Supplementary:

Supplementary Section A: Genotyping and quality control

We genotyped DNA from blood samples using 2 customized versions of Illumina HumanCoreExome v12.1 array which we refer to as UM_HUNT_Biobank and UM_HUNT_Biobank_v1-1, with 22367 and 16626 samples genotyped, respectively (before applying quality control and other filters) [For details on the arrays see **Supplementary Section B.**]. Sample and genotype quality controls were performed similar to Fritsche et al[1]. For each array, genotypes were called using Illumina GenomeStudio (module 1.9.4, algorithm GenTrain 2.0). After initial genotype clustering and calling, we excluded individuals with call rate < 99% and then re-clustered and called the genotypes. We excluded samples with: (1) call rate < 99%, (2) estimated contamination>2.5% (BAF Regression (http://genome.sph.umich.edu/wiki/BAFRegress)[2], (3) large chromosomal copy number variants (single chromosome with missing-ness ≥ five times larger than other chromosomes), (4) gonosomal constellations other than XX and XY, or (5) inferred sex not consistent with the reported sex. For sets of technical duplicates and monozygotic twins we retained the sample with the highest call rate. We excluded genetic variants with: (1) a probe that could not be perfectly mapped or mapped perfectly to multiple positions in the human genome assembly (Genome Reference Consortium Human genome build 37 and revised Cambridge Reference Sequence of the human mitochondrial DNA; http://genome.ucsc.edu; BLAST) [3]; (2) Hardy Weinberg equilibrium p-value <0.0001 in reported European ancestry samples; (3) a call rate < 99%; (4) another variant with higher call rate that assayed the same variant (PLINK v1.90) [4]; (5) GenTrain score < 0.15, (6) cluster separation < 0.3 or (7) difference > 20% in allele frequencies between the two versions of the array. After quality control, 462,868 polymorphic variants remained.

Supplementary Section B: Genotype array description

UM_HUNT_Biobank: This is a customized version Illumina HumanCoreExome v12.1 array that in addition to standard genome-wide tagging SNPs (N ~ 240,000) and exonic variants (N ~280,000) contained about 70,000 additional custom content variants, e.g. candidate variants from GWAS experiments, nonsense and missense variants from sequencing studies, ancestry informative markers, and Neanderthal variants.

UM_HUNT_Biobank_v1-1: This is another customized version of HumanCoreExome v12.1 with roughly the same content as per genome-wide tagging SNPs and exonic variants, containing a set of 65,000 additional custom content variants.

Supplementary Section C:

Principal Component (PC) analysis was done on the genotype data to infer population structure[5] and to remove outliers in the samples that identify themselves as Europeans. This analysis was carried out without LD-pruning. After removing the outliers in the PC-space, we had a distribution of the top two PC-scores as shown in **Supplementary Figure 1**. In subsequent analysis of heritability and co-heritability we included the top 10 PC scores as covariates which accounts for the population structure of the sample. The principal component analysis was done with GCTA[6,7] software.

Supplementary Section D

Following Wolfe et al. (2016), we defined the body regions as:

Region	Components
Left upper region	*Jaw left; Shoulder girdle left; Upper arm left; Lower arm left;*
Right upper region	*Jaw right; Shoulder girdle right; Upper arm right; Lower arm right;*
Axial region	*Neck; Upper back; Lower back; Chest; Abdomen;*
Left lower region	*Hip, left; Upper left leg; Lower left leg;*
Right lower region	*Hip, right; Upper right leg; Lower right leg;*

Wolfe et al (2016) have revised the 2011 ACR criteria for detecting fibromyalgia and have proposed the following criteria for the same:

(1) Generalized pain, defined as pain in at least 4 of 5 regions, is present.
(2) Symptoms have been present at a similar level for at least 3 months.

(3) Widespread pain index (WPI) ≥ 7 and Symptom Severity Index (SSI) score ≥ 5 OR WPI of 4–6 and SSI score ≥ 9.

(4) A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses.

We narrowed this set of conditions down to the following according to the availability of information on the patients in our cohort:

(1) pain in at least 4 of 5 regions (as defined by the above the regions), is present.

(2) WPI ≥ 7 and SSI ≥ 5 or WPI 4–6 and SSI ≥ 9

This is referred to in the Methods Section as FM-2016-modified.

Supplementary Section E:

For two individuals *l* and *m* with genotypes g_{il} and g_{im} respectively at the ith variant site, the genetic relatedness between individuals is defined as $K_{lm} = \frac{\sum_{i=1}^{V} (g_{il} - 2p_i)(g_{im} - 2p_i)}{2\,p_i\,(1 - p_i)}$, where p_i is the minor allele frequency of the ith variant and V is the total number of variants under consideration.

