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Title:

Sex differences in genetic architecture in the UK Biobank

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1 **Males and females present differences in complex traits and in the risk of a wide array of diseases.**
2 **Gene by sex interactions (GxS) are thought to account for some of these differences. However, the**
3 **extent and basis of these interactions are poorly understood. Here we provide insights into both the**
4 **scope and mechanism of GxS across the genome of circa 450,000 individuals of European ancestry**
5 **and 530 complex traits in the UK Biobank. We found small yet widespread differences in genetic**
6 **architecture across traits. We also found that, in some cases, sex-agnostic efforts might be missing**
7 **loci of interest, and looked into possible improvements in the prediction of high-level phenotypes.**
8 **Finally, we studied the potential functional role of the differences observed through sex-biased gene**
9 **expression and gene-level analyses. Our results suggest the need to consider sex-aware analyses**
10 **for future studies in order to shed light into possible sex-specific molecular mechanisms.**

11 12 **INTRODUCTION**

13
14 In recent years, there has been growing evidence of common genetic variation having different effects
15 on males and females^{1,2}. This, along with sex-biases observed in the human transcriptome^{3–10}, the
16 presence of a distinct hormone milieu in each sex, and differential environmental pressures arising
17 from gender societal roles^{2,11}, has led to an increased study of the potential importance of GxS
18 interactions to understand the underlying biology of complex traits, including the estimation of
19 disease risk. Previous studies have investigated differences in heritability between the sexes (h^2)^{12–15},
20 departure of genetic correlations from 1 (r_g)^{12,14,16–19}, and performed sex-stratified genome-wide
21 association studies (GWAS) to directly assess differences in the effects of genetic variants between
22 the sexes^{6,20–27}. These studies have however been limited with regards to the number of traits studied
23 or statistical power. Furthermore, insights into how differences in genetic architecture translate into
24 differences in complex traits have been lacking. Accounting for sex differences is of great importance
25 as sex-agnostic analyses could potentially be masking sex-specific effects, and which could - if better
26 understood - lead to better personalized treatment and an improved understanding of the biological
27 mechanisms driving these differences^{17,28}.

28
29 The objective of the current study was to assess both the existence and scope of GxS interactions in
30 the human genome by estimating sex-specific heritability and genetic correlations, as well as
31 performing sex-stratified GWAS analyses. To this end, we analysed 530 traits using 450K individuals
32 of European ancestry from the UK Biobank. Furthermore, we evaluated the potential of improving trait
33 predictions using sex-stratified polygenic scores (PGS), as well as looked into the possibility of missing
34 loci of interest in non-sex stratified studies. Finally, to shed light on the downstream effects of sex-
35 differences in genetic architecture, we performed a functional *in silico* analysis.

36 37 **RESULTS**

38 39 **Data overview**

40
41 Using the July 2017 release of the UK Biobank dataset, we performed sex-stratified GWASs and
42 partition of variance analyses for 530 traits (446 binary and 84 non-binary, Supplementary Table 1)
43 within 452,264 individuals of European ancestry (245,494 females and 206,770 males) using
44 DISSECT²⁹. Linear Mixed Models (LMMs) were fitted for each phenotype by sex. We then tested the

45 association of 9,072,751 autosomal and 17,364 X-chromosome genetic variants, obtaining estimates
46 of the genetic effects of each variant in each sex. In our quality control (QC) stage we excluded genetic
47 variants with a minimum allele frequency (MAF) < 10% in the analysis of binary traits due to the general
48 limited number of cases available, thus reducing the number of variants considered for these traits to
49 4,229,346 autosomal and 7,227 genotyped X-chromosome genetic variants (see Methods). The results
50 of the autosomal analyses were used to estimate sex-stratified genetic parameters (such as
51 heritability) and genetic correlations. We then tested for differences in these genetic parameters and
52 between the effects of genetic variants estimated within sexes (see Methods).

53

54 Because of the different QC treatment of binary and non-binary traits, as well as the difference in
55 phenotype characteristics, results are presented separately for both throughout this work, not as a
56 means to compare the results between the two but so as to contain them both to their own separate
57 categories.

58

59 **Heritability differences between the sexes**

60

61 Heritability (here referring to SNP heritability³⁰) is defined as the fraction of the variation of a trait that
62 can be explained by the additive effects of genetic variation. A difference in heritability between the
63 sexes would entail a difference in the fraction of the variance of a trait that is accounted for by the
64 genotype, and thus a possible difference in the underlying genetic mechanisms of said trait. Out of
65 the 530 traits studied, 41/84 (48.88%) non-binary traits and 30/446 (6.73%) binary traits showed
66 significant differences in their heritability between the sexes (FDR corrected p , termed q , < 0.05, Figure
67 1, Supplementary Table 1). Of these, a total of 25/41 (60.98%) non-binary and 14/30 (46.67%) binary
68 traits had a larger heritability in males than in females. Non-binary traits with the largest significant
69 difference in heritability between the sexes included body mass traits, while binary traits included
70 ankylosing spondylitis, disorders of mineral metabolism and soft tissue disorders (Supplementary
71 Table 1).

72

73 Although differences in the heritability of traits between the sexes can offer potential insights into
74 genetic differences, one must also consider that these could arise due to differences in environmental
75 variances. Hence, we looked for differences in genetic variance between the sexes ($q < 0.05$). We found
76 that 65/84 (77.38%) non-binary and 136/446 (30.49%) binary traits showed significant differences in
77 the amount of genetic variance estimated in each sex, including impedance-related traits, and
78 diseases of the thyroid and heart (Extended Data Figure 1, Extended Data Figure 2, Supplementary
79 Table 1). A total of 6/84 (7.14%) non-binary traits and 4/446 (0.90%) binary traits presented a significant
80 difference in heritability but no significant difference in genetic variance between the sexes,
81 indicating differences in environmental variance. These included numerous blood phenotypes (such
82 as lymphocyte percentage and mean reticulocyte volume), ease of skin tanning, venous thrombosis
83 disease, anaphylaxis/allergy and diseases of the digestive system.

84

85 Finally, we observed significant differences in evolvability (a measure of the ability to undergo
86 adaptation) between sexes for 56/84 (66.67%) non-binary and 35/446 (7.85%) binary traits ($q < 0.05$,
87 Extended Data Figure 2, Supplementary Table 1). These included binary traits like ankylosing
88 spondylitis and malabsorption/coeliac disease, as well as non-binary traits like current tobacco

89 smoking. These estimates offer further evidence for differences in the underlying genetic architecture
90 of the traits considered, paralleling previous reports at smaller scales for traits including height, waist-
91 hip circumference ratio and weight¹²⁻¹⁴.

92

93 **Genetic correlations indicate genotype by sex interactions**

94

95 Genetic correlations between two sub-groups of the population are usually interpreted as a measure
96 of shared underlying genetics, and are a means to estimate the size of putative genotype by group
97 interactions. Genetic correlations between the sexes can thus offer insights into the common genetic
98 control of complex traits and diseases of males and females.

99

100 We obtained genetic correlations between the sexes for a total of 83 non-binary and 77 binary traits
101 with over 5,000 cases using LD score regression (LDSC, Supplementary Table 1)³¹ which met our QC
102 criteria (see Methods). Genetic correlations ranged from 0.716 to 0.996 for non-binary traits and from
103 0.226 to 1.099 for binary traits (note that with heritability close to zero application of LDSC can result
104 in r_g exceeding the theoretically valid range $[-1, 1]$ ³²). A total of 58/83 (69.88%) non-binary traits and
105 11/77 (14.29%) binary traits had a r_g significantly different from 1 ($q < 0.05$, Figure 2A). These included
106 binary traits like hernia ($r_g = 0.59$, $q = 4.04 \times 10^{-10}$), eczema ($r_g = 0.61$, $q = 0.04$) and gastric reflux ($r_g =$
107 0.67 , $q = 0.02$), and non-binary traits like waist-hip circumference ratio ($r_g = 0.72$, $q = 8.43 \times 10^{-37}$) and
108 alcohol intake frequency ($r_g = 0.85$, $q = 7.49 \times 10^{-9}$, Figure 2B). Our r_g estimates for several non-binary
109 traits were in line with what has previously been published, noting that one of the compared studies
110 also used UK Biobank data (Supplementary Table 2, Extended Data Figure 3)^{12,14,16}.

