Supplementary Material

a) Materials and methods

Swiss conscription and study population

As described elsewhere [1] all young Swiss men are called up for mandatory conscription at the age of about 19 years of age. Swiss conscription data therefore cover approximately 95 % of a given male birth cohort [2]. Medical assessment during conscription occurs at six centers (mentioned in Supplementary Table 2) and includes the measurement of height, weight, current occupation and the postal code of the officially registered place of residence. The examination offers a voluntary laboratory blood test, to which approximately 65% of the young men voluntarily consent [3]. The blood samples are taken by medical personnel at the conscription centers and shipped to a single certified laboratory center (Viollier AG). Tests are carried out with state-of-the-art equipment and assays, usually within 12 hours. Until 2013, the laboratory test included a small blood chemistry profile, including Hb, ferritin, and CRP levels. Hb was measured on a Siemens Advia 120, CRP on an Advia 1650, and ferritin on an Advia Centaur (all three devices from Siemens Healthcare Diagnostics AG, Switzerland)[1].

Data and study population

Fully anonymized individual conscription records for the period from January 2010 to December 2012 were provided by the Swiss Armed Forces (*Logistikbasis der Armee - Sanität*) under contractual agreement with the study authors [4,5]. The data included categorized age (one-year intervals), height (cm), weight (kg), current occupation (recorded as free-text entry), name and postal (ZIP) code of place of residence, Hb (g/l), ferritin (ng/ml), and CRP (mg/l). The data set was checked for implausible values, but apart from one young man with a recorded weight of 500 kg, none of the individuals were above 200 kg and no unrealistic body mass index (BMI) and laboratory values were found. BMI was categorized according to the official WHO subgroups [6].

We converted the free-text entry of the current occupation to the International Standard Classification of Occupations (ISCO-08) code as specified elsewhere [7]. The ISCO major groups were then aggregated into three major, hierarchical categories of professional status [8]: ‘Low’ (ISCO major groups 7 to 9), ‘Medium’ (3 to 6) and ‘High’ (1 and 2). Students and ‘pupils’ (still in school pursuing higher education at age 18-22) were assigned to the ‘High’ professional status.

We standardized postal (ZIP) codes of places of residence to the state on March 31, 2013. To approximate the residential altitude of the subjects as closely as possible (individual addresses were not available due to data protection), we used high-quality geodata from the Federal Office of Topography (www.swisstopo.ch). We calculated mean altitude (in meters above sea level (masl)) of all 1-m resolution centroids containing all residential buildings of the registry based census Swiss National Cohort (SNC, www.swissnationalcohort.ch) with males aged [18-25) as of December 31, 2012 per postal code. Furthermore, residential altitude was categorized in steps of 300 masl as it has been done in previous studies assessing associations between health and altitude in Switzerland [9]. For mapping, each conscript was also assigned to one of the 705 MedStat-regions (version

2011), which represents the official geographical regions allowing an anonymous indication of a place of residence for each person hospitalized in Switzerland) [2] on the basis of postal (ZIP) code.

Statistical analyses

We calculated descriptive statistics of Hb and other co-variables and displayed mean Hb and mean residential altitude per MedStat-region on a map. We assessed the association between altitude, Hb, and ferritin concentrations with linear regressions. These linear regressions were also performed for conscripts with normal BMI (18.5-24.9 kg/m2), CRP (<5.0 mg/l), ferritin (15-200 ng/ml) and Hb (<175.0 g/l) only. To assess the association between altitude and CRP (which was not symmetrically distributed) we performed a logistic regression to calculate odds ratios (OR) for elevated CRP (>=5.0 mg/l). In all regressions, a residential altitude of 300-599 masl was set as reference category. To test if our results were influenced by age, occupational background or recruitment center we stratified our regressions accordingly. To analyze if ferritin increased with altitude independently of Hb we also calculated a matrix of mean ferritin per quintiles of Hb and per altitude category. Stata version 14 (Stata Corporation, College Station, TX, USA) was used for all analyses and graphs.