This measures the genetic similarity of a pair of individuals in terms of the available V variants. The matrix K for all pairs of l and m is the genetic relatedness matrix (GRM). In this article we have used common variants (minor allele frequency > 5%) to construct the GRM using the GCTA software developed by Yang et al (2011)[6]. We estimated $h^2_{autosomes}$ and h^2_X using separate genetic relatedness matrices constructed for autosomes and chromosome X respectively, where $V_{autosomes}(V_X)$ is the variance explained by the autosomes (chromosome X). The total estimate of heritability that we report is given by:

$$h^2 = \frac{V_{autosomes} + V_X}{V_{Phenotype}} = h^2_{autosomes} + h^2_X$$
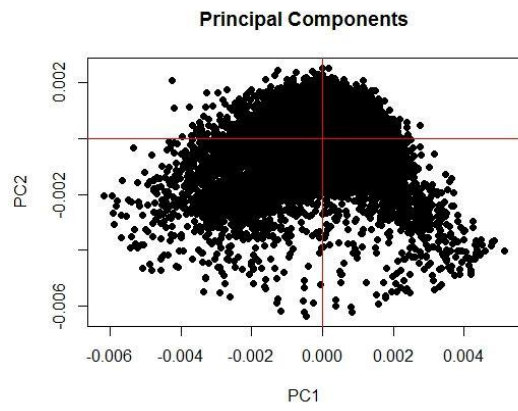

Supplementary Section F:

We used a permutation test to test the difference between estimated heritabilities of males and females. To do this, in a given iteration, we randomly assigned male and female labels to the data. Subsequently, we added a small constant (0.1) to the FM-score, log-transformed it, regressed it on the age and the randomly assigned sex-labels, extracted the residuals, inverse normalized it and estimated the heritability separately for males and females. We carried out this procedure for 100 iterations and estimated the p-value by the proportion of times the absolute value of the observed difference was less than the absolute value of the difference obtained through the 100 permutations. Last column of Supplementary Table 3 shows the permutation p-value for the difference in estimated heritabilities. None of the values are significant indicating that in our sample, there is no evidence for substantial differences in heritabilities for males and females.

References

1.   Fritsche L. G., Gruber S. B., Wu Z., Schmidt E. M., Zawistowiski M., Moser S.E., et al. Association of Polygenic Risk Scores for Multiple Cancers in a Phenome-wide Study: Results from The Michigan Genomics Initiative. American Journal of Human Genetics. 2018. 102(6). 1048-1061

2**.**   Jun G., et al. Detecting and estimating contamination of human DNA samples in sequencing and array-based genotype data. American Journal of Human Genetics 2012. 91(5). 839-48.

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4.   Chang, C.C. et al. Second-generation PLINK: rising to the challenge of larger and richer datasets. Gigascience 2015. 4. 7.

5.   Price AL, Patterson NJ, et al. Principal components analysis corrects for stratification in genome-wide association studies. Nature Genetics 2006; 38(8); 904

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7.   Yang J, Benyamin B, McEvoy BP, Gordon S, Henders AK, Nyholt DR, Madden PA, Heath AC, Martin NG, Montgomery GW, Goddard ME, Visscher PM. Common SNPs explain a large proportion of the heritability for human height. Nature Genetics 2010; 42(7): 565-9.

8.   Manichaikul A, Mychaleckyj JC, et al. Robust relationship inference in genome-wide association studies. Bioinformatics 2010; 26(22); 2867-73