111

112 **Genome-wide genetic effect comparison across traits**

113

114 We directly assessed whether each genetic variant in the genome had different effects in males and
115 females through sex-stratified GWASs. Our genome and trait-wide genetic effect comparison between
116 the sexes (see Methods) yielded a total of 61/84 (72.62%) non-binary and 42/446 (9.42%) binary traits
117 with at least one autosomal genetic variant presenting a significantly different effect at a $p < 1 \times 10^{-8}$
118 threshold (Supplementary Table 3), hereon termed as a sex-dimorphic SNP or sdSNP (Table 1 shows
119 traits with the largest number of independent autosomal sdSNPs, i.e. lead sdSNPs, found). The
120 distribution of sdSNPs across the genome for the traits with most autosomal lead sdSNPs is shown in
121 Figure 3. When testing the X-chromosome variants, we found 28/84 (33.33%) non-binary traits with at
122 least one sdSNP. Considering the autosomal genome, the trait with the largest number of sdSNPs was
123 waist-hip circumference ratio, a complex trait that has appeared frequently in analyses of sex
124 differences in genetic architecture^{12,20,21}. A total of 2,421 sdSNPs were found for this trait, which
125 represent 100 unique loci after linkage disequilibrium (LD) clumping (see Supplementary Note). The
126 trait with the most sdSNPs in the X-chromosome was hematocrit percentage, with a total of 12 that
127 mapped to 5 unique loci after LD clumping (Supplementary Table 1 and 3). Our results include
128 replications of several previously reported loci for traits including anthropometric measurements or
129 diseases like gout^{20-24,33}.

130

131 A total of 4,179 (4,179/9,072,751 = 0.046%) and 4,196 (4,196/4,229,346 = 0.099%) autosomal genetic
132 variants showed evidence of GxS in at least one non-binary or binary trait respectively ($p < 1 \times 10^{-8}$),

133 which mapped to 264 and 88 independent loci respectively. A total of 37 (37/7,227 = 0.213%) X-
134 chromosome variants showed evidence of sex differences in at least one non-binary trait ($p < 1 \times 10^{-8}$),
135 which mapped to 8 unique loci. The sdSNP associated to the highest number of traits (a total of 17) was
136 rs115775278, an imputed intergenic variant found on chromosome 16. The closest genes to this variant
137 include LOC105371341 (an uncharacterized non-protein coding RNA gene, with transcription start site,
138 TSS, ~40kb downstream), LOC390739 (MYC-binding protein pseudogene, TSS ~50kb upstream),
139 PMFBP1 (Polyamine Modulated Factor 1 Binding Protein 1, TSS ~60kb downstream), and LINC01572 (a
140 long intergenic non-protein coding RNA gene, TSS ~470kb upstream). PMFBP1 has been linked to
141 spermatogenesis function³⁴. The distribution of hits across the autosomal and X chromosome genome
142 is shown in Extended Data Figure 4.

143

144 Several sanity checks were performed to support these results (see Supplementary Note), which
145 included fitting alternative models (including Logistic Mixed Models³⁵), comparison to the Genetic
146 Investigation of Anthropometric Traits (GIANT) cohort^{20,21}, and a randomization scheme. These checks
147 suggested results for the nucleated red blood cell percentage trait likely represent false positives (see
148 Supplementary Note), thus its exclusion from future discussion.

149

150 **Phenotype prediction with sex-stratified effect estimates**

151

152 We studied whether genetic prediction could potentially be improved using sex-stratified models. To
153 this end, we estimated genetic effects in a training population of 300,000 UK Biobank white British
154 individuals in two different ways: (1) including both sexes in the model (obtaining sex-agnostic effects)
155 and (2) using each sex in a separate model (obtaining sex-specific effects, see Methods). We then used
156 a testing population consisting of 43,884 white British individuals to compare the performance of
157 these two models in three different ways using PGSs: (1) obtaining predictions from the sex-agnostic
158 effects (*agnostic* PGS), (2) obtaining predictions using the female effects applied to females and the
159 male effects applied to males (*same* PGS), and (3) obtaining predictions using the female effects to
160 predict in males and vice versa (*opposite* PGS). Prediction accuracy was measured as the correlation
161 (r) between or the area under the curve (AUC) for our prediction and the true phenotype value for non-
162 binary and binary traits respectively. Only lead sdSNPs were used in our PGS calculation. Due to the
163 general low number of sdSNPs across traits, we focused our comparison on phenotypes with at least
164 10 lead sdSNPs. These included 7 non-binary traits (waist-hip circumference ratio, standing height,
165 trunk fat percentage, hip circumference, whole body water mass, trunk predicted mass and trunk fat-
166 free mass) and 3 binary traits (ankylosing spondylitis, gout and hypothyroidism/myxoedema).

167

168 Although of the 7 non-binary traits tested only waist-hip circumference ratio showed a moderately
169 significant difference in prediction accuracy (correlation comparison $p = 0.059$, see Methods) between
170 *same* PGS and *agnostic* PGS in males (Supplementary Table 11), all 7 traits consistently presented a
171 larger prediction accuracy when comparing the sex-stratified model with the agnostic model, thus
172 suggesting that the stratified model captures the effect sizes better than the agnostic model. On the
173 other hand, we consistently observed smaller prediction accuracies when the stratified model was
174 used to perform predictions on the opposite sex (*opposite* PGS). We did not observe any consistent
175 prediction improvements for the 3 binary traits considered (Supplementary Table 11).

176

177 A limitation of our approach is the overlap between our discovery data set (used to establish sdSNPs)
178 and our training and testing data sets in our prediction analysis (see Methods). We repeated our
179 analysis with independent data sets (see Methods) for waist-hip circumference ratio, and we found
180 that the *same* PGS and *agnostic* PGS had similar predictive ability in females ($r = 0.132$ with $p = 1.85 \times$
181 10^{-98} and $r = 0.133$ with $p = 4.02 \times 10^{-99}$ respectively), the *same* PGS surpassing the *agnostic* for males
182 ($r = 0.038$ with $p = 7.91 \times 10^{-8}$ and $r = 0.024$ with $p = 9.97 \times 10^{-4}$ respectively), however the differences
183 in predictive power were not significantly different in either case (correlation comparison $p > 0.05$).

184

185 A possible explanation for the modest increase in predictive power found when using our sex-
186 stratified models, when taking observed differences in heritability into account, is the potential
187 existence of large numbers of SNPs of small dimorphic effect across the genome. These small effects
188 remain undetected in a GWAS, and as such, are not being included in our predictions. This reasoning
189 parallels the missing heritability problem³⁶, where the predicted heritability of traits can't be explained
190 by the detected GWAS associations, a hypothesis for which is the existence of large amounts of
191 variants of small effect that are yet to be found. Consistent with this theory, we found that our sdSNPs
192 generally accounted for a very low percentage of the sex-specific heritability for the considered traits
193 (Supplementary Table 12, Methods), which ranged from 0.18% to 0.65%. Waist-hip circumference ratio
194 was the exception, for which our sdSNPs accounted for 12.10% and 1.70% of the female and male
195 specific heritability, respectively, which could be due to the substantially larger number of sdSNPs
196 identified. This could also be, however, due to sdSNPs having a generally small effect on the
197 phenotypes considered.

198

199 **Potential masking of loci in sex-agnostic studies**

200

201 Currently, many GWASs fit non-sex-stratified models. However, a situation could arise in which (1) a
202 locus possesses a differentially signed genetic effect in each sex or (2) a genetic variant shows a larger
203 effect in one of the sexes and a small or no effect in the other. In any of these situations, the power of
204 detecting the variant will be reduced in a non-stratified analysis, and the variant effect size
205 misestimated in both sexes. This phenomenon we term as "masking" of a genetic effect.

206

207 To assess masking effects in the UK Biobank, we evaluated the total number of genetic variants that
208 were found to be significantly associated with a trait in a sex-stratified GWAS (i.e. associated to a trait
209 in males and/or females), but were not significantly associated in a sex-agnostic model. We performed
210 this analysis on the 530 traits in our study, considering a genetic variant as potentially masked if it is
211 significantly associated in females and/or males but not for the mixed population at a $p < 1 \times 10^{-8}$
212 threshold (see Methods).

