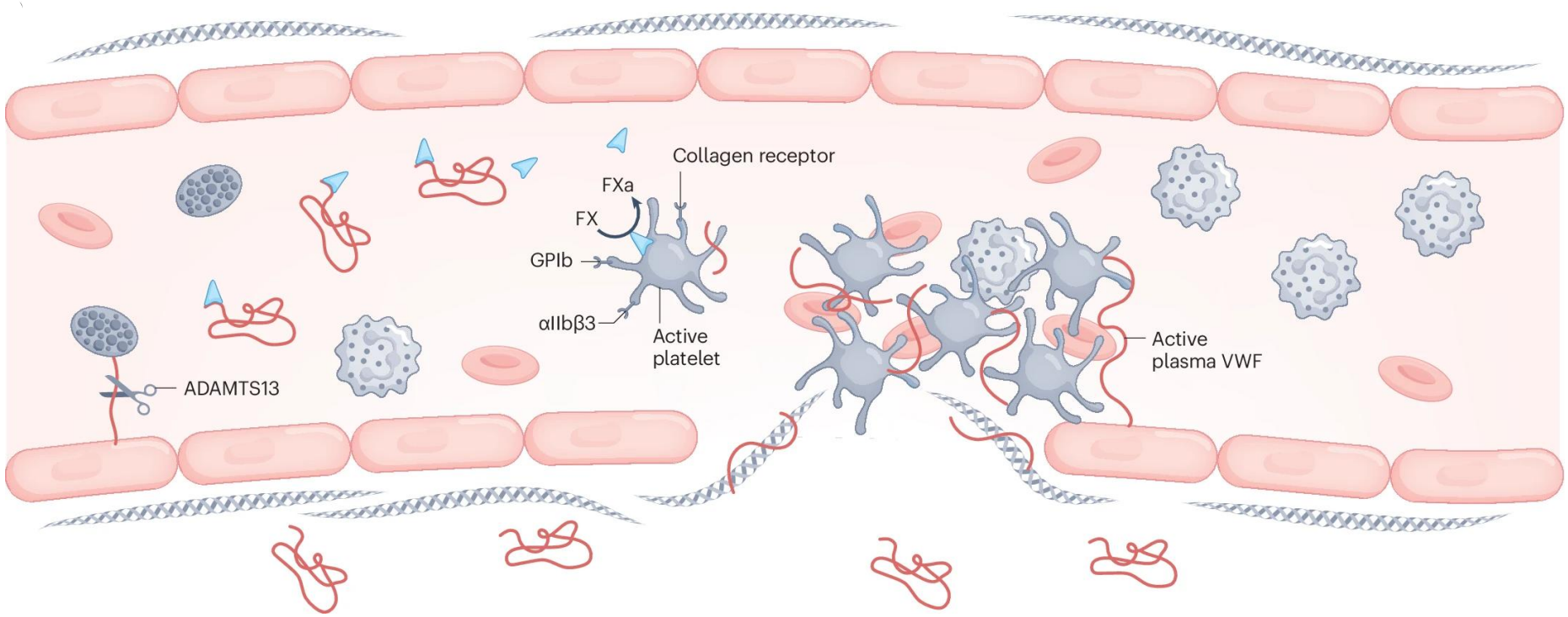
Von Willebrand factor and von Willebrand disease in ageing: mechanisms, evolving phenotypes, and clinical implications

Omid Seidizadeh, Ferdows Atiq, Nathan T Connell, Parnian Alavi, Giancarlo Castaman, David Lillicrap, Flora Peyvandi

Seidizadeh O, et al, Lancet Haematology. 2025

The role of von Willebrand factor (VWF) in hemostasis

- Platelet adhesion
- Factor VIII protection



Seidizadeh O, et al, Nature Reviews Disease Primers. 2024

von Willebrand disease (VWD)

type 1 VWD
(partial) quantitative VWF deficiency

type 2 VWD
qualitative VWF deficiency

type 3 VWD
(complete) quantitative VWF deficiency

2A: decrease VWF-dependent platelet adhesion; loss of HMWM

2B: increased affinity for platelet glycoprotein Ib

2M: decrease VWF-dependent platelet adhesion; normal multimer

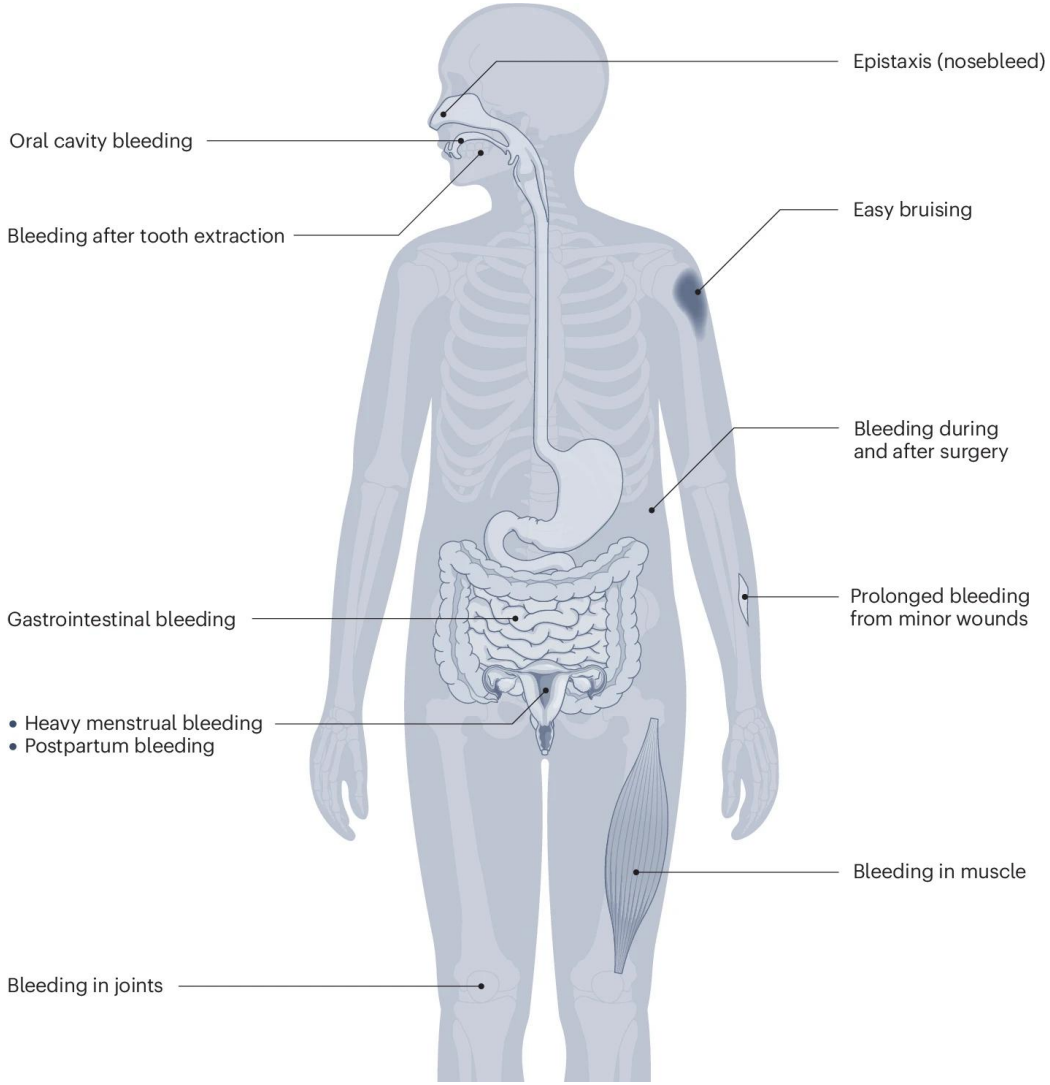
2N: markedly decreased binding affinity for factor VIII

HMWM: High-Molecular-Weight Multimers

Sadler JE et al, JTH. 2006

Clinical manifestations in patients with VWD

- Patients present a **wide spectrum** of bleeding manifestations, depending on their **VWD type** and **severity**



Seidizadeh O, et al, Nature Reviews Disease Primers. 2024

VWF concentrations in the general population

- **Normal range:** approximately 50–200 IU/dL, influenced by genetic variations, environmental factors, physiological changes, and ageing.
- **Influence of ABO blood group system:**
  - Individuals with blood group O typically have ~20–30 IU/dL lower VWF levels compared with non-O blood groups (A, B, AB).
  - This difference is related to faster clearance of VWF in group O individuals.
- **Ageing:** VWF levels increase by ~10–15 IU/dL per decade with ageing in healthy individuals.