Supplementary Figure 1: Distribution of the top 2 principal component scores for the samples included in the analysis.
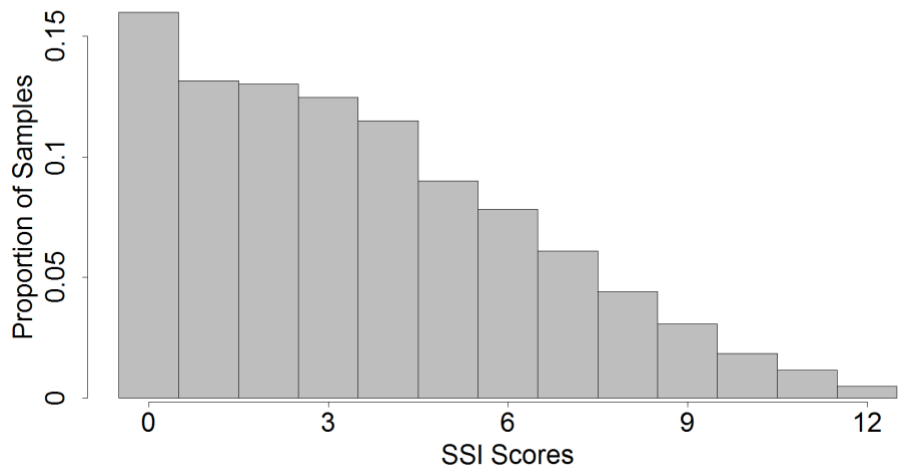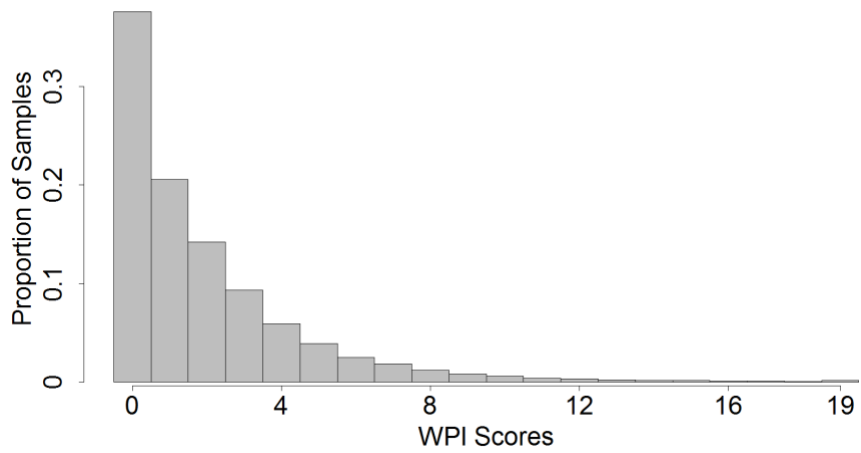
Supplementary Figure 2: Distribution of WPI and SSI scores in the sample included for analysis. The upper panel shows the distribution for WPI scores ranging from 0 to 19. The lower panel shows the corresponding distribution for SSI scores ranging from 0 to 12.

FM-2011
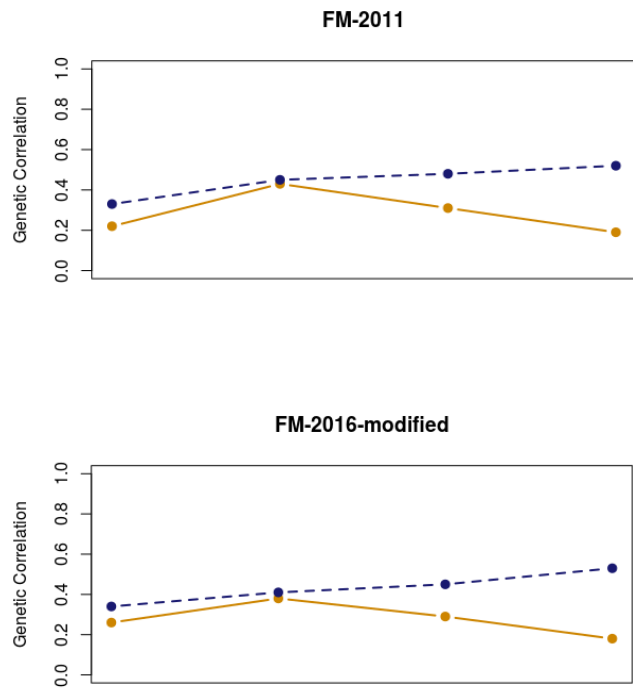
FM-2016-modified

Supplementary Figure 3: Genetic correlations between FM-WPI and FM-SSI across age categories for FM as a case-control phenotype using the (a) FM-2011 and (b) FM-2016-modified definitions. (See Methods).

Age category	β	SE	p-value
40 - 50	0.755	0.086	3.9×10^{-17}
50 - 60	0.548	0.081	2.1×10^{-11}
60 - 70	-0.147	0.082	7.4×10^{-02}
70 - 80	-0.736	0.101	3.5×10^{-13}
80 - 90	-0.724	0.174	3.4×10^{-05}

Supplementary Table 1: Estimated regression coefficients, standard errors and p-values for the regression of FM scores on age categories using the individuals with age ≤ 40 as reference category.

Age Category (years)		N	% Females	Age		FM		Mean female FM score/Mean male FM score
				Mean	SD	Mean	SD	
Age ≤ 50	Female	6,206	60.7	37.2	9.2	6.3	4.9	1.33
	Male	3,995		36.5	9.9	4.7	4.3	
	Total	10,201		36.9	9.5	5.7	4.8	
Age > 50	Female	8,023	48.5	63.3	8.5	6.2	4.9	1.34
	Male	8,525		64.8	8.7	4.6	4.1	
	Total	16,548		64.1	8.6	5.3	4.6	
Total	Female	14,229	53.2	51.8	15.7	6.2	4.9	1.34
	Male	12,520		55.7	16.1	4.6	4.2	
	Total	26,749		53.6	15.9	5.5	4.6	

Supplementary Table 2: Distribution of age and FM scores in younger (≤ 50) and older (> 50) individuals as well as the whole sample by gender.