213

214 We found that 98/446 (21.97%) binary and 78/84 (92.86%) non-binary traits had at least one genetic
215 variant that showed potential masking across the autosomal genome (Supplementary Table 14,
216 Extended Data Figure 5A). On average, the percentage of these variants that presented opposite signs
217 in each sex was 20.03% (SD 36.25%) in binary traits and 5.34% (SD 9%) in non-binary traits (Extended
218 Data Figure 5B). This may indicate that for a small percentage of traits opposite signed genetic effects
219 are leading to masking. However, this could also be the result of smaller sample sizes leading to false
220 positives in one sex but not the other.

221
222 A total of 93 traits (33 binary and 60 non-binary) presented at least one sdSNP and one potentially
223 masked variant. We also found a significant correlation between the number of potentially masked
224 variants and the number of sdSNPs ($r = 0.624$, $p = 9.793 \times 10^{-8}$) for non-binary traits, as shown in
225 Extended Data Figure 6. On average, the percentage of masked variants that presented sex differences
226 in binary traits was 3.83% (SD 18.97%), and 1.39% (SD 2.22%) in non-binary traits (Extended Data Figure
227 5C). These low percentages could indicate that masked variants may have different effects on the two
228 sexes, just not surpassing our significance threshold to be considered sdSNPs. On the other hand, 42
229 of our 103 traits with at least one sdSNP had one of these sdSNPs potentially masked, and, on average,
230 the percentage of sdSNPs that were potentially masked in binary traits was 12.30% (SD 30.59%) and
231 18.44% (SD 21.99%) in non-binary traits (Extended Data Figure 5D). This could suggest a large number
232 of potentially interesting variants that present a difference in genetic effect between the sexes could
233 be being missed in sex-agnostic studies.

234

235 **Gene-level analyses**

236

237 To gain insight into the biological meaning of these results, gene enrichment analyses were carried
238 out for all 103 phenotypes with at least one sdSNP. To do this, the two-tailed sex-comparison p -values
239 for the sdSNPs found were converted to two one-tailed p -values (p_F and p_M) according to the sex which
240 presented the largest genetic effect (see Methods). Using these two sets of p -values in combination
241 with MAGMA we then estimated the degree of sex dimorphism of each gene, thus obtaining dimorphic
242 gene lists, which were dominant in females or males (i.e. which presented a significantly larger effect
243 in one sex versus the other, see Methods, Supplementary Table 15 and 16, Supplementary Note). The
244 GENE2FUNC tool in FUMA was then used to investigate any functional enrichments among these
245 dimorphic gene lists (Supplementary Table 17, 18 and 19, Supplementary Note) for the 10 traits with
246 the largest number of sexually different genes. These were largely all of the anthropometric class and
247 were: standing height, waist-hip circumference ratio, trunk predicted mass, trunk fat-free mass, trunk
248 fat percentage, whole body fat-free mass, basal metabolic rate, impedance of arm (left), body fat
249 percentage and hip circumference. As a background to compare our results to, this procedure was
250 repeated using sex-agnostic GWAS results, obtaining gene sets enriched in genes associated to each
251 of our 10 phenotypes (see Methods).

252

253 A total of 4,840 gene sets were found to be enriched in either male or female dominant genes across
254 the 10 traits considered ($q < 0.05$, Supplementary Table 18 and 19). Genes dominant in one sex or the
255 other were found to be enriched in sets in an exclusive manner (i.e. sets would not show a larger
256 amount of both male and female dominant genes than what would be expected by random), with the
257 average percentage of shared enriched sets across traits being 3.3%, SD = 3.34% (Supplementary Table
258 17). A total of 383/4,840 gene sets were found to be significantly differentially enriched between male
259 and female dominant genes in at least one of the traits considered (Fisher's exact test $q < 0.05$), with
260 an average of 12.88% (SD 12.96%) of gene sets being differentially enriched across traits
261 (Supplementary Table 17). Furthermore, 251/383 gene sets were found to also show a significant
262 difference in enrichment when comparing with the results of our background of sex-agnostic
263 associated genes (Fisher's exact test $q < 0.05$, see Methods), the mean percentage of gene sets
264 presenting this behaviour across traits being 67.30% (SD 18.87%, Supplementary Table 17).

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Heatmaps were produced considering the aforementioned 251 gene sets, with hierarchical clustering both by gene set and by trait (Extended Data Figure 7). Most notably, we find clusters of sets pertaining to small non-coding RNA (sncRNA) biogenesis and RNA-mediated silencing, enriched in female dominant genes for body mass-related traits. It has previously been postulated that miRNA may play a role in the regulation of phenotypic sex differences due to its ability to regulate large numbers of genes with a high degree of specificity, with intervention of the sex chromosomes and/or gonadal hormones³⁷.

Sex differences in gene expression regulation

Differences between the sexes in complex traits could be partially explained by sex-specific gene expression regulation, which could lead to differences downstream across biological pathways and traits, and thus to the detection of GxS interactions in GWASs. Although studies have been carried out searching for differential gene expression between the sexes (sex-DE) in a variety of tissues of interest, studies linking sex to differences in gene expression regulation (sex-specific or sex-biased eQTLs) are few, with often contradictory results^{5,38–41}. These mixed results could be due to the contribution of GxS to gene expression being tissue specific, a lack of sufficient statistical power, or the fact that this contribution occurs only on a small number of genes⁴⁰. Overall, a system-wide analysis (i.e. across a wide variety of tissues) is yet to be carried out in order to determine whether there is evidence of sex-biased eQTLs and whether some tissues are more prone to sex-specific regulation than others.

In order to bring light to potential intermediary mechanisms underlying differences in genetic architecture between the sexes we investigated whether our lead sdSNPs could also be acting as sex-biased eQTLs. To do this, we performed an eQTL analysis, looking for GxS interactions in gene expression, considering genes within a 1Mb window to our lead sdSNPs (Supplementary Table 3, see Methods). This was done for a total of 39 tissues from the Genotype-Tissue Expression (GTEx) consortium v6, originating from up to 450 individuals.

A total of 8 sex-biased eQTLs were found at a $q < 0.05$ threshold (Supplementary Table 20, 21, 22 and 23). We also checked for enrichment of GxS in gene-variant pairs for variants that presented evidence of sex dimorphism (genetic effect comparison between the sexes $p < 1 \times 10^{-8}$) versus those that did not (genetic effect comparison between the sexes $p > 0.5$), using contingency tables (see Methods). We found enrichment for a small number of the tissues considered (see Supplementary Note, Supplementary Table 24).

The variant rs56705452 from chromosome 6 was found to be a sex-biased eQTL for the transcript ENSG00000204520.8, which corresponds to the gene MICA (Extended Data Figure 8), in muscle skeletal tissue. This gene encodes the highly polymorphic major histocompatibility complex class I chain-related protein A, and variations of this gene have been associated to susceptibility to psoriasis, psoriatic arthritis and ankylosing spondylitis, amongst others⁴². Interestingly, this sdSNP has been shown to bind FOXA1 through ChIP-Seq experiments⁴³, a protein that dictates the binding location of androgen and oestrogen receptors, and that has been found to play a role in the sexually dimorphic

309 presentation of various cancers^{44,45}. Furthermore, this sdSNP was found to act in a sexually different
310 manner in regards to its association to ankylosing spondylitis in our genome-wide sdSNP analysis.
311 This result would be consistent with a hypothesis where this sdSNP is regulating MICA in a sex-
312 dependent manner in the muscle tissue, thus leading to differences in ankylosing spondylitis
313 presentation between the sexes when one possesses a particular variant.

314

315 The small number of significant sex-biased eQTLs found parallels the findings of recent study by Porcu
316 et al⁴¹, where they conclude that millions of samples would be necessary to observe sex-specific trait
317 associations that are fully driven by sex-biased eQTLs. Overall, this type of pipeline could help in the
318 future when short-listing biomarkers for risk susceptibility in males and females, help develop
319 precision medicine strategies for each of the sexes, and bring light into the underlying mechanisms
320 of the disease/trait of interest as well as possible underlying sexually different molecular networks,
321 once larger sample sizes become available.

322

323 **DISCUSSION**

324

325 In this study, we have delved into the differences in genetic architecture between the sexes in the UK
326 Biobank for a total of 530 traits from around half a million individuals. This has enabled us to assess
327 the genetics of sex dimorphism at a depth and breadth not previously achieved.