Data availability and ethics statement

The Swiss Armed Forces provided fully anonymized records. Because the anthropometric and laboratory data are defined as nonclinical, governmental data we were authorized to use it for academic research. Therefore, no additional ethical approval was needed. Moreover, all conscripts signed a detailed informed consent form allowing the voluntary laboratory.

b) Participant cohort

This study uses the data of male conscripts appearing for their first, regular assessment at a recruitment centre. It excludes data from men older than 22 years of age, who were appearing for conscription with a large delay (<2% of the original cohort). The final sample consisted of N=110,810 male conscripts and from those N=71,798 consented to the laboratory blood test. The comparison between participants and non-participants is reported in Supplementary Table 2. The blood-test participation rate was steady, lying at between 63.8% and 66.6% for each of the conscription years between 2010 and 2012. The blood analysis participation rate was similar throughout the altitude categories (Supplementary Table 1). Overall (Supplementary Table 2), voluntary blood test participants and non-participants were similar in terms of mean age (19.61 versus 19.70 years) and mean BMI (23.43 versus 23.44 kg/m^2). Correspondingly, distributions of age, ISCO-groups, and BMI categories were similar among participants and non-participants. Non-participants were more likely to be residents in the areas surrounding the three recruitment centers Lausanne, Rüti and Monte Ceneri.

Importantly, 94.0% of the young men showed no signs of inflammation as determined by a CRP <5.0 mg/l. Table 1 reports descriptive statistics of Hb concentrations per altitude. Blood test participants resided at an average altitude of 543.5 masl (min=205 masl, max=1,989 masl), with 91.1% of the conscripts living between

300-900 masl. The higher the residential altitude, the lower the number of participants: only 1,269 conscripts (1.8%) lived above 1200 masl. Overall, average Hb was 156.28 g/l (95%CI 156.22-156.34, SD=8.66 g/l; min=67 g/l, max=217 g/l). The prevalence of low Hb (<140 g/l) was 2.6%, while the prevalence of high Hb (>=175 g/l) was 1.8%.

c) Strengths and limitations

This is the first study analyzing Hb and ferritin concentrations at low to moderate altitude in a large and very homogenous cohort of young men with a high coverage of the population. The strength of this study is also its limitation. The study population is restricted to young men with Swiss citizenship. The residential history of the young men during the past years prior to conscription is not known, and we are not aware as whether longer travels to higher or lower altitude occured in the months before conscription. For students in particular, the officially listed place of residence (which we had in the data) might not always reflect the effective place of residence during the week (more likely a larger city). However, stratification by occupational groups did not change the general results and we therefore conclude that such inaccuracies do not affect the observed pattern. Unfortunately, the dataset did not contain any variables that would allow controlling for potential confounding factors that may be important, such as smoking behavior, overall fitness level, diet, or medications. Future studies should look at these factors more closely. The described increase in Hb is in the range of the measurement error of most hemoglobinometers. Thus, our conclusion is only possible based on the very large sample size. However, the increasing detection accuracy of these devices in the next future will allow such fine effects to be clinically detectable in the future.

d) Supplementary tables and figures

Supplementary Table 1: Descriptive statistics of Hb (g/l) per altitude. (masl=meters above sea level; Part.-Rate=percentage of conscripts volunteering to blood test; N=absolute frequency; SD=standard deviation; CI=confidence interval; %<140=percentage of conscripts with Hb <140 g/l, Anemia (%<130)=percentage of conscripts with anemia as defined by Hb<130 g/l, EE (%>=210)=percentage of conscripts with excessive erythrocytosis as defined by Hb>=210 g/l).

Altitude (masl)	Part.-Rate (%)	N	Mean	SD	95%CI (+/-)	Median	%<140	%140-174	%>=175	Anemia (%<130)	EE (%>=210)
>=1800	70.14	101	159.61	8.76	1.71	159	0.99	94.06	4.95	0.00	0.00
1500-1799	66.73	369	159.05	8.25	0.84	159	0.81	96.21	2.98	0.00	0.00
1200-1499	68.17	799	157.94	8.48	0.59	158	1.88	96.37	1.75	0.13	0.00
900-1199	67.01	2720	157.98	8.66	0.33	158	1.36	95.63	3.01	0.15	0.00
600-899	68.49	13821	156.65	8.52	0.14	157	2.13	95.99	1.88	0.17	0.00
300-599	64.46	51567	156.09	8.67	0.07	156	2.74	95.61	1.66	0.27	0.00
<300	51.51	2421	155.2	8.77	0.35	155	3.1	95.46	1.45	0.50	0.00
Total	64.79	71798	156.28	8.66	0.06	156	2.56	95.69	1.76	0.25	0.00

