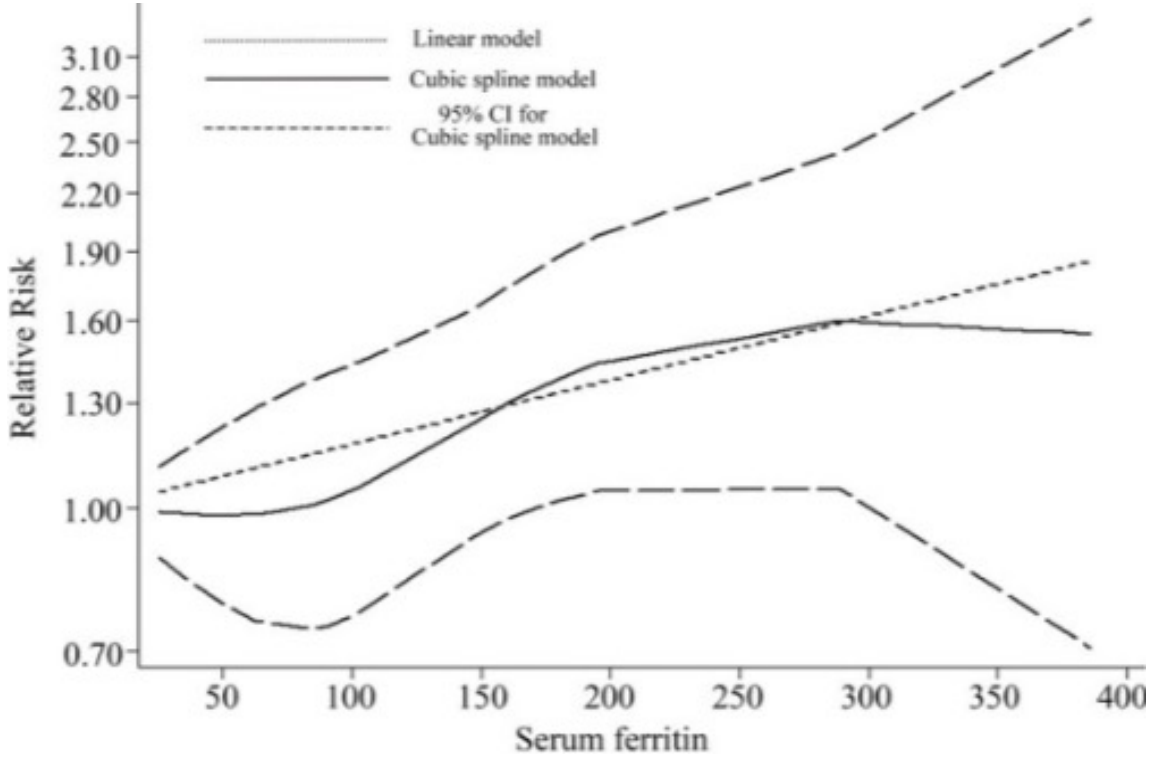
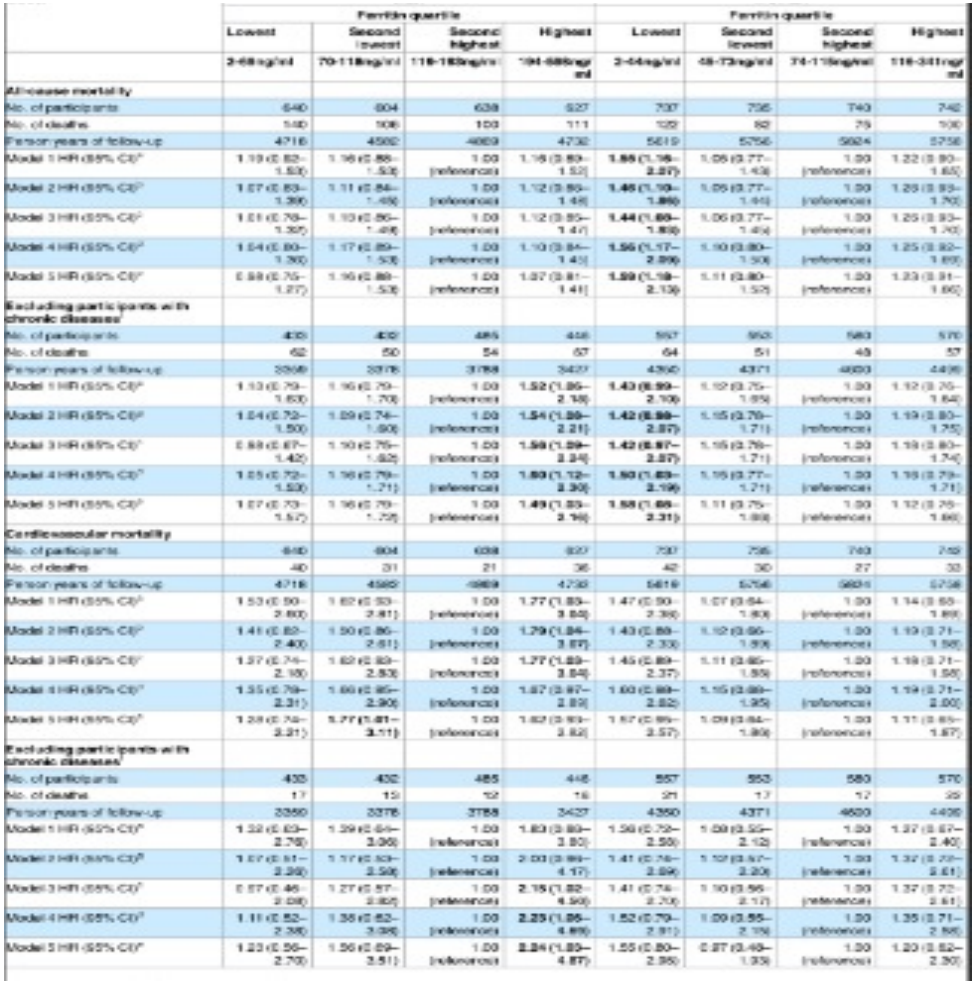
Iron Status Biomarkers and Current Normal Ranges