328

329 Overall, we have found evidence of sex differences for a large number of the traits considered, though
330 be it of generally modest magnitude, through a thorough investigation of sex-specific genomic
331 parameters. A total of 71 traits were found to present significantly different heritability estimates
332 between the sexes, while a total of 69 presented genetic correlations between the sexes that
333 significantly differed from one, indicating the presence of genetic heterogeneity across these
334 complex traits. In order to dissect this heterogeneity and pin-point genetic sites that could be
335 differentially associated to these traits, sex-stratified GWASs were performed, yielding over 100 traits
336 with at least one sdSNP. These traits included those of the anthropometric class as well as diseases
337 like gout, ankylosing spondylitis or hypothyroidism. These results reinforce the need for future studies
338 to account for genetic sex heterogeneity to fully understand the genetic underpinnings of disease and
339 ultimately shed light on potential sex-specific biological mechanisms.

340

341 Having found evidence of GxS across the genome, we investigated whether sex-specific genetic
342 models could improve phenotypic prediction. While no statistically significant improvement in
343 prediction was found for the traits considered, a consistent trend of increased predictive accuracy
344 was seen when comparing the results of sex-specific models to those of a sex-agnostic model. Putting
345 our results in context with the heritability differences found, we postulate the potential existence of
346 large numbers of loci presenting small amounts of dimorphism with insufficient statistical power to
347 be detected in our analysis that could account for both this missing heritability difference as well as
348 the absence of increased predictive power. We also investigated whether sex-agnostic models could
349 potentially be missing loci of interest, and found indications of potential masking for 176 traits, with
350 further investigation being needed to replicate these results.

351

352 Finally, gene set enrichment and eQTL analyses were performed in an effort to translate our GWAS
353 results to function and bring light to potential mechanisms underlying the observed dimorphism
354 across traits. Our eQTL analysis found a total of 8 sex-biased eQTLs, but our results parallel previous
355 reports on the need for larger sample sizes to truly uncover potential links between sex-biased eQTLs
356 and sdSNPs. Our gene-set enrichment analysis suggests a link to miRNA regulation, which has been
357 hypothesized in the past to underlie sex differences. Further studies are needed to truly understand
358 what underlies sdSNPs, moving beyond gene expression regulation mechanisms and looking at other
359 biological regulatory mechanisms and omics data sets.

360

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362

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368

369 **AUTHOR CONTRIBUTION**

370

371 A. Tenesa conceived the study. A. Tenesa, O. Canela-Xandri, K. Rawlik and E. Bernabeu designed the
372 genetic architecture, prediction, masking and eQTL analyses. A. Talenti and J. Prendergast designed
373 the gene-level analyses. O. Canela-Xandri, K. Rawlik and E. Bernabeu pre-processed the data and
374 conducted modelling. E. Bernabeu conducted the statistical analyses and prepared the initial
375 manuscript. All authors contributed and commented on the development of the manuscript.

376

377 **ETHICS OVERSIGHT**

378

379 The UK Biobank project was approved by the National Research Ethics Service Committee North West-
380 Haydock (REC reference: 11/NW/0382). An electronic signed consent was obtained from the
381 participants (more information on UK Biobank participant consent can be found here:
382 <https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/Consent.pdf>). This research has been conducted
383 using the UK Biobank Resource under project 788.

384

385 **COMPETING INTEREST STATEMENT**

386

387 The authors declare no competing interests.

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FIGURES

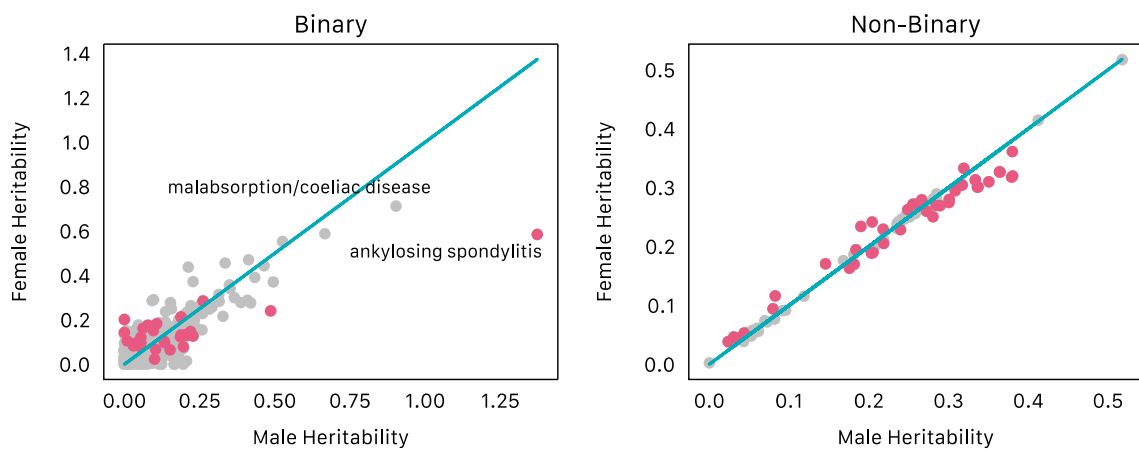
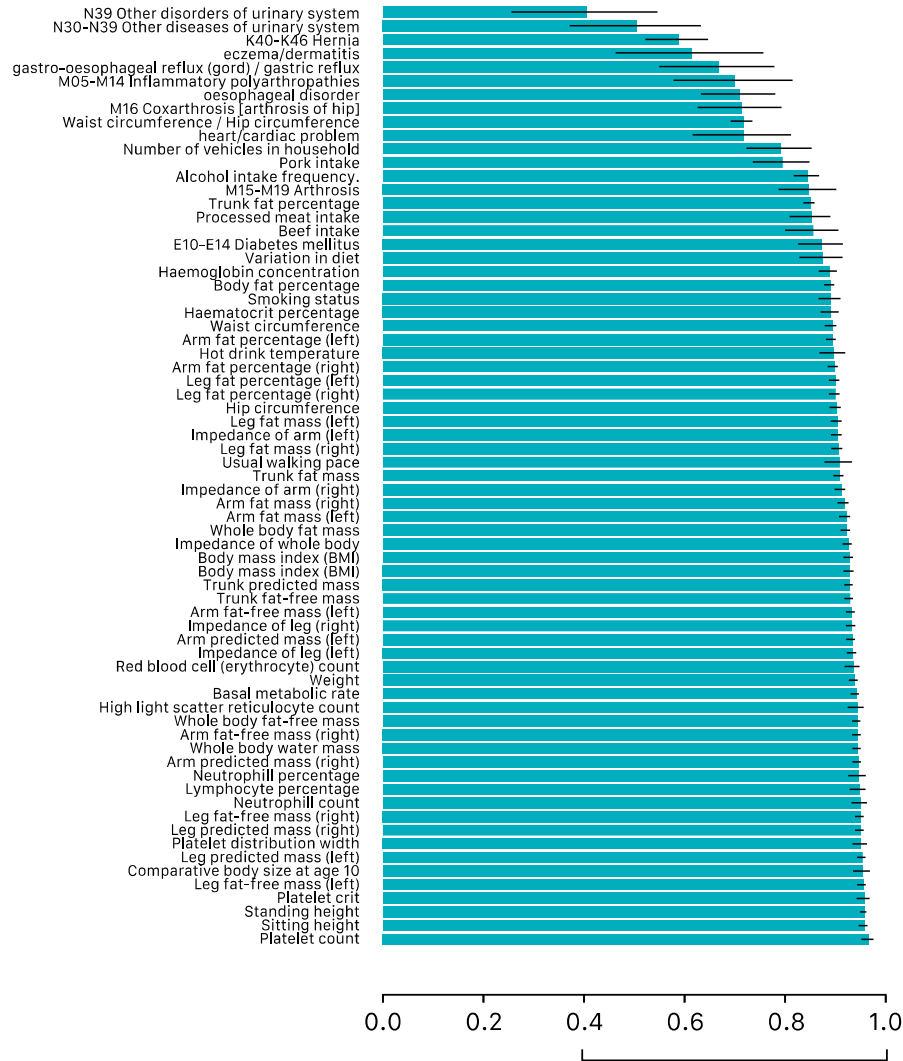


Figure 1. Sex-specific heritability estimate comparison. Scatterplots of male heritability estimates against female heritability estimates for binary traits (on the left) and non-binary traits (on the right) are shown. Each point represents a trait, which is marked in pink when heritability between the sexes is significantly different (see Methods) at a threshold of $q < 0.05$. Note that for the binary traits, heritability estimates were considered on the liability scale, which led to some estimates over 1 (see Methods). Blue line corresponds to $x = y$, and traits straying the furthest away from said line are annotated.