Supplementary Table 2: Descriptive statistics of blood sample volunteers vs. non-participating conscripts. (Part.-Rate=participation rate; Freq.=absolute frequency; y=years; SD=standard deviation)

			Participants		Non-Participants	
		Part.-Rate (%)	Freq.	Percent	Freq.	Percent
Year	2010	66.6	24551	34.2	12295	31.5
	2011	63.8	23847	33.2	13553	34.7
	2012	64.0	23400	32.6	13164	33.7
	Total	64.8	71798	100.0	39012	100.0
Age (y)	[18-19)	67.3	17714	24.7	8618	22.1
	[19-20)	65.6	33358	46.5	17460	44.8
	[20-21)	62.4	15449	21.5	9301	23.8
	[21-22)	59.2	5277	7.3	3633	9.3
	Total	64.8	71798	100.0	39012	100.0
	Mean (SD)		19.61 (0.84)		19.70 (0.87)	
ISCO Groups	Low	67.1	27138	37.8	13312	34.1
	Medium	65.9	16346	22.8	8464	21.7
	High	62.7	22092	30.8	13118	33.6
	Imprecise	60.2	6222	8.7	4118	10.6
	Total	64.8	71798	100.0	39012	100.0
Recruitment Center	Lausanne	59.5	13914	19.4	9454	24.2
	Sumiswald	70.7	11705	16.3	4849	12.4
	Windisch	68.8	16673	23.2	7573	19.4
	Rüti	60.1	16295	22.7	10799	27.7
	Mels	72.3	10916	15.2	4180	10.7
	Mt. Ceneri	51.5	2295	3.2	2157	5.5
	Total	64.8	71798	100.0	39012	100.0
BMI (kg/m2)	<18.5	55.2	2253	3.1	1830	4.7
	18.5-24.9	65.4	51345	71.5	27190	69.7
	25.0-29.9	66.2	14340	20.0	7323	18.8
	>=30.0	59.1	3860	5.4	2669	6.8
	Total	64.8	71798	100.0	39012	100.0
	Mean (SD)		23.43 (3.60)		23.44 (4.10)	
CRP (mg/l)	<1		55458	77.2		
	[1-5)		12052	16.8		
	[5-10)		2344	3.3		
	>=10		1944	2.7		
	Total		71798	100.0		
	Mean (SD)		1.33 (4.29)			

Supplementary Table 3: Detailed results of the linear regressions A and B for Hb (g/l) as well as D and E (ng/ml) presented as coefficient plots in Figure 2. B) Hb for conscripts with normal ferritin (15-200 ng/ml), CRP (<5.0 mg/l) and BMI (18.5 – 24.9 kg/m^2) only. E) ferritin for conscripts with normal Hb (<175 g/l), CRP (<5.0 mg/l) and BMI (18.5 – 24.9 kg/m^2) only.

Hemoglobin		**A) All**			**B) Normal ferritin, BMI & CRP only**	
Altitude (masl)	**Coef.**	**SE**	**p**	**Coef.**	**SE**	**p**
>=1800	3.52	0.86	0.000	3.25	1.02	0.002
1500-1799	2.96	0.45	0.000	2.89	0.54	0.000
1200-1499	1.85	0.31	0.000	1.69	0.37	0.000
900-1199	1.89	0.17	0.000	1.95	0.21	0.000
600-899	0.56	0.08	0.000	0.54	0.10	0.000
300-599	Ref.			Ref.		
<300	-0.89	0.18	0.000	-0.93	0.22	0.000
Constant	156.09	0.04	0.000	155.75	0.05	0.000