- Serum Iron (shortest term measurement, past several hours)
  - Women 60-170 ug/dL
  - Men 80-200 ug/dL
- Hematocrit (reflects the average life of a red blood cell)
  - Women 36-48%
  - Men 39-54%
- Hemoglobin (iron status over life of red blood cell)
  - Women 12-16 g/dL
  - Men 13-18 g/dL
- Serum Ferritin (circulatory stores of 4-6 months)
  - Women 15-300 ng/mL
  - Men 30-330 ng/mL

Dose–response for relationship between serum ferritin and risk of stroke by linear and a cubic spline model



Zheng W, Wang Y, Xia Z, Liu D. Serum ferritin and risk of stroke: a meta-analysis of observation studies. Front Neurol. 2025 Jul 1;16:1539407. doi: 10.3389/fneur.2025.1539407. PMID: 40667468; PMCID: PMC12259440.



	Ferritin quartile				Ferritin quartile			
	Lowest	Second lowest	Second highest	Highest	Lowest	Second lowest	Second highest	Highest
	3-69ng/ml	70-118ng/ml	119-193ng/ml	194-689ng/ml	3-44ng/ml	45-73ng/ml	74-119ng/ml	120-331ng/ml
All-cause mortality								
No. of participants	640	604	638	627	737	735	740	740
No. of deaths	140	108	103	111	122	82	79	100
Person-years of follow-up	4716	4582	4669	4732	5419	5756	5624	5758
Model 1 HR (95% CI)*	1.19 (0.82–1.53)	1.16 (0.85–1.53)	1.00 (reference)	1.15 (0.83–1.53)	**1.85 (1.16–2.27)**	1.05 (0.77–1.43)	1.00 (reference)	1.22 (0.90–1.65)
Model 2 HR (95% CI)*	1.27 (0.83–1.39)	1.11 (0.84–1.45)	1.00 (reference)	1.12 (0.83–1.46)	**1.46 (1.10–1.86)**	1.05 (0.77–1.41)	1.00 (reference)	1.23 (0.93–1.70)
Model 3 HR (95% CI)*	1.01 (0.76–1.39)	1.10 (0.86–1.48)	1.00 (reference)	1.12 (0.85–1.47)	**1.44 (1.09–1.83)**	1.05 (0.77–1.40)	1.00 (reference)	1.25 (0.93–1.70)
Model 4 HR (95% CI)*	1.04 (0.80–1.39)	1.17 (0.89–1.53)	1.00 (reference)	1.10 (0.84–1.45)	**1.56 (1.17–2.09)**	1.10 (0.80–1.50)	1.00 (reference)	1.25 (0.92–1.69)
Model 5 HR (95% CI)*	0.98 (0.75–1.27)	1.16 (0.88–1.53)	1.00 (reference)	1.07 (0.81–1.41)	**1.59 (1.19–2.13)**	1.11 (0.80–1.52)	1.00 (reference)	1.23 (0.91–1.66)
Excluding participants with chronic diseases†								
No. of participants	435	432	485	446	557	553	580	570
No. of deaths	62	50	54	57	64	51	49	57
Person-years of follow-up	3569	3378	3788	3427	4360	4371	4600	4408
Model 1 HR (95% CI)*	1.13 (0.79–1.63)	1.16 (0.79–1.70)	1.00 (reference)	**1.52 (1.06–2.18)**	**1.43 (0.99–2.10)**	1.12 (0.75–1.65)	1.00 (reference)	1.12 (0.75–1.64)
Model 2 HR (95% CI)*	1.04 (0.72–1.50)	1.09 (0.74–1.60)	1.00 (reference)	**1.54 (1.09–2.21)**	**1.42 (0.99–2.07)**	1.15 (0.78–1.71)	1.00 (reference)	1.19 (0.80–1.75)