a

Genetic correlations (r_g) $\neq 1$



b

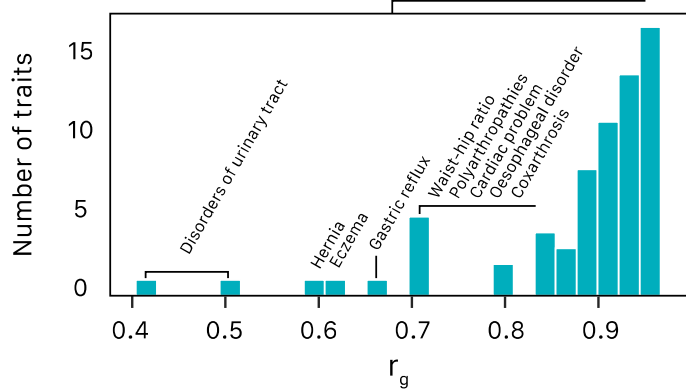


Figure 2. Genetic correlations between the sexes across traits. (a) Barplot of genetic correlations (r_g) between the sexes for traits that were found to have a r_g significantly different from one ($q < 0.05$, see Methods). Black bars indicate the standard errors of the r_g estimates ($r_g \pm SE_{r_g}$). (b) Histogram of genetic correlations that were found to be significantly different from one ($q < 0.05$) for both binary and non-binary traits.

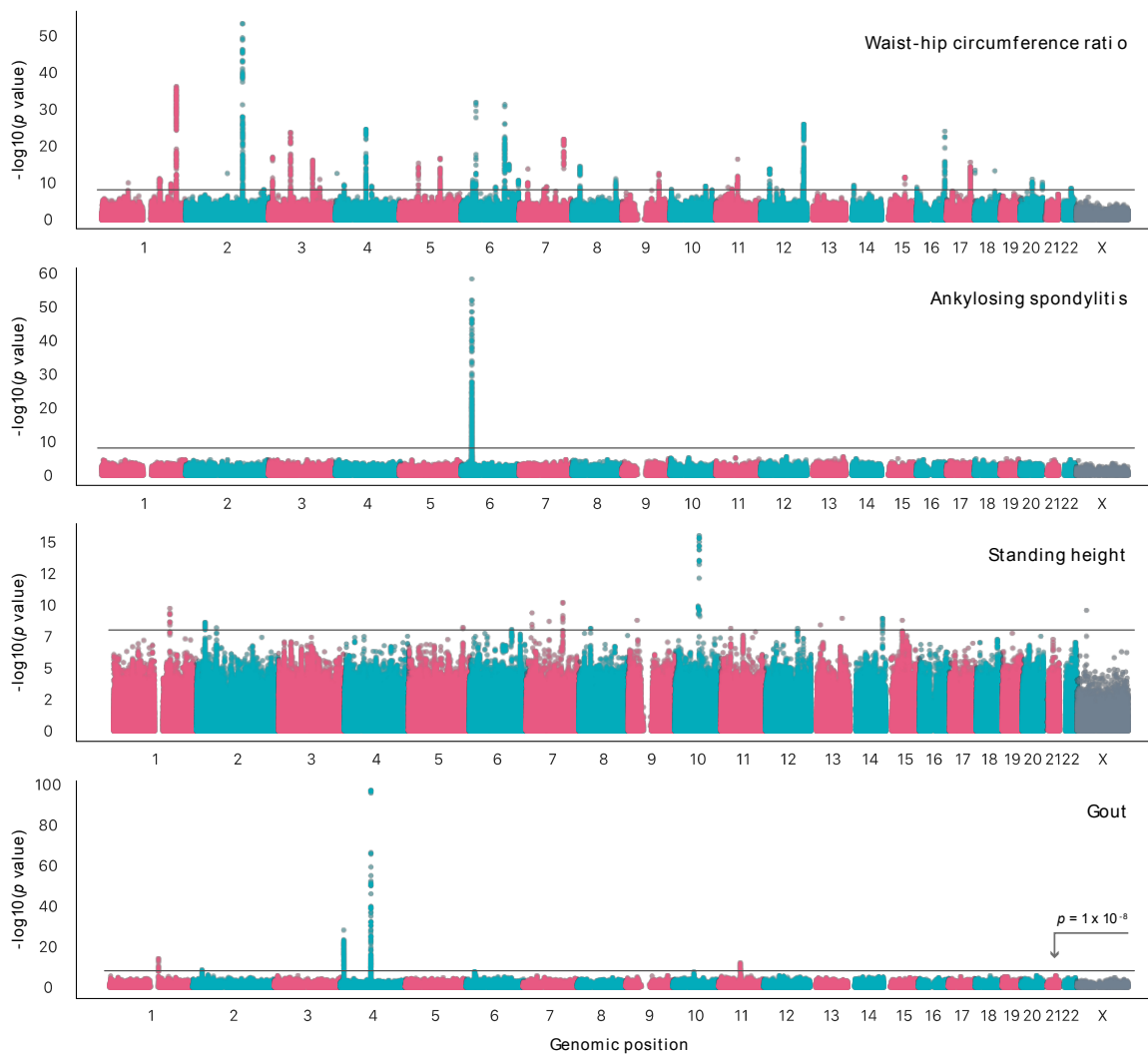
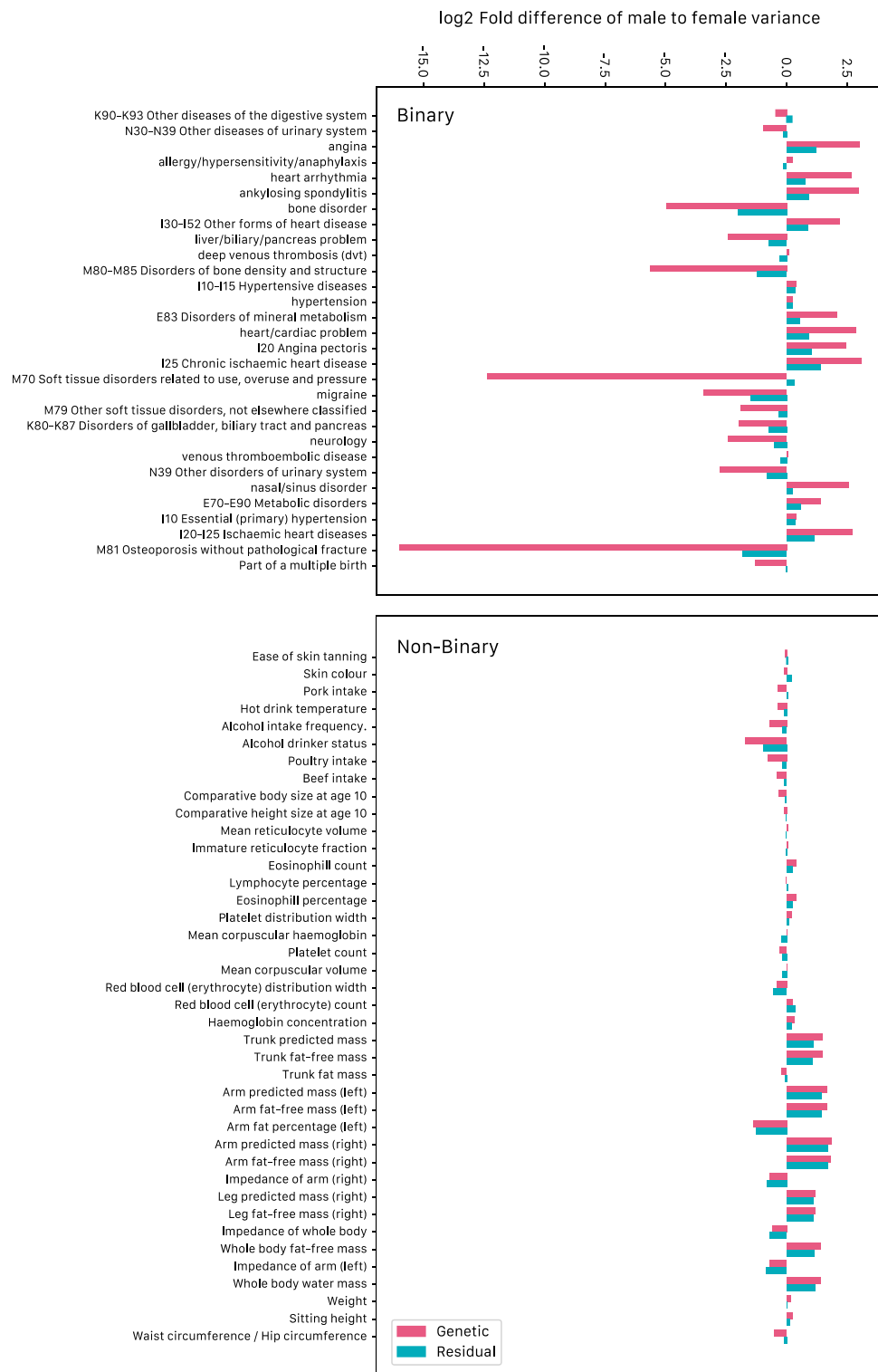
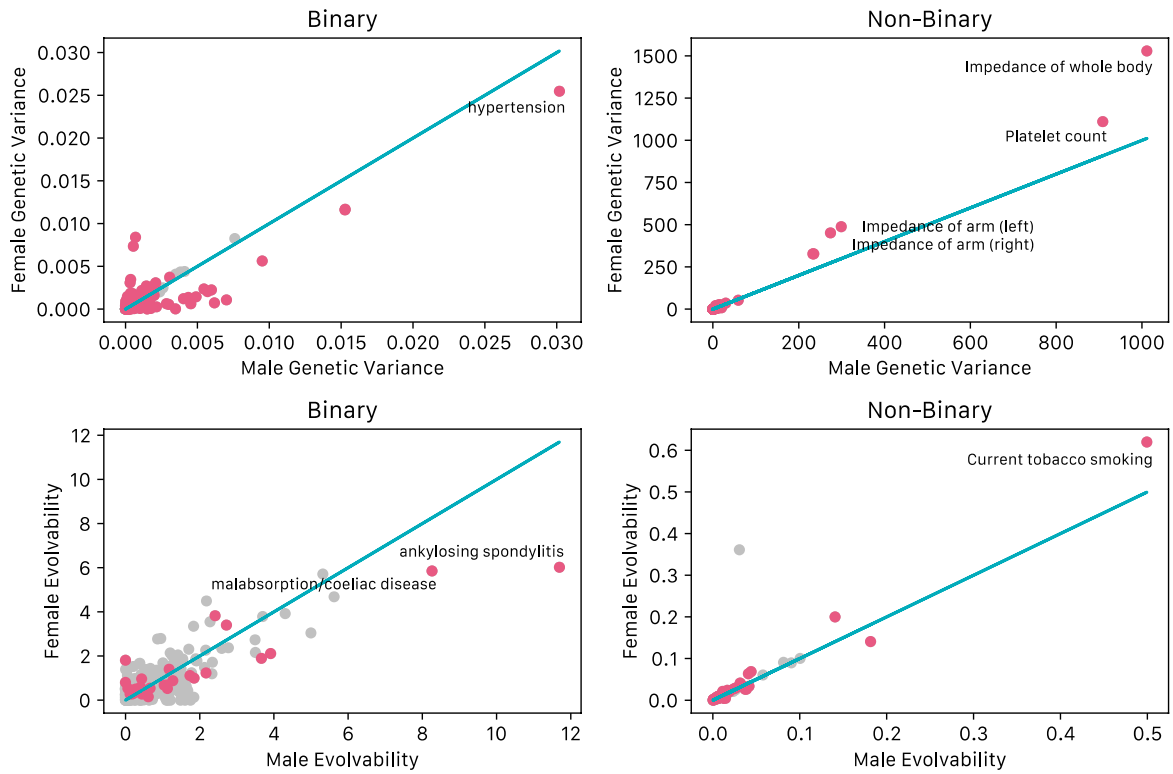