Seidizadeh O, et al, Lancet Haematology. 2025

Effects of ageing on VWF concentrations in the general population

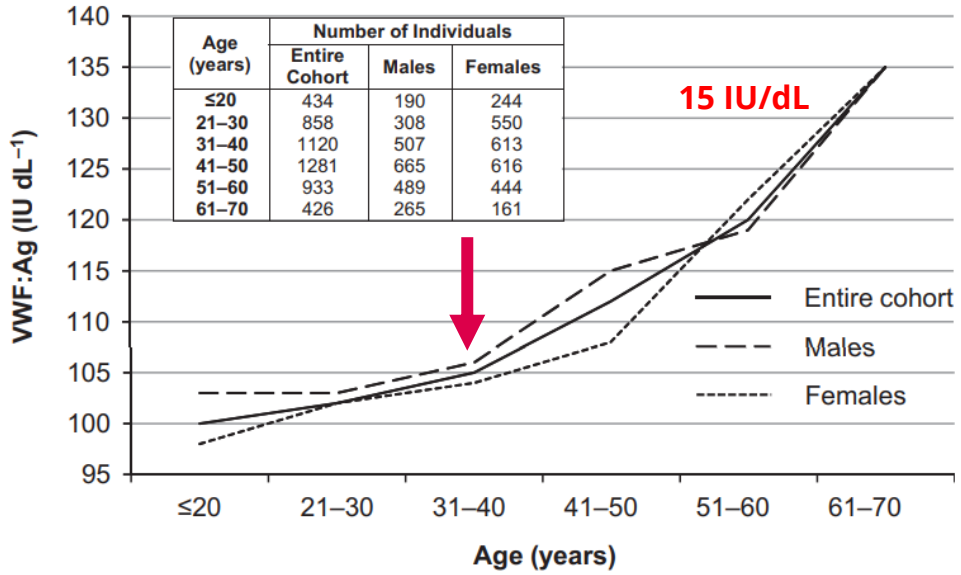
Haemophilia

LETTERS TO THE EDITORS e79

von Willebrand factor: demographics of plasma protein level in a large blood donor cohort from South Wales in the United Kingdom

n = 5052 blood donors

Age (years)	Number of Individuals		
	Entire Cohort	Males	Females
≤20	434	190	244
21–30	858	308	550
31–40	1120	507	613
41–50	1281	665	616
51–60	933	489	444
61–70	426	265	161



Davies JA et al, Haemophilia. 2012

Effects of ABO blood group on VWF concentrations with ageing

Haemophilia

LETTERS TO THE EDITORS e79

von Willebrand factor: demographics of plasma protein level in a large blood donor cohort from South Wales in the United Kingdom

n = 5052 blood donors

Table 1. Plasma VWF level according to ABO blood group and gender.

ABO Blood Group	All individuals *n*	All individuals VWF:Ag (IU dL^{-1}) (mean ± 1 SD)	Men *n*	Men VWF:Ag (IU dL^{-1}) (mean ± 1 SD)	Women *n*	Women VWF:Ag (IU dL^{-1}) (mean ± 1 SD)	*P* (men vs. women)
Group O	2330	94 ± 29	1131	98 ± 30	1199	91 ± 28	<0.05
Group A	2089	123 ± 37	983	126 ± 39	1106	121 ± 36	<0.05
Group B	452	130 ± 37	233	129 ± 34	219	131 ± 40	NS
Group AB	181	137 ± 43	77	139 ± 35	104	135 ± 48	NS
All Groups	5052	111 ± 37	2424	114 ± 37	2628	109 ± 37	<0.05

NS, not significant.

Davies JA et al, Haemophilia. 2012

Journal of Thrombosis and Haemostasis, **14**: 953–963 DOI: 10.1111/jth.13294

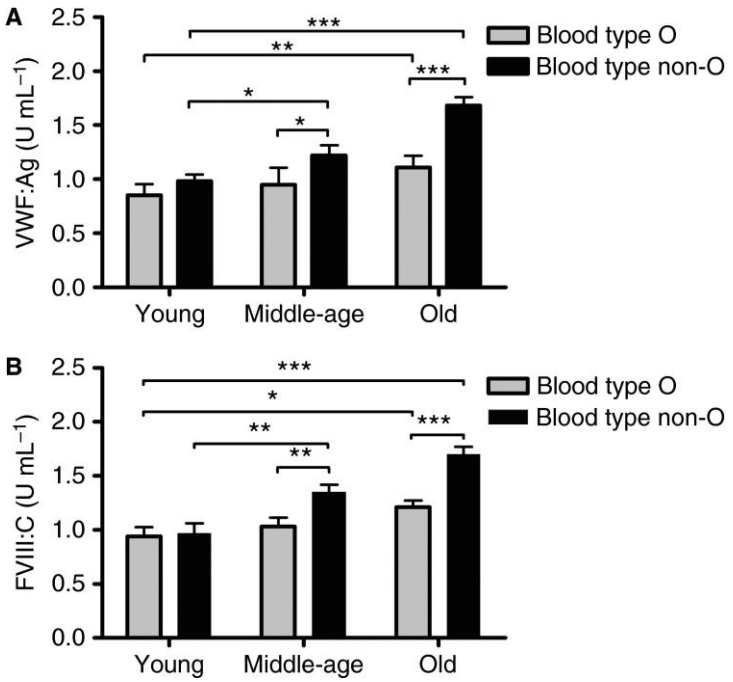
ORIGINAL ARTICLE

Aging and ABO blood type influence von Willebrand factor and factor VIII levels through interrelated mechanisms

S. ALBÁNEZ,* K. OGIWARA,* A. MICHELS,* W. HOPMAN,† J. GRABELL,‡ P. JAMES‡ and D. LILLICRAP*

*Department of Pathology and Molecular Medicine; †Department of Public Health Sciences; and ‡Department of Medicine, Queen's University, Kingston, ON, Canada

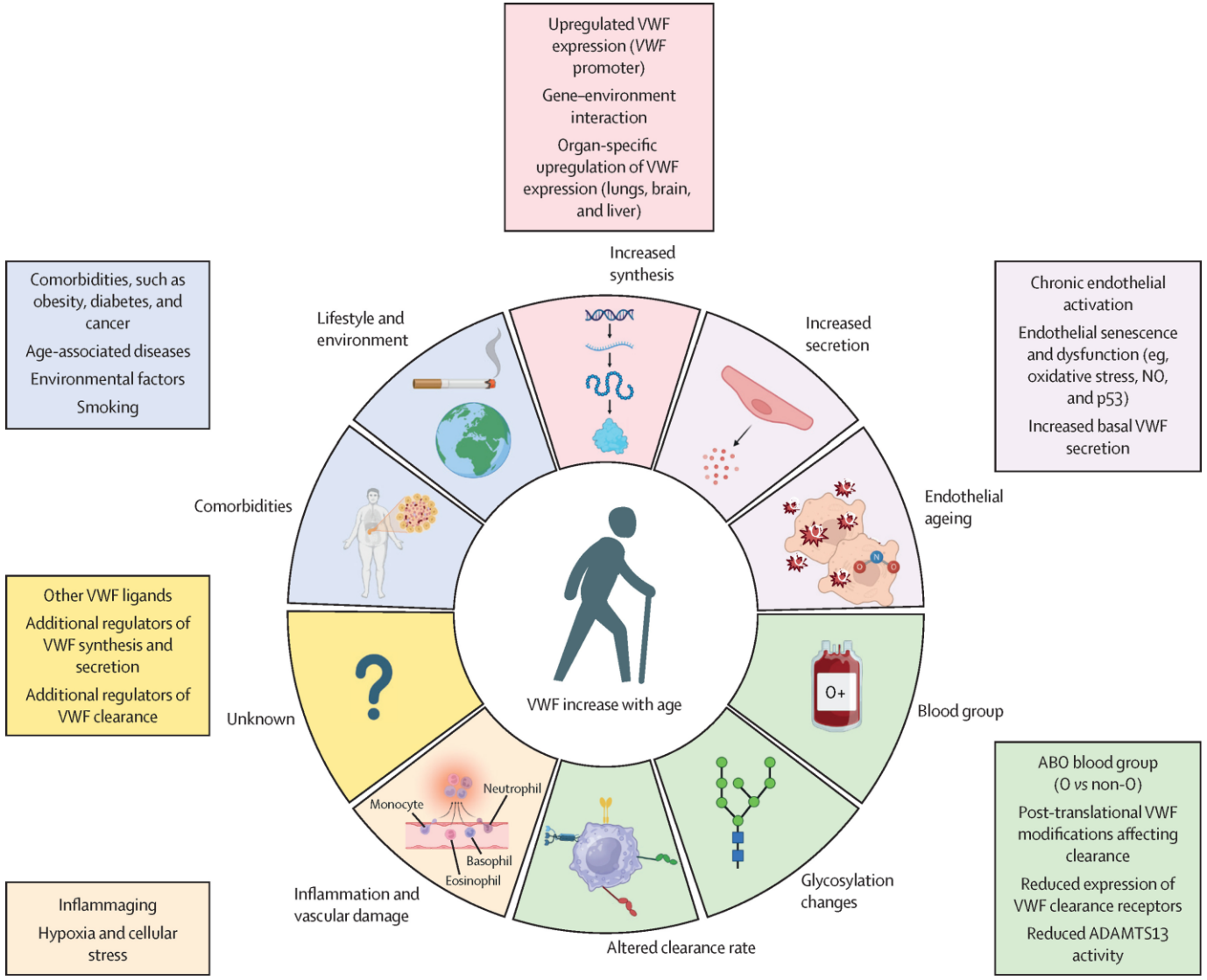
n = 207 healthy individual



Albánez S et al, JTH. 2016

Causes of increasing VWF concentrations with ageing

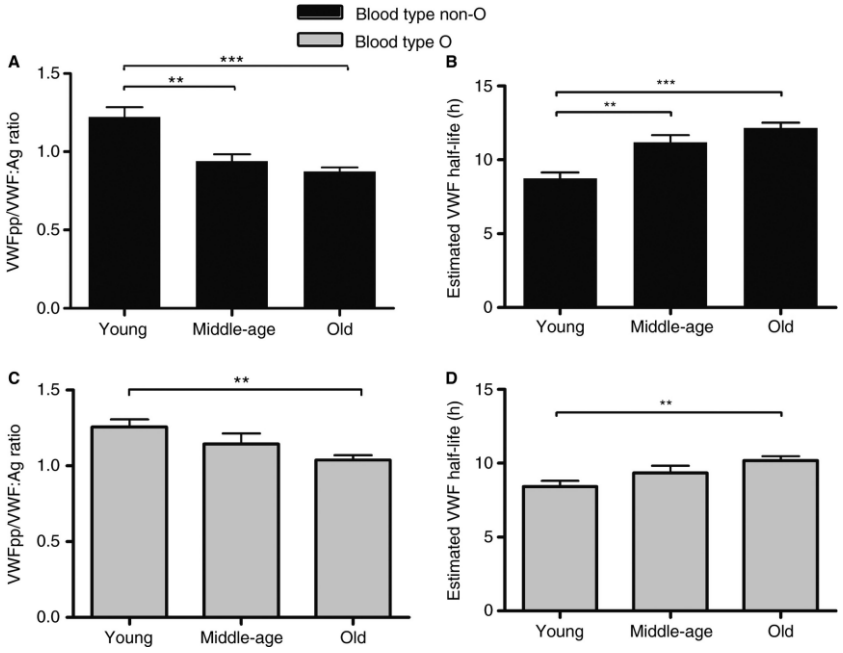
The molecular mechanisms underlying age-related changes in VWF remain **largely unknown**