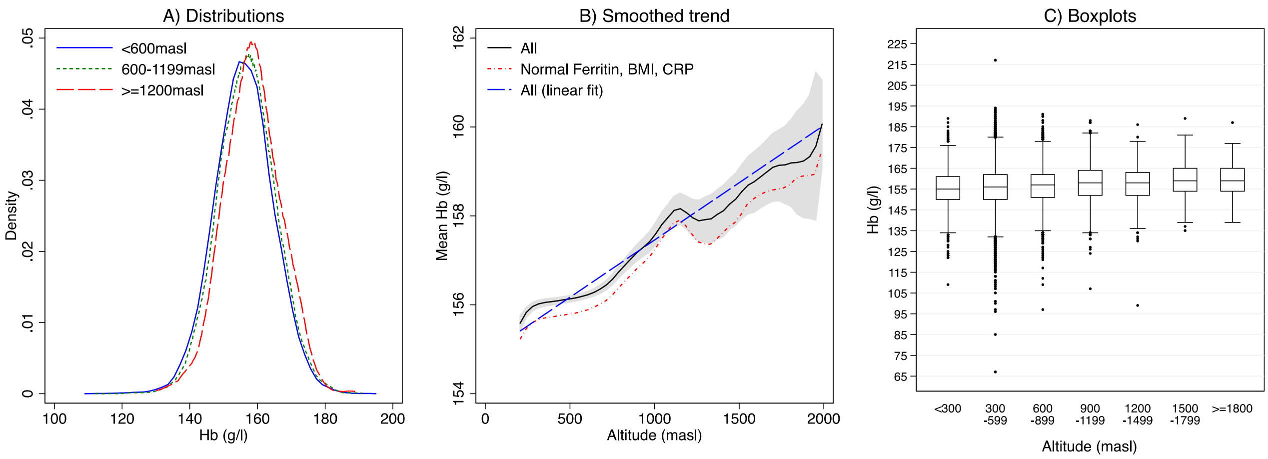
Ferritin		**D) All**			**E) Normal Hb, BMI & CRP only**	
Altitude (masl)	**Coef.**	**SE**	**p**	**Coef.**	**SE**	**p**
>=1800	9.89	5.37	0.065	10.90	5.72	0.057
1500-1799	9.21	2.83	0.001	8.43	2.97	0.005
1200-1499	9.95	1.92	0.000	7.91	2.04	0.000
900-1199	7.57	1.06	0.000	6.71	1.14	0.000
600-899	1.66	0.52	0.001	1.54	0.55	0.005
300-599	Ref.			Ref.		
<300	-4.83	1.12	0.000	-5.42	1.23	0.000
Constant	92.28	0.24	0.000	84.81	0.25	0.000

Supplementary Table 4: Enhanced table of adjustments to hemoglobin (g/l) by 500-m increments of altitude by population group, as outlined in Sharma et al. 2019 [10] (Table 2). WHO after [11], MMWR/CDC after [12], PSC (preschool age children) and WAR (women in reproductive age) after [10], US (US male adults) and SA (Central/South America male adults) after [13], CH based on the data presented in this paper (young Swiss men).