Figure 3. Manhattan plots for traits with most lead sdSNPs. The x axis corresponds to the genomic position in the genome, and the y axis to the $-\log_{10} p$ -value of the two-sided t-test (see Methods) for which the null hypothesis is that no difference between the sexes exists. Each point corresponds to a genetic variant. Points that go above the statistical significance line at $-\log_{10} p = 1 \times 10^{-8}$ are considered to be sdSNPs. Traits represented: waist-hip circumference ratio, ankylosing spondylitis, standing height, and gout.

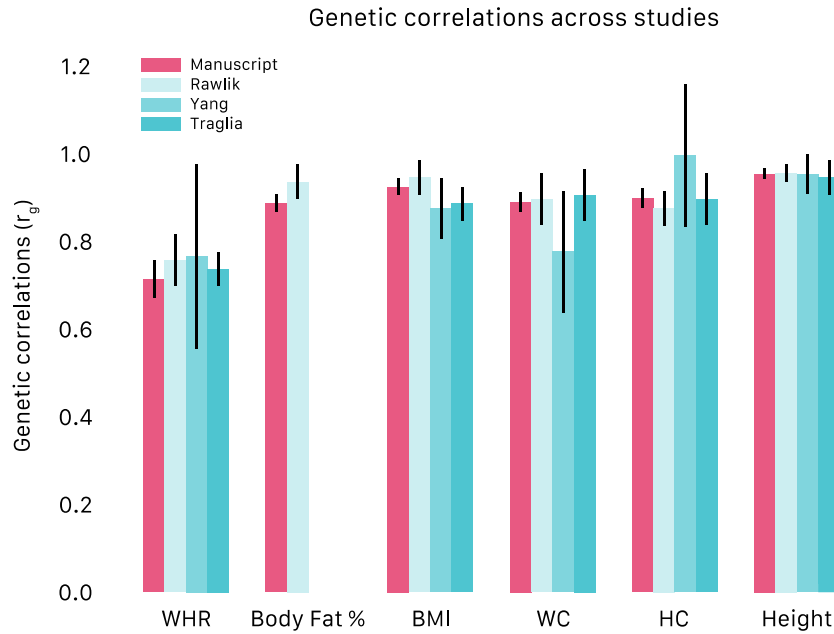
EXTENDED DATA FIGURES



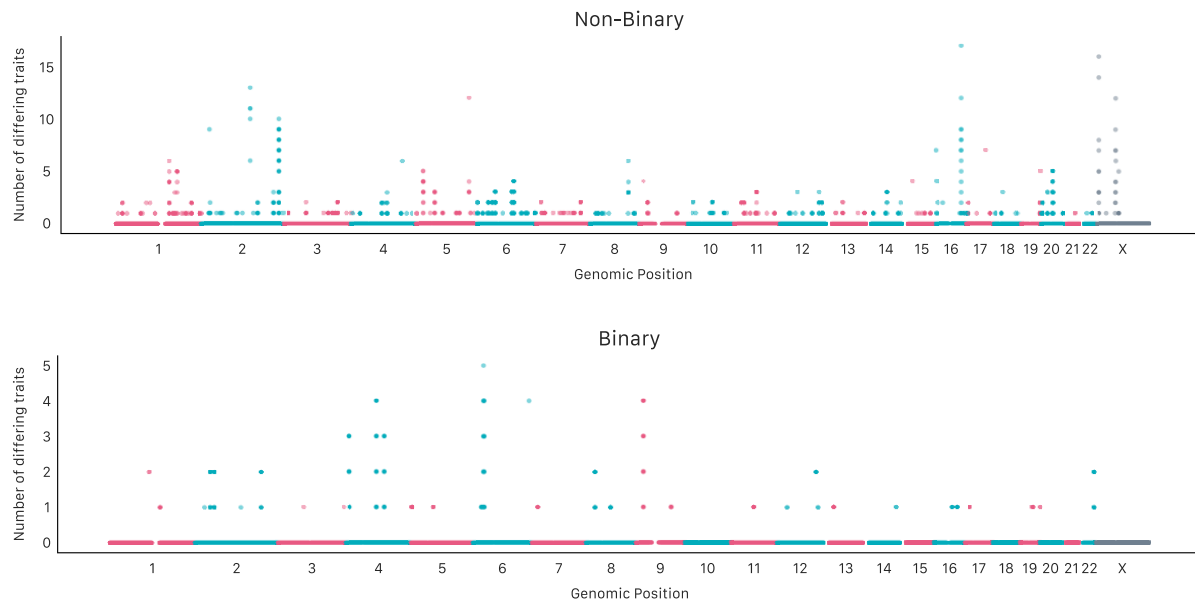
Extended Data Figure 1. Barplot of log2 fold difference in variance between males and females for binary (top) and non-binary (bottom) traits with a significantly different heritability between the sexes at a $q < 0.05$ threshold. Pink bars represent fold change between the sexes in genetic variance, and blue bars represent fold change between the sexes in residual variance. Fold change is calculated as $\log_2(\text{male variance}/\text{female variance})$, thus positive fold change = larger variance in males, negative fold change = larger variance in females.