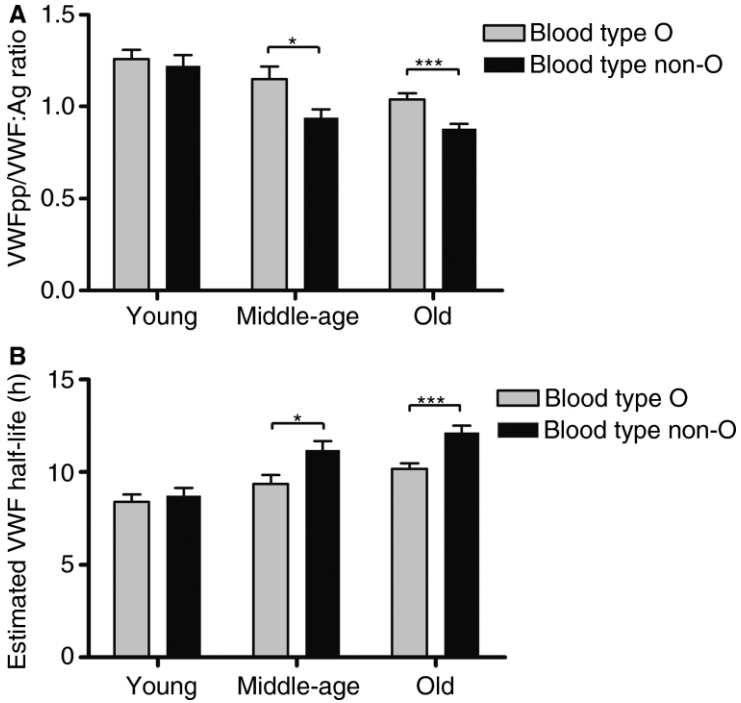


Seidizadeh O, et al, Lancet Haematology. 2025

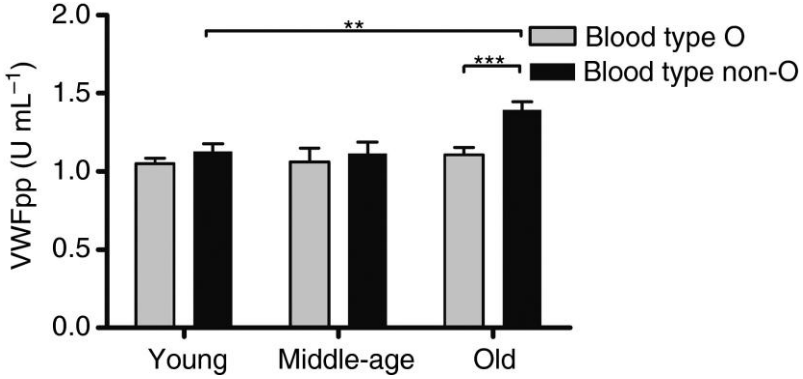
Causes of increasing VWF concentrations with ageing

Decreased VWF clearance





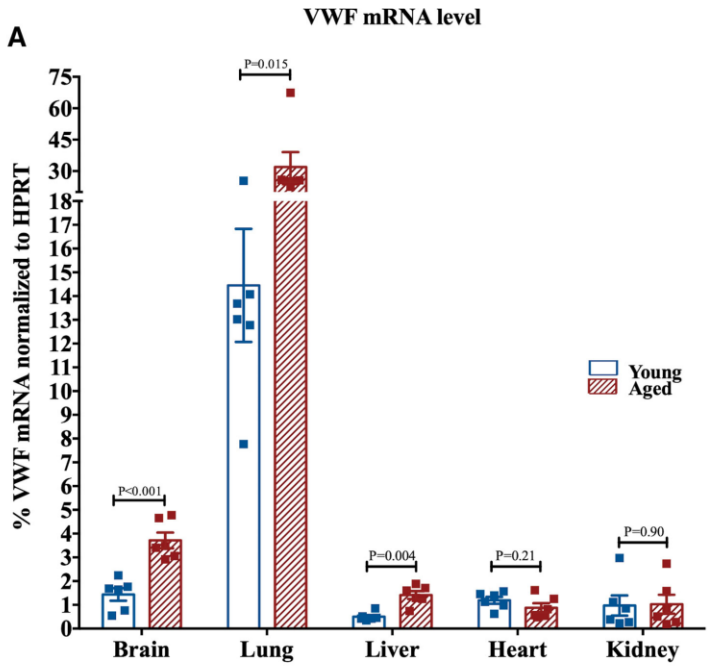
Increased VWF synthesis



Albánez S et al, JTH. 2016

Age-related upregulation of VWF expression occurs in an organ-specific manner

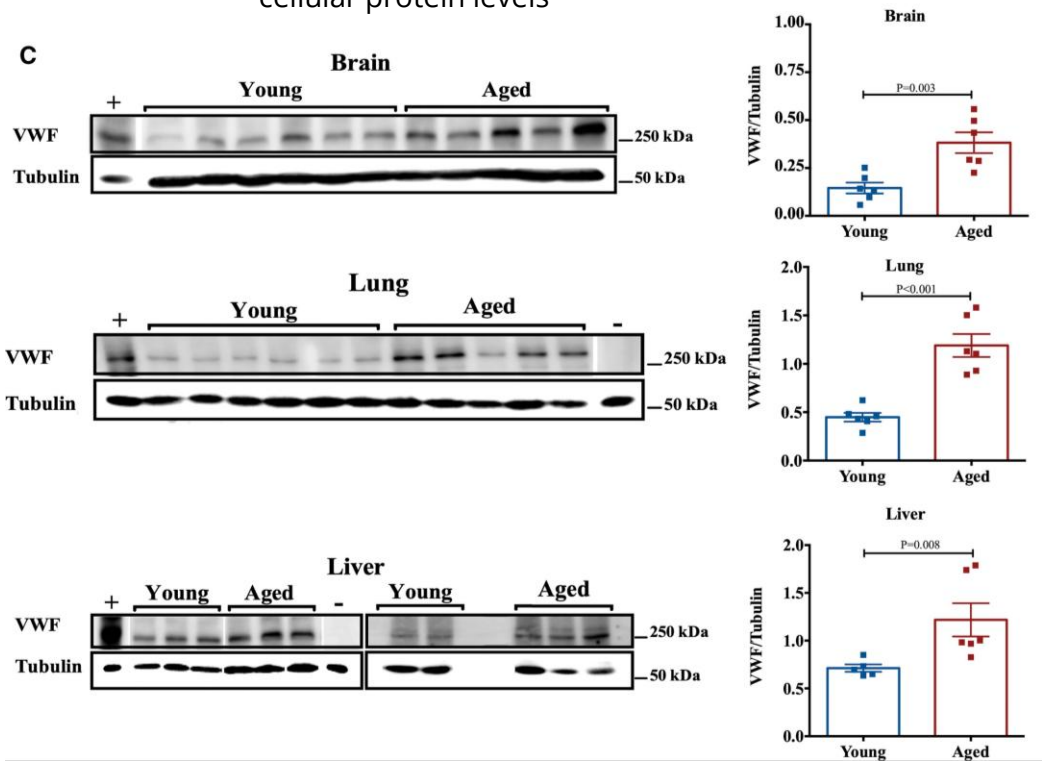
vascular bed heterogeneity could contribute to the age-associated increase



B

Organs	Young	Aged	Fold of induction
Brain	1.43998057	3.713995	2.6
Lung	14.4519287	31.9547733	2.2
Liver	0.50197343	1.41319425	2.8
Heart	1.19084767	0.87747767	0.73
Kidney	0.97077967	1.0255505	1.05

cellular protein levels



Mediated by cell senescence and p53 transcription factor

Alavi P et al, ATVB. 2023

Effects of ageing on VWF concentrations in VWD

	Design and population	Key findings on age and VWF concentration
Rydz et al (2015)[14]	Retrospective cohort; 31 patients with type 1 disease; Canada	VWF antigen concentration increased by approximately 30 IU/dL per decade; VWF ristocetin cofactor activity increased by approximately 20 IU/dL per decade; VWF concentrations normalised over 11 years in 58% of patients
Abou-Ismail et al (2018)[15]	Longitudinal; 126 patients with type 1 disease or low VWF concentrations; USA	VWF antigen concentration increased by 2·4 IU/dL per year; VWF concentrations normalised over 10·5 years in 27·8% of patients
Borghi et al (2017)[16]	Cross-sectional; 195 patients with type 1 disease; Italy	VWF antigen concentration increased by 14 IU/dL; 94% of patients with mild disease had normalised VWF concentrations versus 6% of patients with moderate-to-severe disease; median follow-up 6·6 years
Flood et al (2016)[17]	Multicentre cohort; 310 patients with type 1 disease; USA	36% of patients had normalised VWF antigen concentrations at enrolment (median 76 IU/dL)
Sanders et al (2014)[18]	Cross-sectional; 664 patients with moderate-to-severe disease; WiN study in the Netherlands	For patients with type 1 von Willebrand disease, VWF antigen concentrations increased by 3·5 IU/dL per decade; FVIII activity increased by 7·1 IU/dL per decade; no increases occurred in patients with type 2 disease; more bleeding occurred in older people with type 2 disease than younger people with type 2 disease
Biguzzi et al (2021)[19]	Retrospective longitudinal; 617 patients including those with type 1 or 2 disease and low VWF concentrations; Italy	VWF antigen and FVIII concentrations increased linearly after age 40 (VWF 3·7 IU/dL per decade; FVIII 7·4 IU/dL per decade); no increase in patients with type 1 disease with the Vicenza variant; 16-year mean follow-up
Atiq et al (2024)[20]	Combined analysis of LoVIC and WiN cohorts; 565 patients with type 1 disease or low VWF concentrations; the Netherlands and Ireland	VWF concentrations remained <30 IU/dL in 47% of patients with type 1 von Willebrand disease; concentrations increased to 30–50 IU/dL in 30% of patients; concentrations normalised in 23% of patients; age-dependent phenotype evolution

VWF=von Willebrand factor.

