Hemophilia is associated with accelerated biological aging

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Supplementary data

Supplementary Table 1 Baseline characteristics of the study population

	Persons with Hemophilia			Healthy controls
	All (n=99)	Non-severe PwH (n=33)	Severe PwH (n=66)	(n=61)
Age; years, median (IQR)	36.0 (24.0–45.5)	44.0 (28.0 – 50.0)	32.0 (23.0 -43.0)	36.3 (27.0–53.0)
BMI, kg/m²; median IQR)	24.3 (21.9-26.7)	25.1 (23.4-28.4)	24.1 (21.6-26.3)	24.7 (22.4-26.2)
Hemoglobin, g/dL;median (IQR)	15.1 (14.4-15.9)	15.1 (14.6-15.9)	15.1 (14.4-15.9)	14.9 (14.5-15.6)
Leukocytes, x10^9/L; median (IQR)	5.8 (4.8-6.6)	6.2 (5.2-7.0)	5.7 (4.8-6.5)	5.4 (4.8-6.7)
Neutrophils, x10^9/L; median (IQR)	3.2 (3.1-4.0)	3.2 (2.9-3.4)	3.3 (3.1-4.3)	3.0 (2.6-3.7)
Platelets, x10^9/L; median (IQR)	207 (178-240)	208 (181-248)	207 (178-240)	232 (206-269)
hsCRP, mg/dL, median (IQR)	0.11 (0.06-0.21)	0.13 (0.06-0.19)	0.10 (0.06-0.24)	0.09 (0.05-0.17)
Fibrinogen, mg/dL; median (IQR)	275 (253-322)	270 (248-306)	281 (258-326)	261 (235-302)
Treatment regimens				
Prophylaxis; n[%]	45 [45.5]	1 (3)	44 (67)	NA
On-Demand; n[%]	54 [54.5]	32 (97)	22 (33)	NA
Comorbidities (In at least >2 PwH)				
Hemophilic arthropathy; n[%]	58 [58.6]	6/33 [18.2]	52/66 [78.8]	NA
(History) of hepatitis C; n[%]	38 [38.4]	6/33 [18.2]	32/66 [48.5]	NA
HIV; n[%]	8 [8.1]	0/33 [0.0]	8/66 [12.1]	NA
Hypertension; n[%]	15 [15.2]	6/33 [18.2]	9/66 [13.6]	NA
BMI >30; n[%]	11 [11.1]	4/29 [13.8]	7/61 [11.5]	NA
Psoriasis; n[%]	3 [3.0]	1/33 [3.0]	2/66 [3.0]	NA
None; n[%]	27 [27.3]	15/33 [45.5]	12/66 [18.2]	NA

PwH, persons with hemophilia; BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable;

Supplementary Table 2
Spearman's rank correlation coefficients of telomere length with baseline characteristics of the study population