Model 3 HR (95% CI)*	0.98 (0.67–1.42)	1.10 (0.75–1.62)	1.00 (reference)	**1.59 (1.09–2.34)**	**1.42 (0.97–2.07)**	1.15 (0.78–1.71)	1.00 (reference)	1.19 (0.80–1.74)
Model 4 HR (95% CI)*	1.05 (0.72–1.53)	1.16 (0.79–1.71)	1.00 (reference)	**1.60 (1.12–2.30)**	**1.50 (1.03–2.19)**	1.15 (0.77–1.71)	1.00 (reference)	1.19 (0.79–1.71)
Model 5 HR (95% CI)*	1.07 (0.73–1.57)	1.16 (0.79–1.75)	1.00 (reference)	**1.49 (1.03–2.16)**	**1.58 (1.06–2.31)**	1.11 (0.75–1.69)	1.00 (reference)	1.12 (0.75–1.66)
Cardiovascular mortality								
No. of participants	640	604	638	627	737	735	740	740
No. of deaths	40	31	21	36	42	30	27	33
Person-years of follow-up	4716	4582	4669	4732	5419	5756	5624	5758
Model 1 HR (95% CI)*	1.53 (0.90–2.60)	1.62 (0.93–2.81)	1.00 (reference)	**1.77 (1.03–3.03)**	1.47 (0.90–2.39)	1.07 (0.64–1.80)	1.00 (reference)	1.14 (0.69–1.89)
Model 2 HR (95% CI)*	1.41 (0.82–2.40)	1.50 (0.86–2.61)	1.00 (reference)	**1.79 (1.04–3.07)**	1.43 (0.89–2.30)	1.12 (0.69–1.83)	1.00 (reference)	1.13 (0.71–1.80)
Model 3 HR (95% CI)*	1.37 (0.74–2.16)	1.62 (0.89–2.93)	1.00 (reference)	**1.77 (1.03–3.04)**	1.45 (0.89–2.37)	1.11 (0.68–1.83)	1.00 (reference)	1.13 (0.71–1.80)
Model 4 HR (95% CI)*	1.55 (0.79–2.31)	1.66 (0.85–2.90)	1.00 (reference)	**1.67 (0.97–2.89)**	1.60 (0.98–2.62)	1.15 (0.69–1.95)	1.00 (reference)	1.19 (0.71–1.99)
Model 5 HR (95% CI)*	1.28 (0.76–2.21)	**1.77 (1.01–3.11)**	1.00 (reference)	1.62 (0.93–2.82)	1.57 (0.95–2.57)	1.09 (0.64–1.86)	1.00 (reference)	1.11 (0.65–1.87)
Excluding participants with chronic diseases†								
No. of participants	435	432	485	446	557	553	580	570
No. of deaths	17	15	10	16	21	17	12	22
Person-years of follow-up	3569	3378	3788	3427	4360	4371	4600	4408
Model 1 HR (95% CI)*	1.32 (0.63–2.76)	1.29 (0.64–3.06)	1.00 (reference)	1.83 (0.93–3.60)	1.56 (0.72–3.55)	1.09 (0.55–2.12)	1.00 (reference)	1.37 (0.67–2.40)
Model 2 HR (95% CI)*	1.07 (0.51–2.26)	1.17 (0.59–2.30)	1.00 (reference)	2.03 (0.99–4.17)	1.41 (0.74–2.69)	1.10 (0.57–2.20)	1.00 (reference)	1.32 (0.70–2.51)
Model 3 HR (95% CI)*	0.87 (0.46–2.08)	1.27 (0.67–2.82)	1.00 (reference)	**2.15 (1.02–4.50)**	1.41 (0.74–2.70)	1.10 (0.56–2.17)	1.00 (reference)	1.37 (0.72–2.61)
Model 4 HR (95% CI)*	1.11 (0.52–2.38)	1.38 (0.62–3.08)	1.00 (reference)	**2.25 (1.06–4.80)**	1.52 (0.79–2.91)	1.09 (0.55–2.15)	1.00 (reference)	1.35 (0.71–2.56)
Model 5 HR (95% CI)*	1.23 (0.56–2.70)	1.56 (0.69–3.51)	1.00 (reference)	**2.24 (1.03–4.87)**	1.55 (0.80–2.95)	0.97 (0.49–1.93)	1.00 (reference)	1.20 (0.62–2.30)