Table: **Effect of ageing on VWF concentrations in patients with von Willebrand disease**

Seidizadeh O, et al, Lancet Haematology. 2025

Effects of ageing on VWF concentrations in VWD

Journal of Thrombosis and Haemostasis
Volume 19, Issue 1, January 2021, Pages 96-106

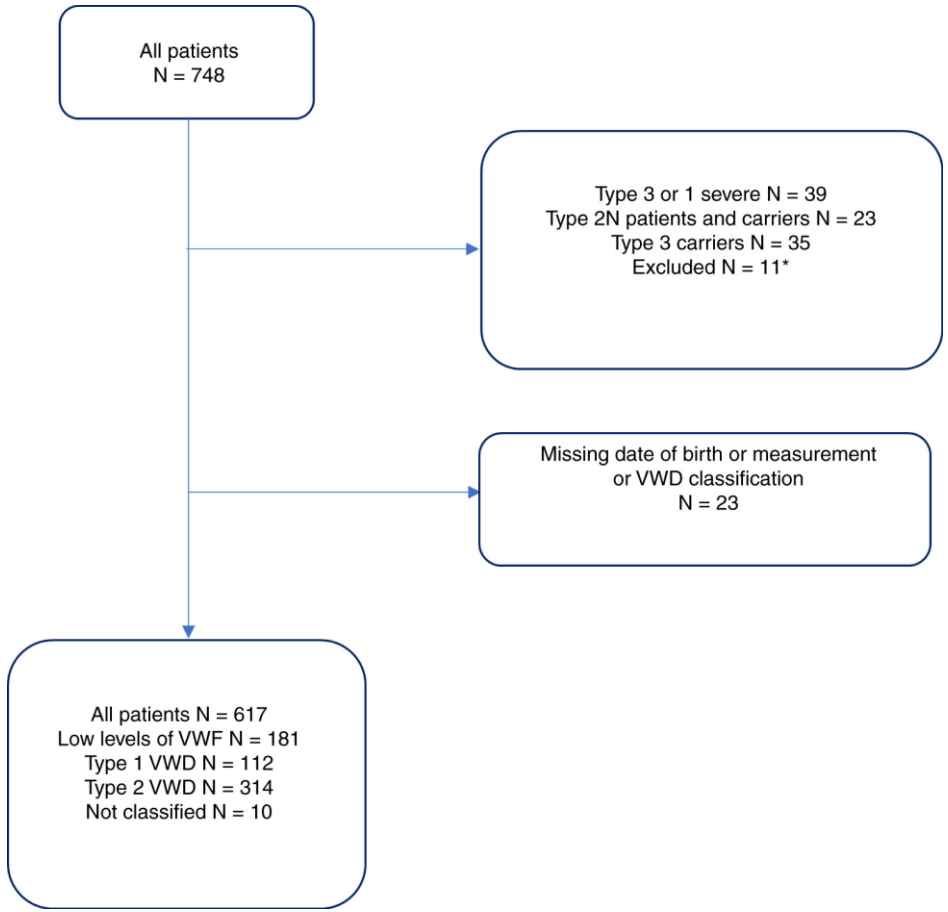
ORIGINAL ARTICLE

Increasing levels of von Willebrand factor and factor VIII with age in patients affected by von Willebrand disease

Eugenia Biguzzi [1], Simona Maria Siboni [1], Saskia le Cessie [2 3], Luciano Baronciani [1], Frits R. Rosendaal [2], Astrid van Hylckama Vlieg [2], Flora Peyvandi [1 4]

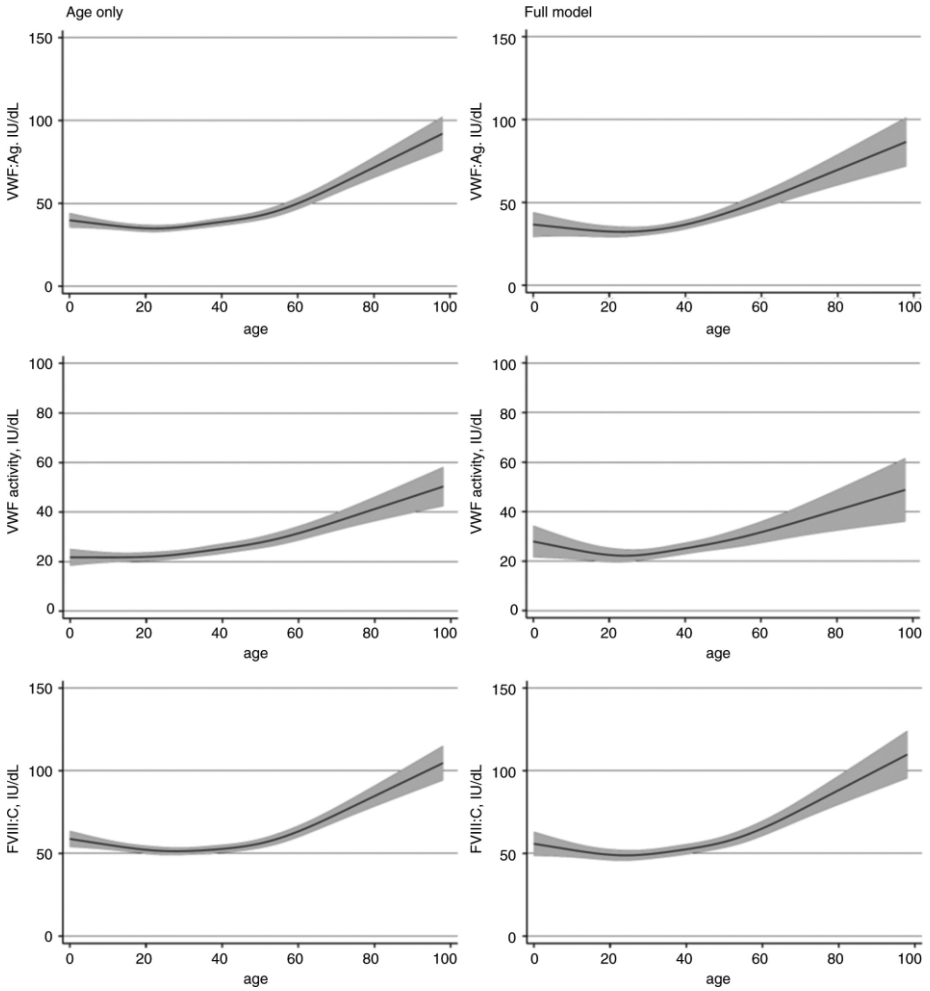
Show more

- Longitudinal intra-individual assessments
- 16-year mean follow-up
- On average 3 measurements over time (range 1-6)