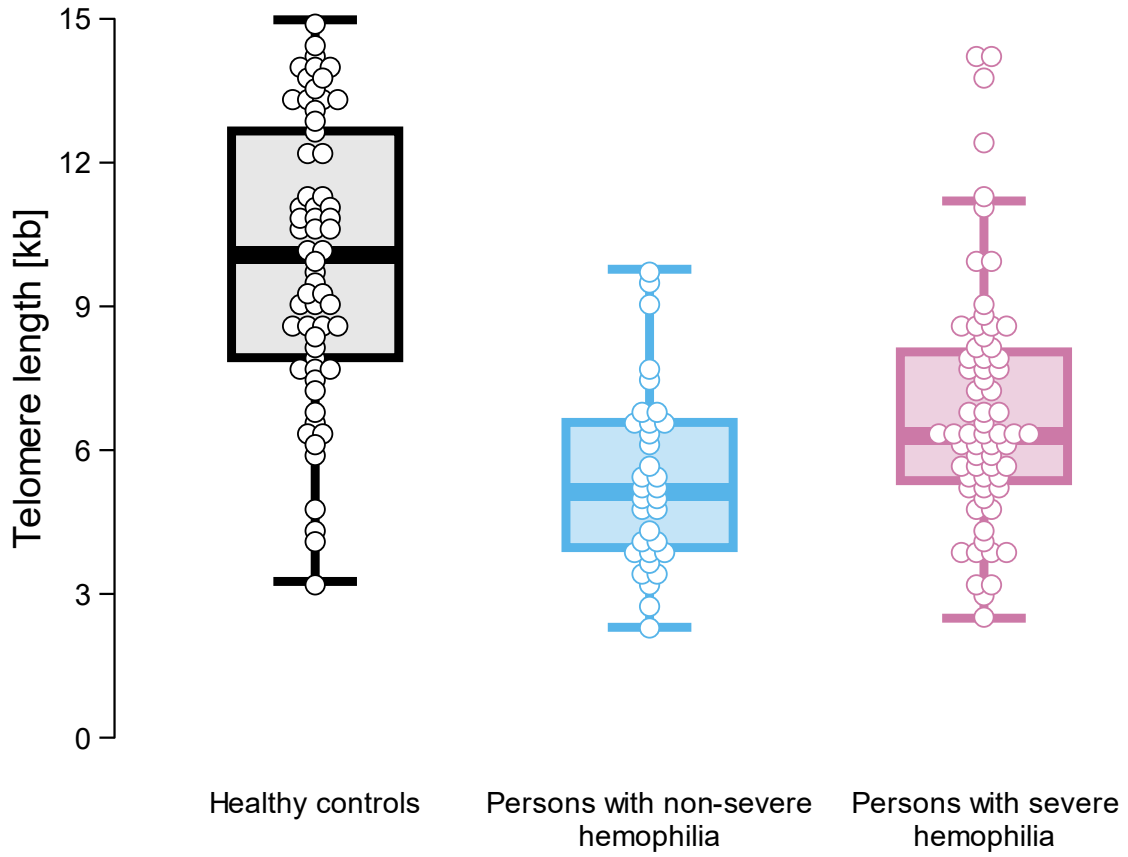
	Persons with Hemophilia									**Healthy controls**		
	All (n=99)			Non-severe PwH (n=33)			Severe PwH (n=66)			(n=61)		
	telomere length, per diploid cell			telomere length, per diploid cell			telomere length, per diploid cell			telomere length, per diploid cell		
	n	ρ	p-value	n	ρ	p-value	n	ρ	p-value	n	ρ	p-value
Clinical data												
Age; years	99	**-0.402**	<0.001	33	**-0.556**	<0.001	66	**-0.286**	0.020	61	-0.114	0.382
BMI, kg/m²	52	-0.248	0.070	20	-0.354	0.126	34	-0.211	0.232	61	0.057	0.661
Laboratory data												
Hemoglobin, g/dL	82	-0.006	0.957	30	-0.048	0.802	55	0.003	0.981	61	0.052	0.690
Leukocytes, $x10^9$/L	85	-0.017	0.880	30	-0.046	0.807	55	0.033	0.814	61	-0.207	0.109
Neutrophils, $x10^9$/L	85	-0.28	0.185	10	-0.462	0.179	14	-0.366	0.199	61	-0.024	0.855
Platelets, $x10^9$/L	85	-0.033	0.761	30	0.051	0.789	55	-0.063	0.647	61	-0.077	0.553
hsCRP, mg/dL	71	-0.199	0.075	30	-0.026	0.892	51	-0.264	0.061	61	-0.12	0.356
Fibrinogen, mg/dL	82	**-0.266**	0.016	31	-0.152	0.415	51	**-0.435**	0.001	61	**-0.295**	0.021
8-oxoG	**99**	-0.050	0.621	33	-0.262	0.140	66	-0.097	0.438	60	-0.089	0.500

BMI, Body Mass Index; hsCRP, high sensitivity C-reactive protein; ρ= Spearman's rank correlation coefficient; 8-oxoG, 7,8-dihydro-8-oxoguanine;