Kadoglou, Nikolaos P E et al. “The association of ferritin with cardiovascular and all-cause mortality in community-dwellers: The English longitudinal study of ageing.” *PloS one* vol. 12,6 e0178994. 7 Jun. 2017, doi:10.1371/journal.pone.0178994

S1 Table: The associations between ferritin and mortality after excluding participants who died within the first 24 months since the baseline interview, and participants with anaemia or increased of hsCRP levels

		Men				Women			
		Ferritin quartile				Ferritin quartile			
Model	**Lowest**	**Second lowest**	**Second highest**	**Highest**		**Lowest**	**Second lowest**	**Second highest**	**Highest**
	2-69ng/ml	**70-118ng/ml**	**119-193ng/ml**	**194-598ng/ml**		**2-44ng/ml**	**45-73ng/ml**	**74-115ng/ml**	**116-341ng/ml**
All-cause mortality									
Excluding deaths that occurred within the first 24months since the baseline interview									
No of participants	611	592	620	602		719	725	729	728
No of deaths	111	94	82	86		104	72	64	86
Person years of follow-up	4688	4568	4845	4717		5599	5744	5809	5746
Fully adjusted HR (95% CI)[a]	0.93 (0.69-1.26)	1.23 (0.91-1.66)	1.00 (reference)	0.98 (0.72-1.34)		**1.65 (1.20-2.26)**	1.15 (0.81-1.61)	1.00 (reference)	1.24 (0.90-1.73)
Excluding participants with anaemia[b]									
No of participants[a]	564	590	617	602		640	713	712	716
No of deaths	107	99	84	95		94	77	67	91
Person years of follow-up[c]	4229	4503	4773	4589		4938	5599	5624	5590
Fully adjusted HR (95% CI)[d]	1.14 (0.85-1.53)	1.26 (0.94-1.70)	1.00 (reference)	1.21 (0.90-1.63)		**1.58 (1.15-2.18)**	1.07 (0.77-1.50)	1.00 (reference)	1.24 (0.90-1.71)
Excluding participants with high C-reactive protein levels[e]									
No of participants	424	429	412	402		487	481	455	397
No of deaths	67	60	52	53		73	47	39	39
Person years of follow-up	3253	3323	3221	3118		3748	3797	3593	3128
Fully adjusted HR (95% CI)[a]	0.80 (0.55-1.18)	1.04 (0.71-1.52)	1.00 (reference)	0.84 (0.57-1.25)		1.40 (0.94-2.08)	0.95 (0.61-1.47)	1.00 (reference)	0.87 (0.55-1.37)
Cardiovascular mortality									
Excluding deaths that occurred within the first 24months since the baseline interview									
No of participants	611	592	620	602		719	725	729	728
No of deaths	28	27	17	30		34	26	22	28
Person years of follow-up	4688	4568	4845	4717		5599	5744	5809	5746
Fully adjusted HR (95% CI)[a]	1.04 (0.55-1.97)	**1.94 (1.05-3.60)**	1.00 (reference)	1.56 (0.84-2.91)		1.64 (0.95-2.85)	1.23 (0.69-2.21)	1.00 (reference)	1.19 (0.67-2.12)
Excluding participants with anaemia[b]									
No of participants[a]	564	590	617	602		640	713	712	716
No of deaths	27	27	15	31		33	27	23	32
Person years of follow-up[c]	4229	4503	4773	4589		4938	5599	5624	5590
Fully adjusted HR (95% CI)[d]	1.63 (0.85-3.12)	**2.12 (1.11-4.07)**	1.00 (reference)	**2.26 (1.19-4.29)**		1.55 (0.90-2.66)	1.00 (0.57-1.77)	1.00 (reference)	1.18 (0.68-2.05)
Excluding participants with high C-reactive protein levels[e]									
No of participants	424	429	412	402		487	481	455	397
No of deaths	10	15	10	15		73	47	39	39
Person years of follow-up	3253	3323	3221	3118		3748	3797	3593	3128
Fully adjusted HR (95% CI)[a]	0.47 (0.17-1.24)	1.63 (0.70-3.79)	1.00 (reference)	1.20 (0.51-2.82)		1.59 (0.78-3.22)	1.18 (0.54-2.59)	1.00 (reference)	0.72 (0.31-1.67)