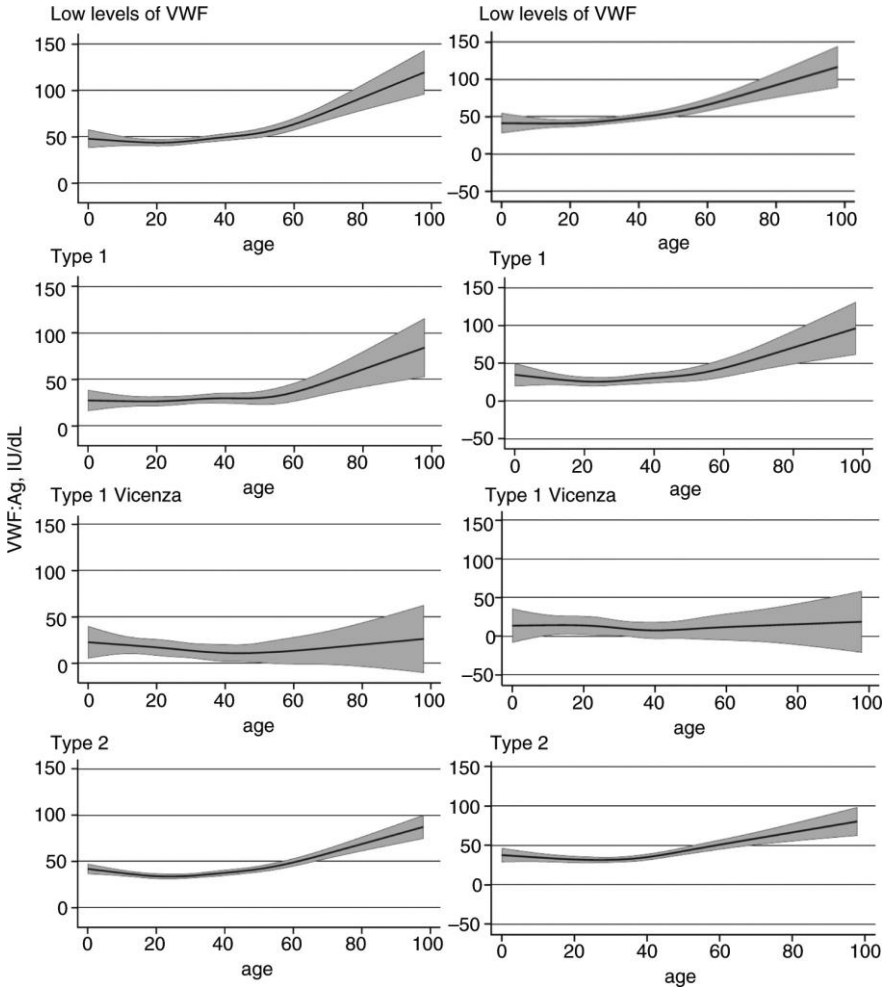


Biguzzi E et al, JTH. 2021

Effects of ageing on VWF concentrations in VWD

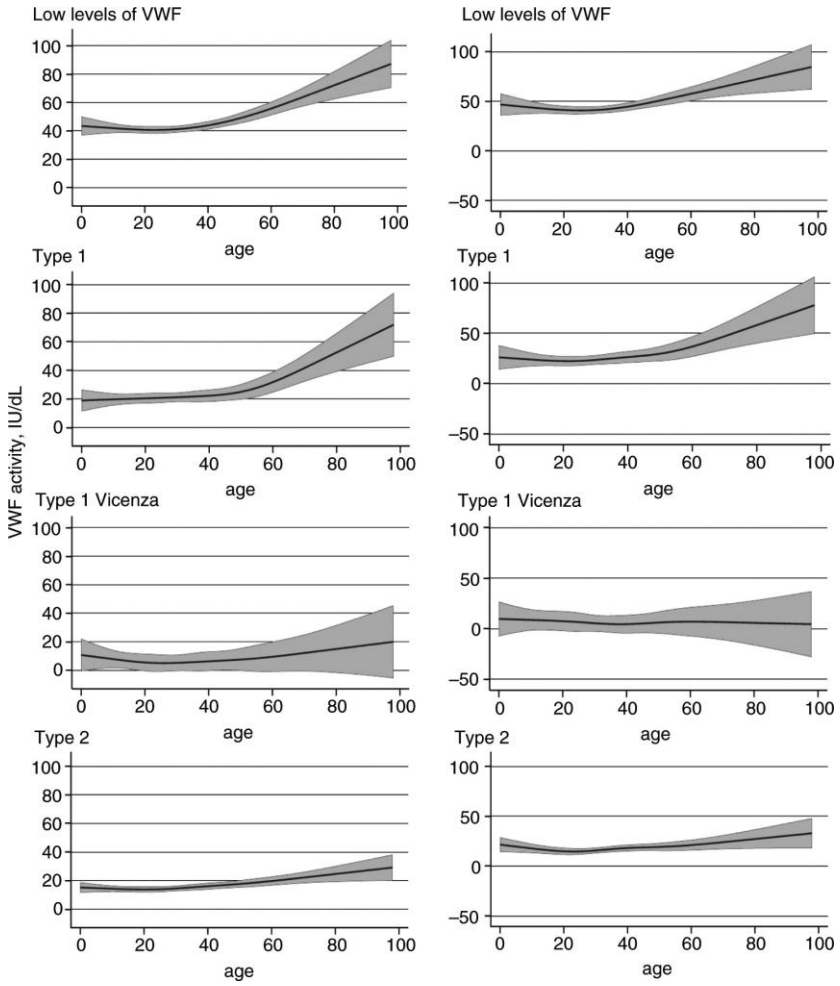


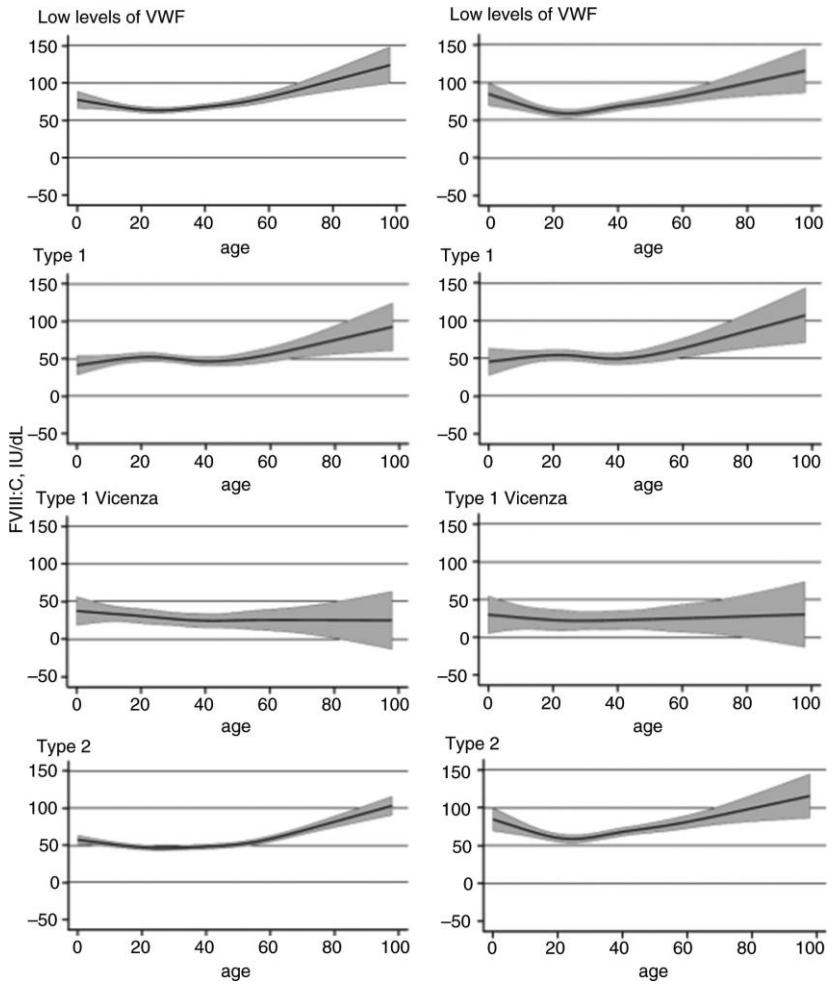
Full model=
Adjusted for age at first measurement, sex, blood group, comorbidities, and test type.



Biguzzi E et al, JTH. 2021

Effects of ageing on VWF concentrations in VWD





Full model=
Adjusted for age at first measurement, sex, blood group, comorbidities, and test type.

Biguzzi E et al, JTH. 2021

Effects of ageing on VWF concentrations in VWD

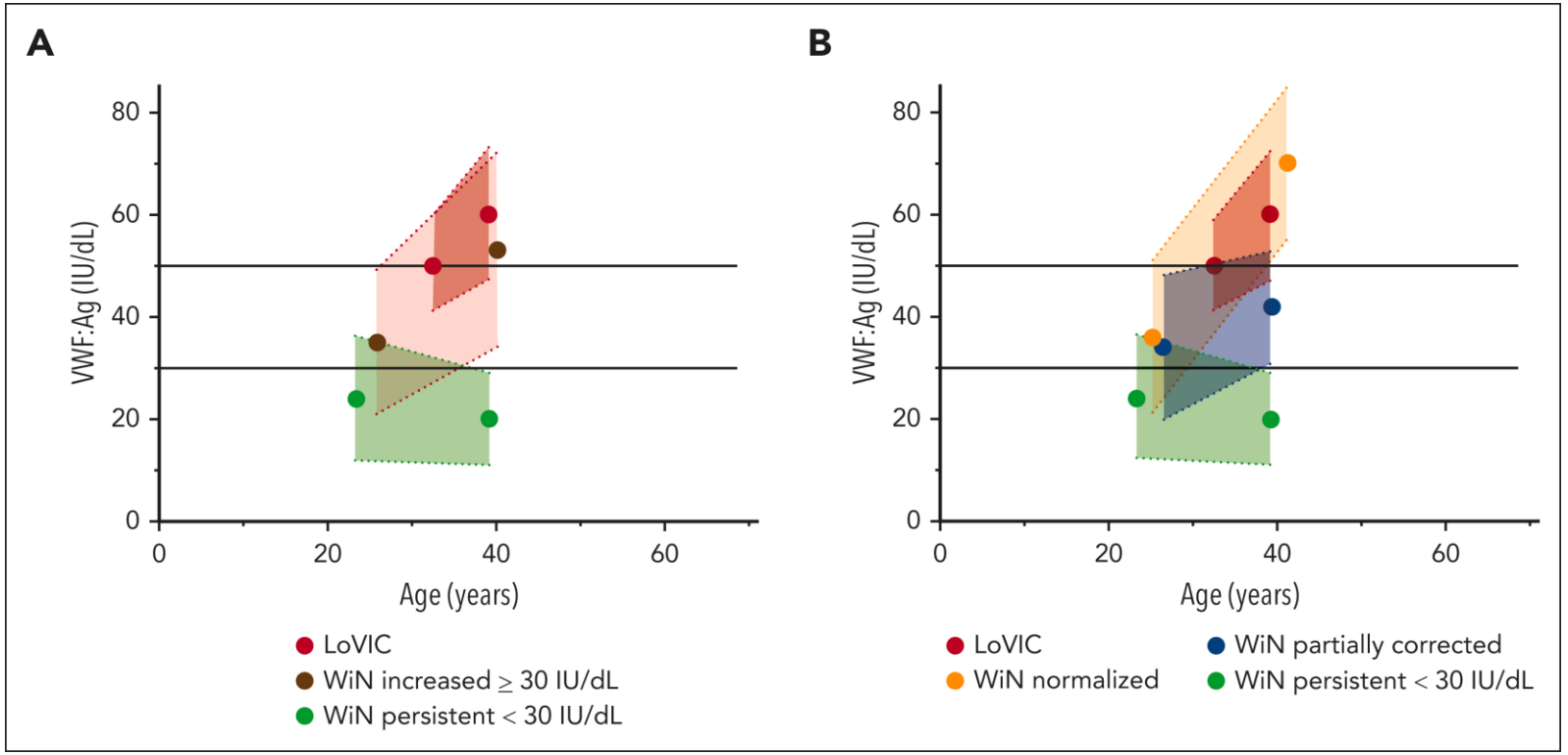
TABLE 2 Regression slope β coefficient per decade and its 95% CI, calculated after the age of 40 y (after this age a linear regression was shown by the linear mixed models with restricted cubic splines)