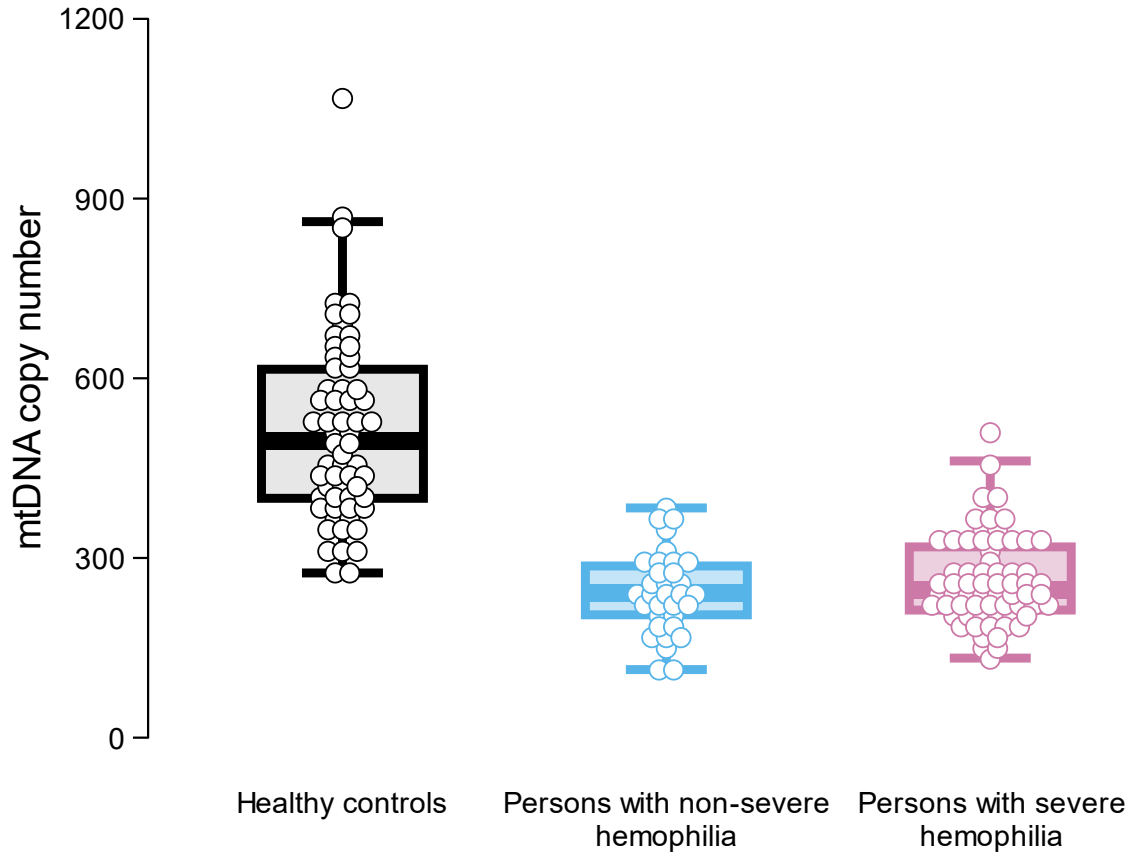
Supplementary Table 3
Spearman's rank correlation coefficients of mtDNA copy number with baseline characteristics of the study population

	Persons with Hemophilia									**Healthy controls**		
	All (n=99)			Non-severe PwH (n=33)			Severe PwH (n=66)			(n=61)		
	mtDNA CN, per diploid cell			mtDNA CN, per diploid cell			mtDNA CN, per diploid cell			mtDNA CN, per diploid cell		
	n	ρ	p-value	n	ρ	p-value	n	ρ	p-value	n	ρ	p-value
Clinical data												
Age; years	99	-0.028	0.785	33	-0.205	0.252	66	0.073	0.561	61	-0.009	0.946
BMI, kg/m²	52	-0.000	0.999	20	-0.181	0.444	34	0.152	0.392	61	0.137	0.293
Laboratory data												
Hemoglobin, g/dL	82	-0.056	0.614	30	0.062	0.743	55	-0.112	0.416	61	0.113	0.385
Leukocytes, $x10^9$/L	85	0.186	0.089	30	0.030	0.877	55	**0.313**	0.020	61	-0.188	0.147
Neutrophils, $x10^9$/L	85	0.082	0.703	10	0.049	0.894	14	0.130	0.658	61	-0.172	0.186
Platelets, $x10^9$/L	85	**0.244**	0.025	30	0.168	0.375	55	**0.303**	0.024	61	0.058	0.658
hsCRP, mg/dL	71	**0.110**	0.328	30	0.122	0.522	51	0.134	0.347	61	-0.133	0.308
Fibrinogen, mg/dL	82	0.160	0.150	31	0.110	0.555	51	0.187	0.188	61	0.049	0.705
8-oxoG	**99**	-0.168	0.096	33	-0.233	0.192	66	-0.166	0.182	60	-0.088	0.506

mtDNA CN, mtDNA copy number; BMI, Body Mass Index; hsCRP, high sensitivity C-reactive protein; ρ= Spearman's rank correlation coefficient; 8-oxoG, 7,8-dihydro-8-oxoguanine;



Supplementary Figure 1 Distribution of telomere length in healthy controls, non-severe, and severe hemophilia. Healthy controls (10.07 [7.93-12.66] kb) had significantly ($p<0.001$) longer telomeres than persons with hemophilia (non-severe 5.12 [IQR 3.97-6.58] kb, and severe hemophilia 6.29 [IQR 5.36-8.05] kb).



Supplementary Figure 2 Distribution of mtDNA copy number in healthy controls, non-severe, and severe hemophilia. Healthy controls (494.52 [399.50-615.06]) had significantly ($p<0.001$) higher mtDNA copy numbers than persons with hemophilia (non-severe 241.30 [205.09-286.65], and severe hemophilia 246.86 [213.05-318.51]).