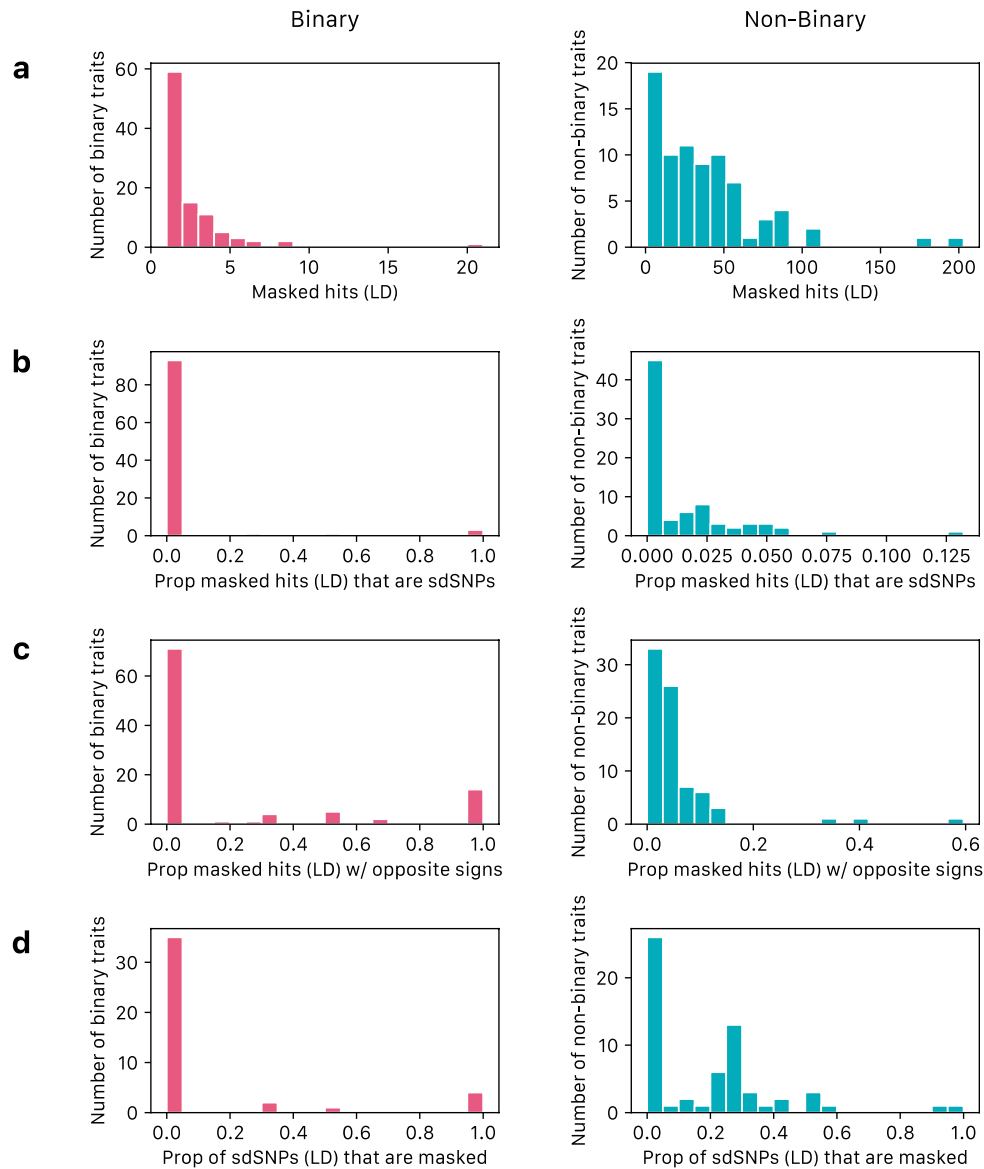
Extended Data Figure 2. Top plots: scatterplots comparing male genetic variance to female genetic variance for binary (left) and non-binary (right) traits. Bottom plots: scatterplots comparing male evolvability to female evolvability for binary (left) and non-binary (right) traits. Each point represents a trait, and pink points indicate traits for which the genomic parameter considered (genetic variance, evolvability) between the sexes is significantly different ($q < 0.05$, see Methods). Basal metabolic rate was removed as an outlier.



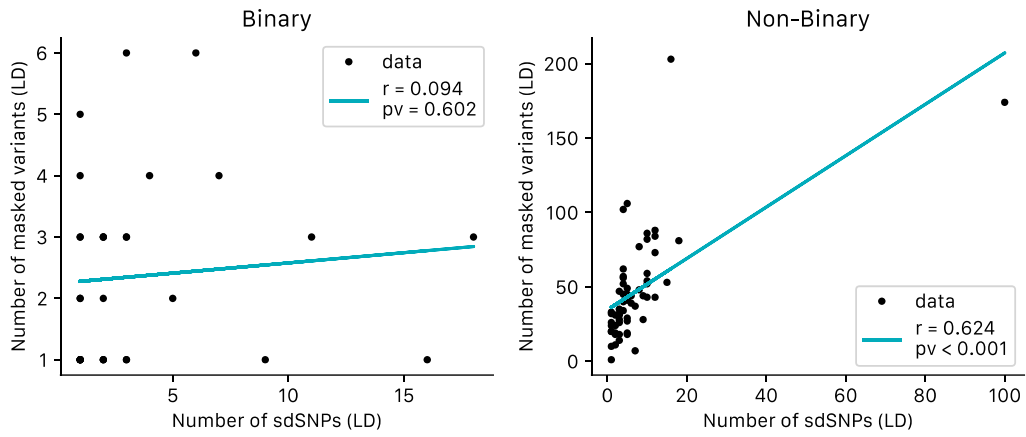
Extended Data Figure 3. Barplot comparing genetic correlation estimates from this effort to the literature for several non-binary traits (“WHR”: waist-hip circumference ratio, “Body Fat %”: body fat percentage, “BMI”: body-mass index, “WC”: waist circumference, “HC”: hip circumference, and “Height”: standing height). Height of bar indicates genetic correlation estimate (r_g), different colors corresponding to different publications, as represented in legend by surname of first author^{12,14,16} and the values of which, are shown in Supplementary Table 2. Error bars represent 95% confidence intervals of r_g estimates ($r_g \pm 1.96SE_{r_g}$).