	Patients, n	Measurements, n	All Patients β Coefficient per Decade (95% CI) IU/dL	Low VWF Levels β Coefficient per Decade (95% CI) IU/dL	Type 1 VWD β Coefficient per Decade (95% CI) IU/dL	Type 1 Vicenza VWD β Coefficient per Decade (95% CI) IU/dL	Type 2 VWD β Coefficient per Decade (95% CI) IU/dL
VWF antigen							
Not adjusted	276	893	5.43 (3.52-7.45)	8.36 (4.39-12.32)	4.69 (−1.42 to 10.81)	2.12 (−5.84 to 10.08)	4.31 (1.89-6.74)
Adjusted for age at 1st measurement, sex, blood group, comorbidities, and assay type	156	657	6.48 (3.43-9.54)	10.36 (5.36-15.36)	10.53 (3.47-17.59)	1.91 (−0.68 to 10.63)	7.00 (3.07-10.73)
VWF activity							
Not adjusted	275	901	2.32 (0.82-3.81)	4.96 (2.09-7.83)	3.79 (−0.63 to 8.21)	2.36 (−3.40 to 8.11)	0.60 (−1.21 to 2.41)
Adjusted for age at first measurement, sex, blood group, comorbidities, and assay type	155	660	3.68 (0.62-6.75)	4.85 (0.40-9.30)	5.54 (−0.92 to 12.01)	3.09 (−5.40 to 11.57)	1.10 (−2.25 to 4.45)
FVIII:C							
Not adjusted	270	1000	6.87 (5.31-8.43)	7.61 (4.26-10.95)	5.22 (0.67- 9.77)	0.53 (−5.73 to 10.95)	7.00 (5.11-8.90)
Adjusted for age at first measurement, sex, blood group, and comorbidities	151	712	7.44 (5.19-9.70)	6.59 (2.63-10.55)	6.96 (1.48-12.43)	2.38 (−4.72 to 9.48)	7.99 (5.24-10.75)

Biguzzi E et al, JTH. 2021

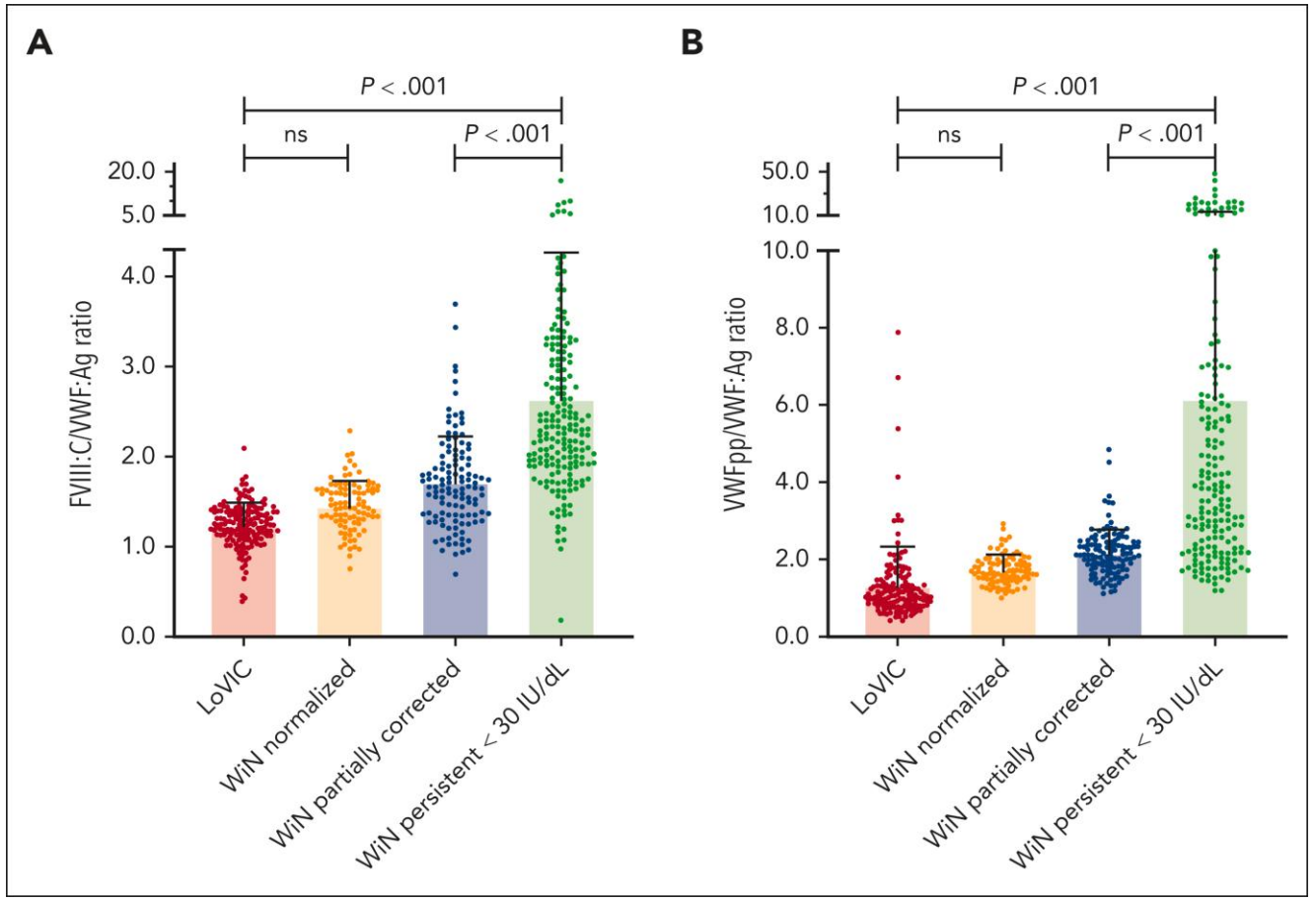
Effects of age on plasma VWF:Ag levels in patients with low VWF compared with those in type 1 VWD subgroups

- **47% remained** <30 IU/dL with ageing
- **30% increased** to 30–50 IU/dL
- **23% normalized** (>50 IU/dL)



Atiq F et al, Blood. 2024

Pathophysiological mechanisms in patients with low VWF compared with type 1 VWD subgroups



Atiq F et al, Blood. 2024

Effects of ageing on bleeding symptoms

- Ageing effects on bleeding symptoms are poorly understood.
- Conflicting data complicate interpretation of bleeding trends with age.
- Lifetime-accumulating BAT scores are inherently age-dependent.
- Current BATs may overestimate bleeding severity in older individuals.
- Need for age-adjusted assessment tools to accurately capture bleeding risk.
- Age-adjusted ISTH-BAT reference ranges have been recently developed.

Table 1 | International Society on Thrombosis and Haemostasis Bleeding Assessment Tool bleeding score normal ranges and cut-offs by age and sex

Population	Normal range	Cut-off/abnormal bleeding score
Women, 18–30 years	0–4	≥5
Women, 31–51 years	0–5	≥6
Women, 52–88 years	0–6	≥7
Men, 18 years and older	0–3	≥4
Children, <18 years	0–2	≥3

Seidizadeh O, et al, Lancet Haematology. 2025
Doherty D et al, JTH. 2023

Effects of ageing on bleeding symptoms

Journal of Thrombosis and Haemostasis, 4: 766–773

ORIGINAL ARTICLE

A quantitative analysis of bleeding symptoms in type 1 von Willebrand disease: results from a multicenter European study (MCMDM-1 VWD)

A. TOSETTO,* F. RODEGHIERO,* G. CASTAMAN,* A. GOODEVE,† A. B. FEDERICI,‡ J. BATTLE,§ D. MEYER,¶ E. FRESSINAUD,¶ C. MAZURIER,** J. GOUDEMAND,†† J. EIKENBOOM,‡‡ R. SCHNEPPENHEIM,§§ U. BUDDE,¶¶ J. INGERSLEV,*** Z. VORLOVA,††† D. HABART,††† L. HOLMBERG,‡‡‡ S. LETHAGEN,‡‡‡ J. PASI,§§§ F. HILL¶¶¶ and I. PEAKE†

*San Bortolo Hospital, Vicenza, Italy; †University of Sheffield, Sheffield, UK; ‡Foundation IRCCS Maggiore Policlinico Hospital, Mangiagalli, Regina Elena and University of Milano, Milan, Italy; §Hospital Teresa Herrera, La Coruna, Spain; ¶INSERM, Paris; **LFB, Lille; ††University of Lille, Lille, France; ‡‡Leiden University Medical Center, Leiden, the Netherlands; §§University Medical Center Hamburg-Eppendorf, Hamburg; ¶¶Coagulation Laboratory, Hamburg, Germany; ***University Hospital Skejby, Aarhus, Denmark; †††Institute of Hematology and Blood Transfusion, Prague, Czech Republic; ‡‡‡University of Lund, Malmo, Sweden; §§§Leicester Royal Infirmary, Leicester; and ¶¶¶Children's Hospital, Birmingham, UK