Genetically predicted iron status and life expectancy

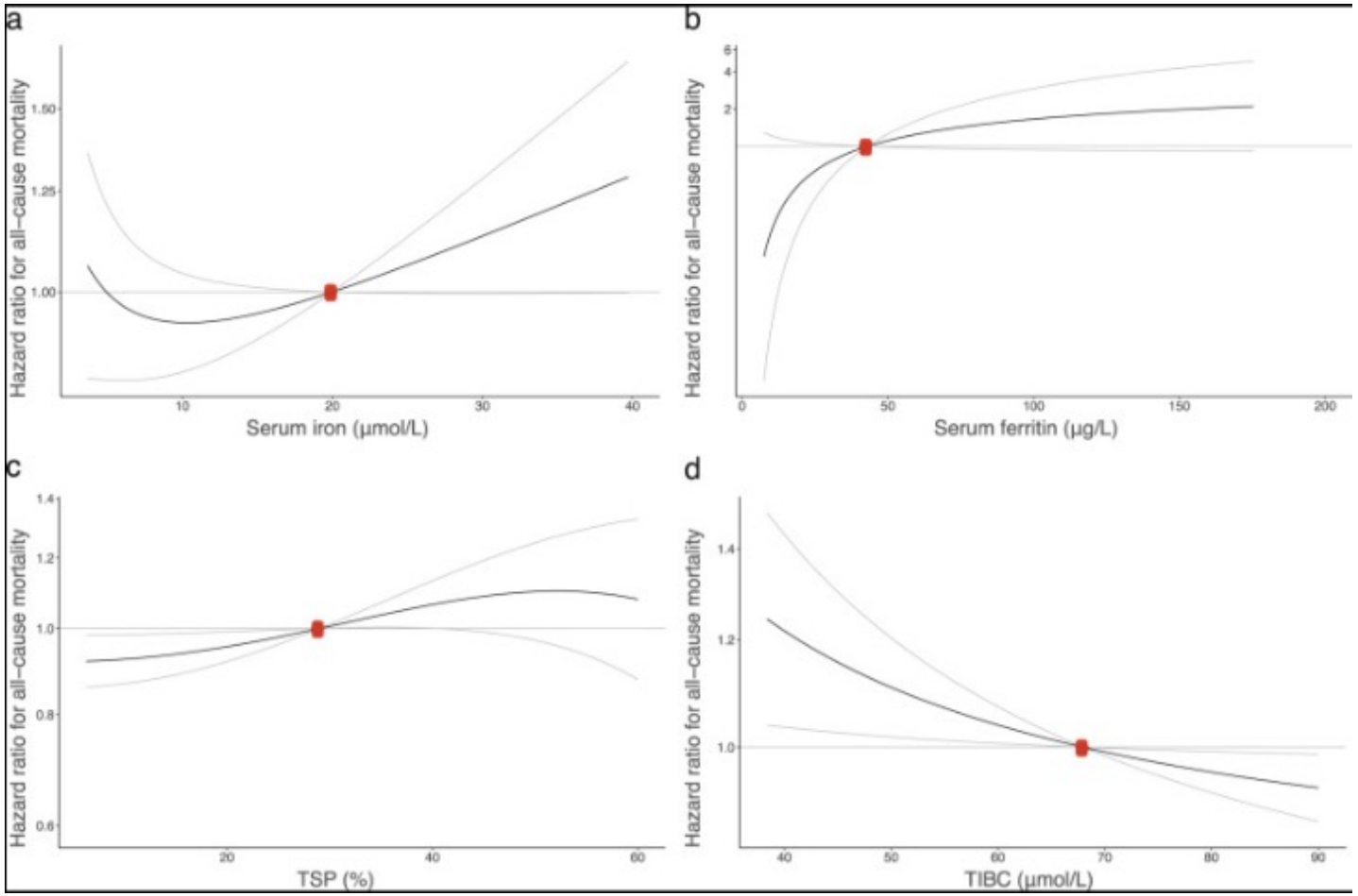
Background & aims: Systemic iron status affects multiple health outcomes, however its net effect on life expectancy is not known. We conducted a two-sample Mendelian randomization (MR) study to investigate the association of genetically proxied iron status with life expectancy.

Methods: Using genetic data from 48,972 individuals, we identified three genetic variants as instrumental variables for systemic iron status. We obtained genetic associations of these variants with parental lifespan (n = 1,012,240) and individual survival to the 90th vs. 60th percentile age (11,262 cases and 25,483 controls). We used the inverse-variance weighted method to estimate the effect of a 1-standard deviation (SD) increase in genetically predicted serum iron on each of the life expectancy outcomes.