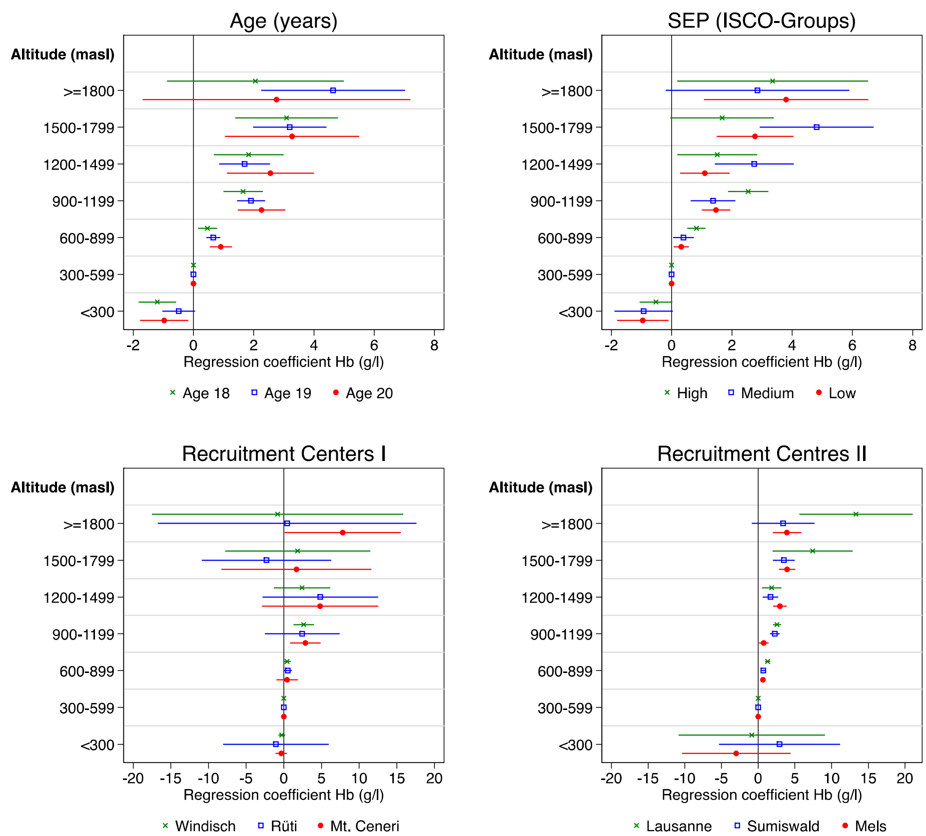
<table>
<tr><th>Altitude (masl)</th><th>WHO</th><th>MMWR</th><th>PSC/WAR</th><th>US</th><th>SA</th></tr>
<tr><td>-50 to -1</td><td>0</td><td>0</td><td>0</td><td></td><td></td></tr>
<tr><td>0</td><td>0</td><td>0</td><td>0</td><td></td><td></td></tr>
<tr><td>1-499</td><td>0</td><td>0</td><td>1</td><td rowspan="2">Ref</td><td rowspan="2">Ref</td></tr>
<tr><td>500-999</td><td>0</td><td>1</td><td>4</td></tr>
<tr><td>1000-1499</td><td>2</td><td>2</td><td>7</td><td rowspan="2">9</td><td rowspan="2">4</td></tr>
<tr><td>1500-1999</td><td>5</td><td>5</td><td>10</td></tr>
<tr><td>2000-2499</td><td>8</td><td>10</td><td>13</td><td rowspan="2">14</td><td rowspan="2">17</td></tr>
<tr><td>2500-2999</td><td>13</td><td>15</td><td>16/17</td></tr>
<tr><td>3000-3499</td><td>19</td><td>22</td><td>20</td><td rowspan="2">17</td><td rowspan="2">30</td></tr>
<tr><td>3500-3999</td><td>27</td><td>29</td><td>24</td></tr>
<tr><td>4000-4499</td><td>35</td><td>38</td><td>28</td><td>28</td><td>46</td></tr>
</table>

Altitude (masl)	CH
1-249	Ref
250-499	1.2
500-749	1.3
750-999	2.2
1000-1249	3.3
1250-1499	3.1
1500-1749	4.3
1750-1999	4.3

Supplementary Figure 1: A) Hb distribution by three levels of residential altitude (kernel density plot, bandwidth=1.0). B) Mean Hb versus residential altitude (continuous data). Black line and 95%CI: Local polynomials (bandwidth 100masl) for all. Red dotted line: Local polynomials (bandwidth 100masl) for conscripts with normal ferritin (15-200 ng/ml), CRP (<5.0 mg/l) and BMI (18.5 – 24.9 kg/m^2) only. Blue dashed line: Linear fit for all. C) Boxplots Hb by categorized altitude.



Supplementary Figure 2: Coefficient plots of linear regressions on Hb, stratified by age groups (top left), occupational (SEP) background (ISCO-groups, top right), and recruitment centers (bottom line, results from the same regression but split into two graphs). The second group of recruitment centers on the right shows those centers (Lausanne, Sumiswald, and Mels) that cover the majority of the Alpine area in Switzerland. The vertical lines indicate the reference levels of the regressions.



e) Supplementary bibliography

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