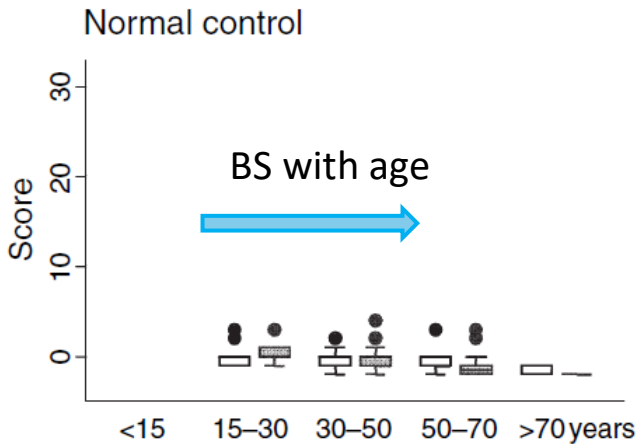
Bleeding score: -1 to 4

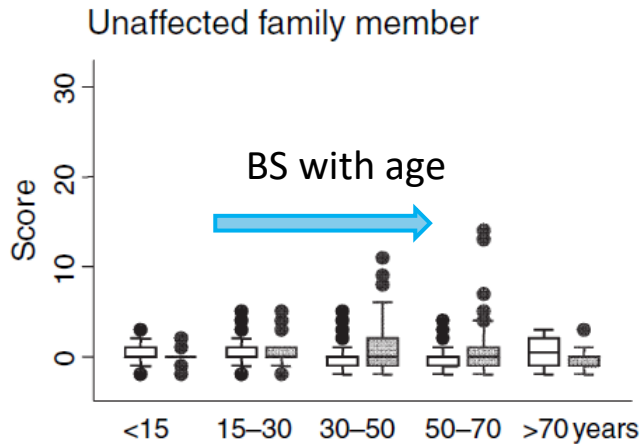
	Index case ($n = 144$)	Affected family members ($n = 273$)	Unaffected family members ($n = 295$)	P	Controls ($n = 195$)
Females (%)	91 (63.2)	151 (55.3)	145 (49.1)	0.02*	100 (51.3)
Median age, years (range)	40 (1–80)	32 (2–91)	41 (3–90)	0.002*	40 (8–78)
Age groups†					
Below 15 years	15	52	45		–
15–30 years	34	72	49		41
30–50 years	66	83	92		55
50–70 years	24	48	88		89
>70 years	5	18	21		4
Blood group O (%)	96 (66.6)	161 (58.9)	141 (47.8)	0.001*	75 (38.4)
Median VWF:RCo, IU dL^{-1} (25–75 percentile)	34 (11–49)	35 (12–54)	87 (65–112)	0.12‡	106 (83–138)
Median VWF:Ag, IU dL^{-1} (25–75 percentile)	33 (19–49)	36 (21–54)	92 (70–118)	0.11‡	99 (76–121)
Median FVIII:C, IU dL^{-1} (25–75 percentile)	56 (28–77)	63 (34–88)	100 (78–133)	0.08‡	113 (95–113)
Median BS (range)	9 (−1 to 23)	4 (−2 to 27)	0 (−2 to 14)	–	−1 (−3 to 4)

Tosetto A et al, JTH. 2006

Effects of ageing on bleeding symptoms

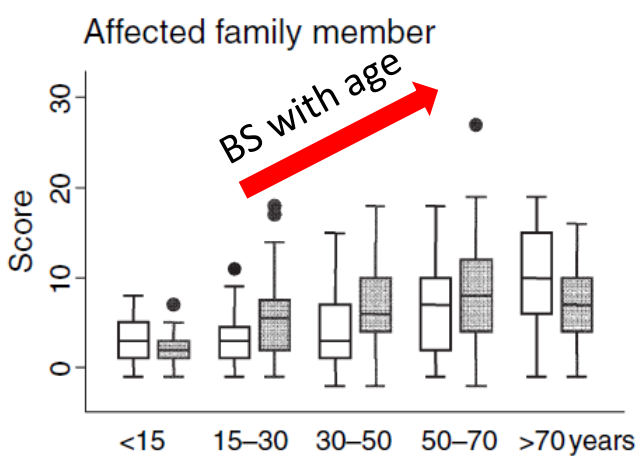
Median BS: -1

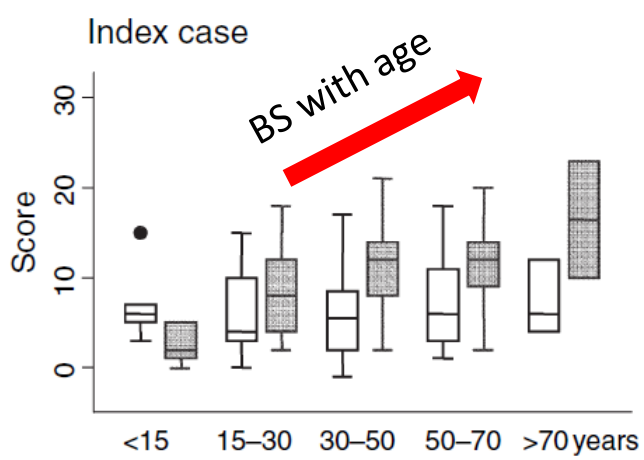




Median BS: 0

Median BS: 4





Median BS: 9

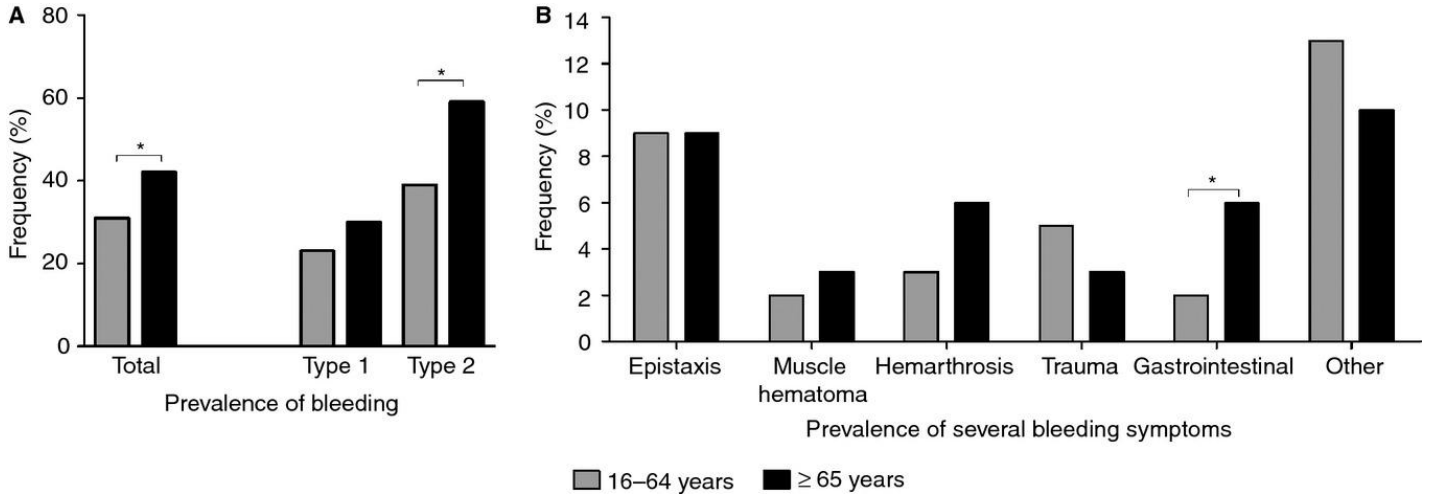
Male Female

Tosetto A et al, JTH. 2006

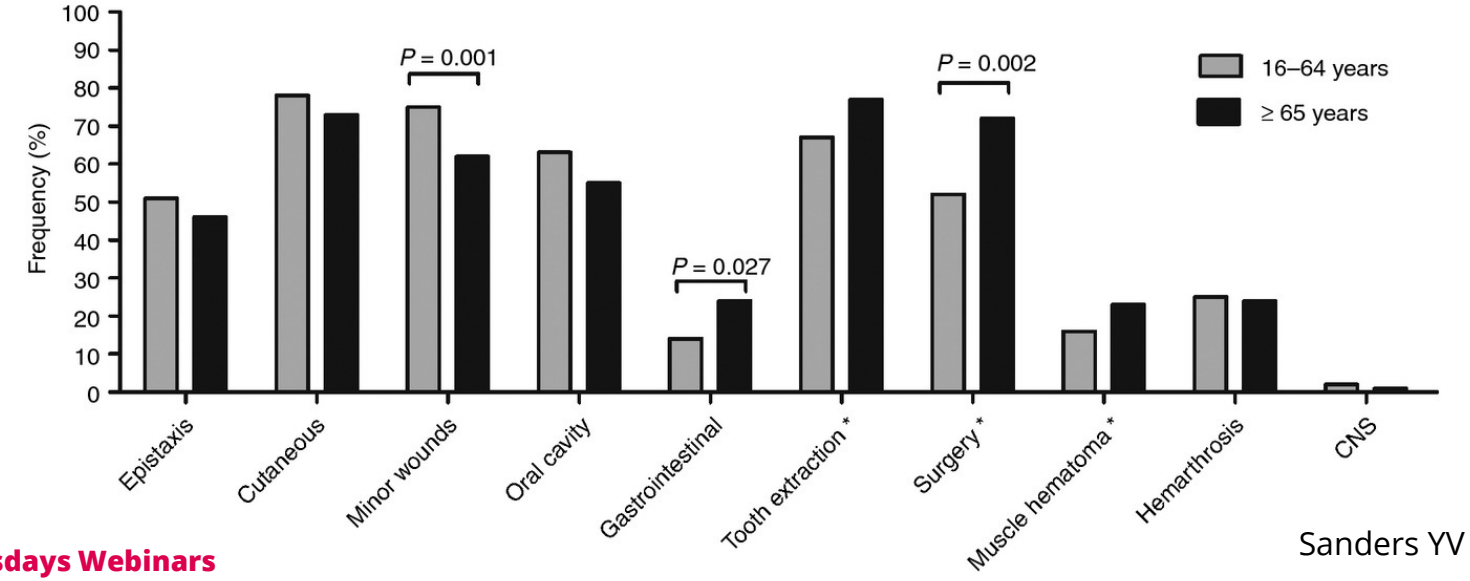
Effects of ageing on bleeding symptoms

Frequency of bleeding requiring DDAVP or replacement therapy in the prior year

Cohort: VWD patients ≥65 years (n=71)
vs.
16–64 years (n=593)