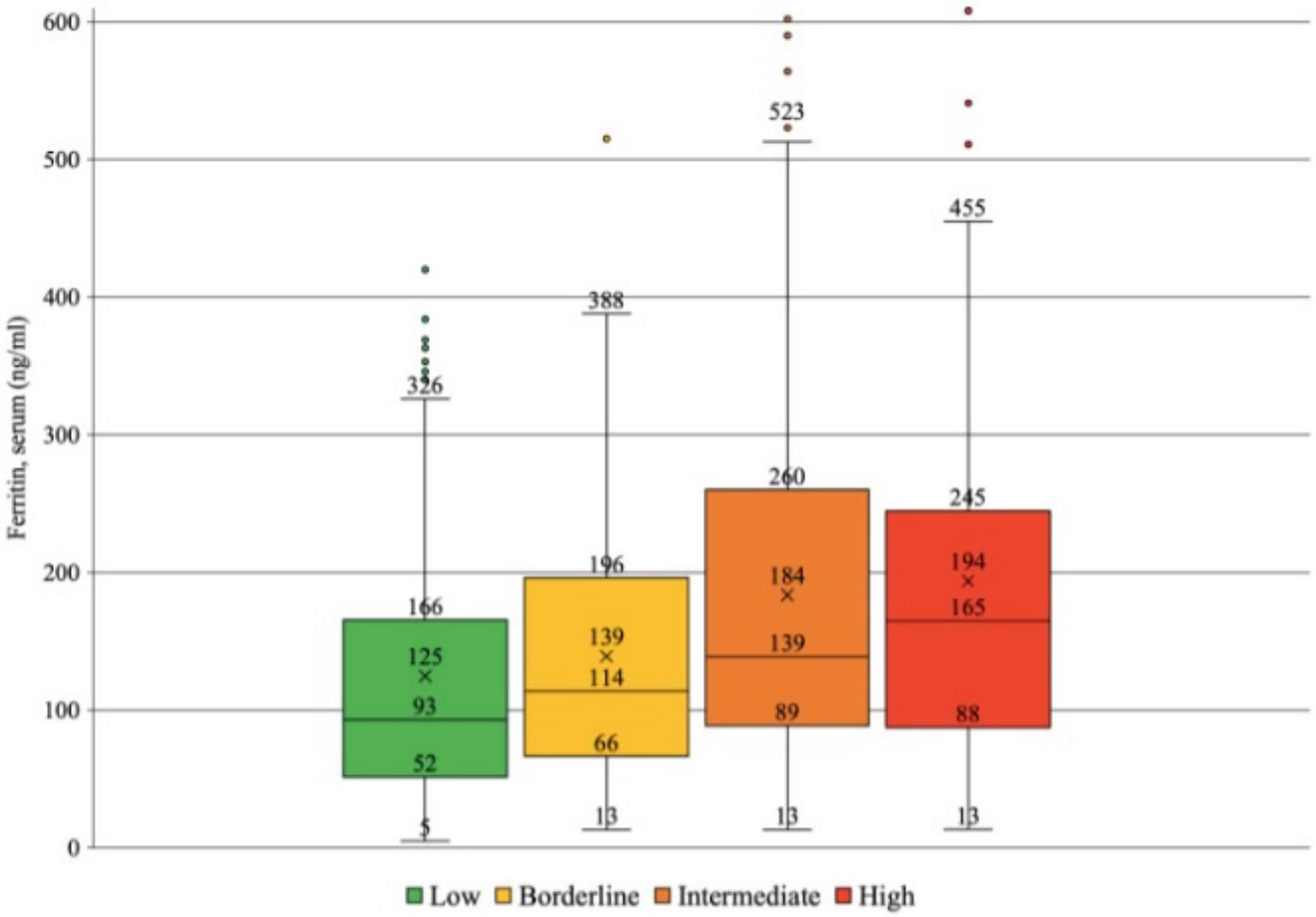
Results: We found a detrimental effect of genetically proxied higher iron status on life expectancy. A 1-SD increase in genetically predicted serum iron corresponded to 0.70 (95% confidence interval [CI] -1.17, -0.24; $P = 3.00 \times 10^{-3}$) fewer years of parental lifespan and had odds ratio 0.81 (95% CI 0.70, 0.93; $P = 4.44 \times 10^{-3}$) for survival to the 90th vs. 60th percentile age. We did not find evidence to suggest that these results were biased by pleiotropic effects of the genetic variants.