Age Category (years)		N	Females (%)	WPI Mean	WPI SD	Mean female WPI score/Mean male WPI score	SSI Mean	SSI SD	Mean female SSI score/Mean male SSI score
Age ≤50	Female	6206	60.7	2.0	2.7	1.26	4.3	3.0	1.36
	Male	3995		1.6	2.2		3.2	2.8	
	Total	10201		1.8	2.6		3.8	2.9	
Age > 50	Female	8023	48.6	2.3	2.8	1.36	3.8	2.8	1.33
	Male	8525		1.7	2.3		2.9	2.6	
	Total	16548		2.0	2.6		3.4	2.8	
Total	Female	14229	53.3	2.1	2.8	1.31	4.1	2.9	1.35
	Male	12520		1.6	2.3		3.0	2.6	
	Total	26749		1.9	2.6		3.6	2.9	

Supplementary Table 3: Distribution of age, WPI scores and SSI scores in younger (≤ 50) and older (> 50) individuals as well as the whole sample by gender.

	FM			WPI			SSI		
	Beta	SE	P Value	Beta	SE	P Value	Beta	SE	P Value
Age	-0.039	0.0029	1.22×10^{-41}	0.052	0.0034	2.17×10^{-52}	-0.033	0.0029	9.56×10^{-30}
Age^2	4.01×10^{-4}	2.79×10^{-5}	2.87×10^{-46}	4.59×10^{-4}	3.29×10^{-5}	3.47×10^{-44}	3.71×10^{-4}	2.86×10^{-5}	2.68×10^{-38}
Gender (Female)	0.423	0.0167	2.98×10^{-139}	0.267	0.0197	4.19×10^{-42}	0.466	0.0171	3.02×10^{-161}

Supplementary Table 4: Estimated coefficients of age and gender from the regressions on log-transformed FM, WPI and SSI and corresponding standard errors and p-values.

Age Category (years)	Female				Male				Permutation P-value for difference
	N	Heritability (%)	SE	P-value (Heritability)	N	Heritability (%)	SE	P-value (Heritability)	
≤40	3312	23.1	15.1	0.34	2381	18.0	15.4	0.46	0.56
>40	10319	12.0	8.1	0.39	10737	7.8	7.9	0.53	0.91
≤50	6206	23.8	11.6	0.03	3995	17.9	13.9	0.39	0.43
>50	8023	11.4	10.8	0.51	8525	7.6	10.1	0.71	0.66
≤60	9319	12.1	9.3	0.48	7386	12.8	9.3	0.23	0.82
>60	4312	8.6	13.5	0.67	5750	6.9	12.3	0.77	0.31
All	14229	14.5	4.8	0.004	12520	12.1	5.2	0.008	0.57

Supplementary Table 5: Heritability of inverse normalized FM scores (see Methods) in different age and gender categories with the corresponding p-values.

Age Category (years)	FM cases (N)	FM cases (%)	Heritability		
			Estimate	SE	P-value
δ 40	459	7.6	9.3	10.3	0.43
> 40	1,845	8.4	5.8	4.4	0.38
δ 50	963	8.9	12.4	6.1	0.004
> 50	1,341	7.8	6.5	5.8	0.66
δ 60	1,655	9.4	10.9	5.4	0.009
> 60	649	6.1	5.9	6.2	0.71
All	2,304	8.2	8.6	3.8	0.005

Supplemental Table 6A: Heritability of FM as a case-control phenotype using FM-2011 criteria (cases defined as FM-score ≥ 13) over age categories.

Age Category (years)	FM cases (N)	FM cases (%)	Heritability		
			Estimate (%)	SE	P-value
δ 40	261	4.6	8.1	16.4	0.95
> 40	1,058	5.0	6.0	8.9	0.77
δ 50	551	5.4	11.0	10.8	0.30
> 50	768	4.6	5.9	9.4	0.83
δ 60	947	5.7	8.9	9.1	0.54
> 60	372	3.7	6.1	12.7	0.96
All	1,319	4.9	7.9	7.0	0.41

Supplemental Table 6B: Heritability of FM as a case control phenotype using FM-2016-modified criteria (cases defined by the criteria adapted from Wolfe et al) over age categories.