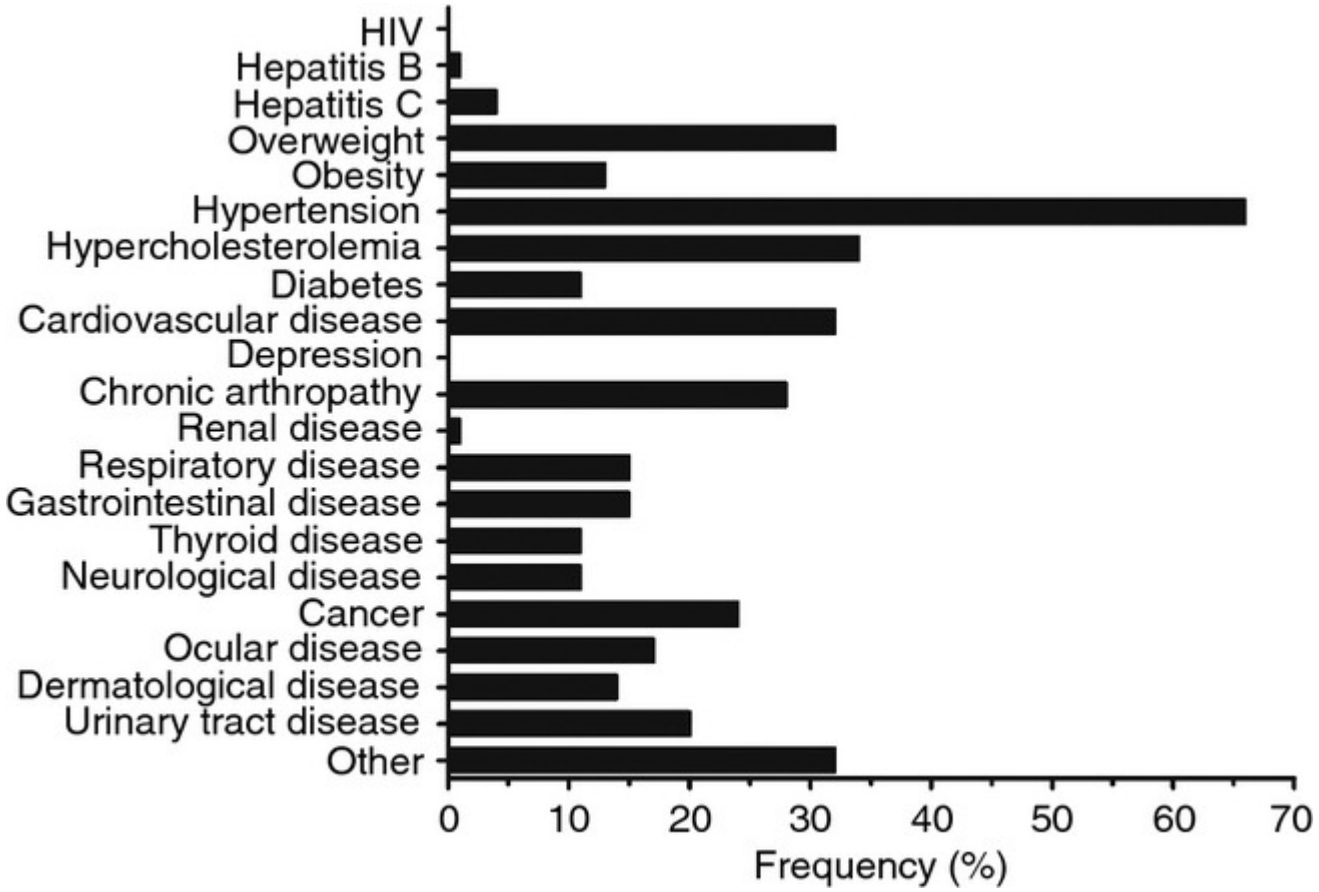


Lifetime prevalence of bleeding symptoms



Sanders YV et al, JTH. 2014

Presence of co-morbidities in the elderly VWD patients



Sanders YV et al, JTH. 2014

Dynamics between VWF and its ligands with ageing

Ageing

↓

↑ VWF → ↑ FVIII

↓

↓ ADAMTS13

↓

Less VWF cleavage

↓

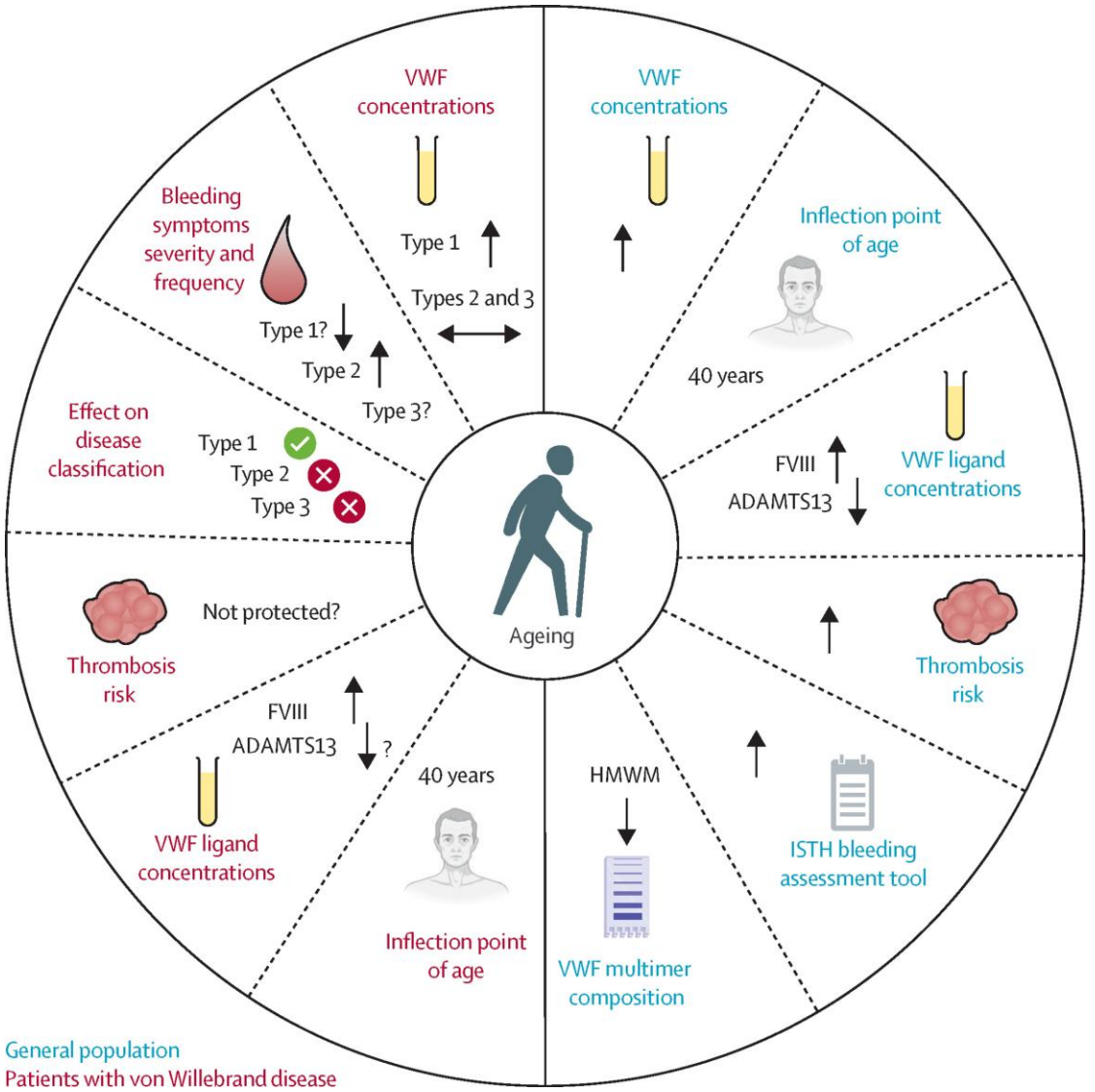
Prothrombotic tendency

↓

Although age increases thrombosis risk in the general population and VWF levels in some VWD cases, the impact on clinical thrombosis risk in older vs. younger VWD patients remains unclear

Albánez S et al, JTH. 2016
Seidizadeh O et al, JTH. 2021
Liu W et al, JTH. 2023

Summary: age-related changes in VWF levels in the general population and patients with VWD



Seidizadeh O, et al, Lancet Haematology. 2025

Perspectives and unknowns

- Age-related VWF increase: mechanisms unclear (genetic, endothelial, clearance)
- Impact on thrombosis risk is uncertain
- Impact on bleeding in VWD is unclear
- Longitudinal studies needed in older patients with VWD

THANK YOU

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