Conclusions: Higher systemic iron status may reduce life expectancy. The clinical implications of this finding warrant further investigation, particularly in the context of iron supplementation in individuals with normal iron status.

Daghlas, Iyas, and Dipender Gill. “Genetically predicted iron status and life expectancy.” *Clinical nutrition (Edinburgh, Scotland)* vol. 40,4 (2021): 2456-2459. doi:10.1016/j.clnu.2020.06.025

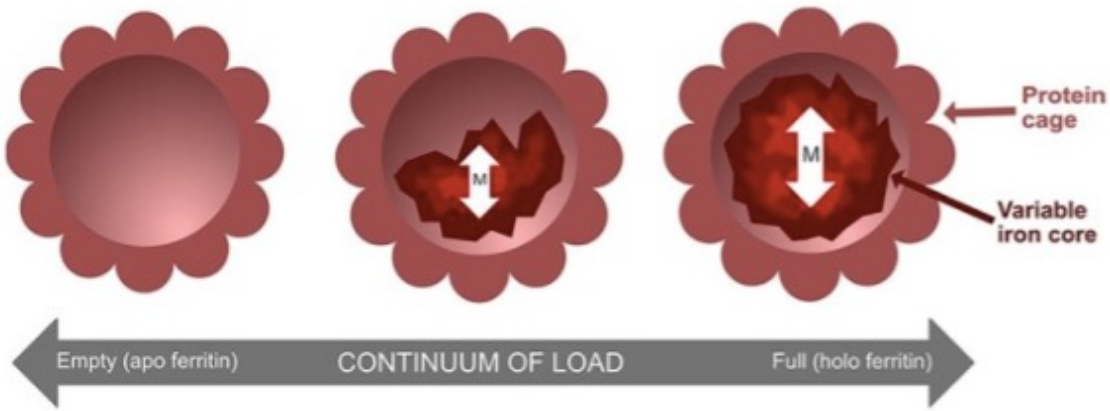


Moksnes, Marta R et al. “Genome-wide meta-analysis of iron status biomarkers and the effect of iron on all-cause mortality in HUNT.” *Communications biology*vol. 5,1 591. 16 Jun. 2022, doi:10.1038/s42003-022-03529-z



Skrzypczak T, Skrzypczak A, Michałowicz J. The Relationship Between Iron Status and Atherosclerotic Cardiovascular Disease Risk in Non-anemic Patients Without a History of Cardiovascular Diseases: A Cross-Sectional Study. Cureus. 2022 Sep 22;14(9):e29439.

Ferritin: Dual iron status measure and inflammatory biomarker



Ferritin, a ~475-481 kilodalton spherical protein, can sequester varying amounts, up to 4500 ferric iron atoms, within a 80nm mineral core.

With permission; Erin S., Clucas, Danielle B., McColl, Gawain, Hall, Liam T. and Simpson, David A.. "Re-examining ferritin-bound iron: current and developing clinical tools" *Clinical Chemistry and Laboratory Medicine (CCLM)*, vol. 59, no. 3, 2021, pp. 459-471. https://doi.org/10.1515/cclm-2020-1095

Optimal Iron Levels Associated with Reduced Risk

- Serum Iron
  - Women 70-120 ug/mL
  - Men 80-130 ug/mL
- Hematocrit
  - Women 36-44%
  - Men 40-45%
- Hemoglobin
  - Women 13-15 g/dL
  - Men 14-16 g/dL
- Serum Ferritin
  - Women 45-100 ng/mL
  - Men 60-120 ng/mL