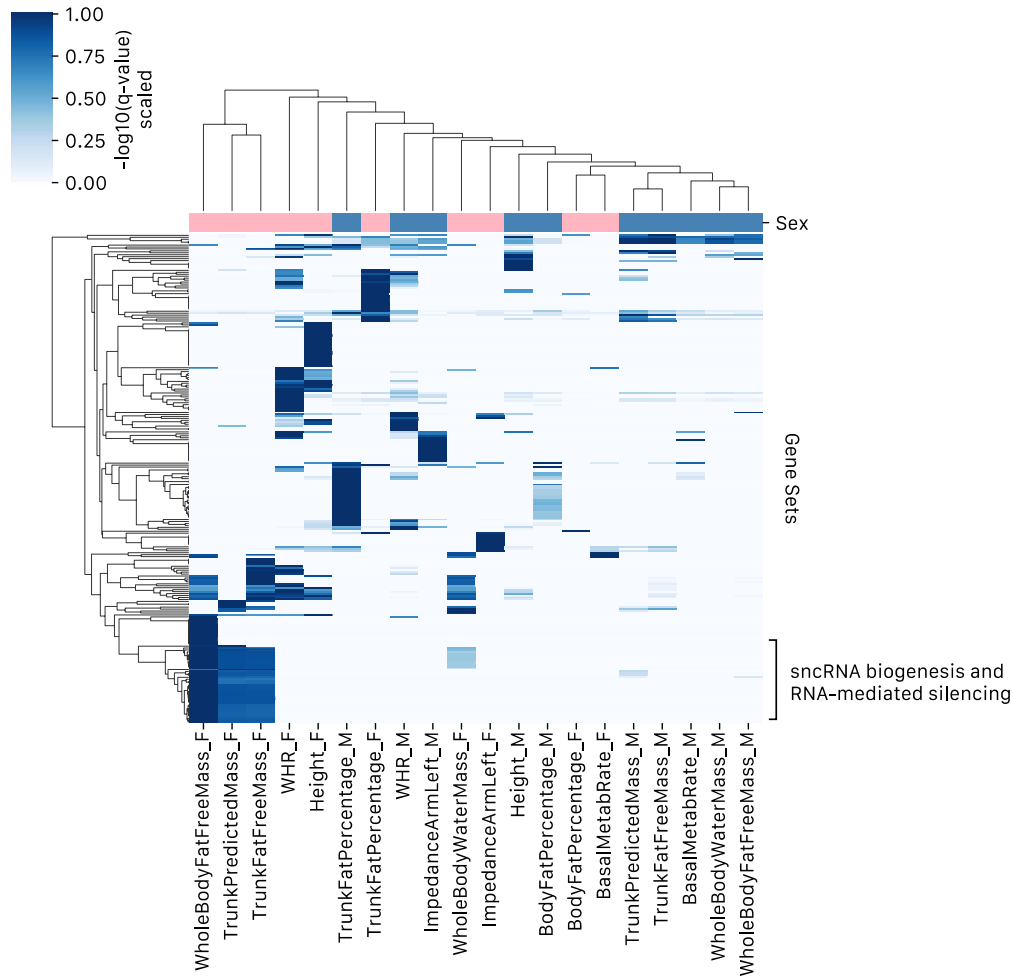
Extended Data Figure 4. Manhattan plot of number of sdSNPs ($p < 1 \times 10^{-8}$, two-sided t-test, see Methods) per genomic position, each point representing a genetic variant, and its height the number of traits it affects in a sexually different manner, for (a) non-binary traits and (b) binary traits.



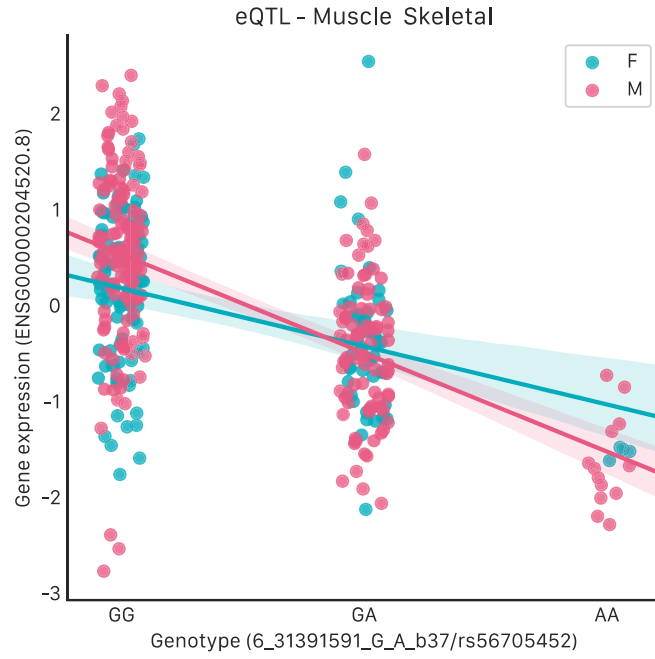
Extended Data Figure 5. For binary (left) and non-binary (right) traits with at least one potentially masked variant: (a) histogram of number of masked genetic variants, (b) histogram of proportion of masked SNPs that presented opposite sign effects between the sexes, (c) histogram of proportion of masked SNPs that were found to possess significantly different genetic effects between the sexes (two-sided t-test, $p < 1 \times 10^{-8}$ threshold, see Methods) and (d) histogram of the proportion of lead sdSNPs that were found to be masked.



Extended Data Figure 6. For binary (left) and non-binary (right) traits with at least one sdSNP and one potentially masked variant, shown is a scatterplot of number of sdSNPs against number of potentially masked variants ($p < 1 \times 10^{-8}$, and LD clumped within sex, see Methods).



Extended Data Figure 7. Heatmap with hierarchical clustering of FUMA set enrichment $-\log_{10} q$ -values for 251 gene sets that were found to be significantly differentially enriched between males and females (Fisher’s exact test $q < 0.05$), as well as significantly differentially enriched to GWAS background genes (Fisher’s exact test $q < 0.05$). x-axis corresponds to male or female dominant genes (see Methods) for different traits, and y axis to gene sets. Color within plot represents scaled $-\log_{10} q$ -value of enrichment, and “Sex” horizontal column indicates the sex in which the genes considered are dominant (pink for females, and blue for males).



Extended Data Figure 8. Relationship of genotype at variant rs56705452 with the expression of the transcript ENSG00000204520.8 in muscle skeletal tissue, for males (pink) and females (blue). Each point represents an individual, the x-axis its genotype at the considered variant, and the y-axis gene expression levels for the considered transcript.

TABLES

Table 1. Number of lead sdSNPs found across traits. Traits with the largest number of autosomal sdSNPs, that is, SNPs which presented a statistically significant difference between male and female genetic effect estimates ($p < 1 \times 10^{-8}$, two-sided t-test, see Methods), are shown. For each trait, total number of sdSNPs found across the genome is shown, along with the total number of independent loci presenting sex differences post-LD clumping (lead sdSNPs). Traits are sorted by number of lead sdSNPs. (*) Our analyses point to nucleated red blood cell percentage likely being a false positive (see Supplementary Note).

Trait	$p < 1 \times 10^{-8}$ (sdSNPs)	$p < 1 \times 10^{-8}$ LD clumped (lead sdSNPs)
Waist circumference / Hip circumference	2421	100
ankylosing spondylitis	626	18
Standing height	86	18
gout	708	16
<i>Nucleated red blood cell percentage*</i>	<i>26</i>	<i>16</i>
Trunk fat percentage	432	15
Hip circumference	124	12
Whole body water mass	39	12
Trunk predicted mass	163	12
Trunk fat-free mass	141	12
hypothyroidism/myxoedema	168	11
Arm predicted mass (left)	52	10
Impedance of arm (left)	149	10
Impedance of whole body	233	10
Impedance of arm (right)	155	10

1 **METHODS**

3 **UK Biobank data**

5 UK Biobank is a large population-based prospective study with participants aged 40 to 69 years at
6 recruitment, with extensive matching phenotypic and genomic data⁴⁶. In this study, of the circa
7 490,000 individuals whose data was released in July 2017, we considered data pertaining to a total of
8 452,264 white European individuals. Of these, 245,494 were females and 206,770 were males, here
9 referring to individuals whose self-proclaimed sex coincided with a XX or XY chromosomal content for
10 females and males respectively, thus excluding individuals whose self-reported sex did not coincide
11 with said genotypes. We also excluded individuals that were identified by UK Biobank as outliers based
12 on genotyping missingness rate or heterogeneity, and individuals whose first or second genomic
13 principal component differed by over 5 standard deviations from the mean of self-reported white
14 Europeans. Finally, we removed individuals with a missingness rate > 5% for the genetic variants that
15 passed quality control (described in Genotypes section), arriving at the aforementioned number of
16 individuals.

18 ***Genotypes***

20 UK Biobank's participants were genotyped using either of two arrays, the Affymetrix UK BiLEVE Axiom
21 or the Affymetrix UK Biobank Axiom array, and later augmented by imputation of over 90 million
22 genetic variants from the Haplotype Reference Consortium, the 1000 Genomes project, and the UK 10K
23 project.

25 We excluded variants which did not pass UK Biobank quality control procedures in any of the
26 genotyping batches and retained only bi-allelic variants with $p > 1 \times 10^{-50}$ for departure from Hardy-
27 Weinberg and $MAF > 1 \times 10^{-4}$, computed on a subset of 344,057 unrelated (Kinship coefficient < 0.0442)
28 individuals of White-British descent with missingness rate > 2% in the study cohort, paralleling the QC
29 procedure followed by Canela-Xandri et al⁴⁷.

31 A second round of QC was done prior to performing everything that followed the sex-stratified GWAS
32 and genetic parameter estimation (described below), including calculation of genetic correlations and
33 genetic effect comparisons between the sexes. This was done to account for the smaller sample sizes
34 (versus those of ⁴⁷) as well as to be more stringent as we are comparing between groups. Variants were
35 further filtered if they possessed $p < 1 \times 10^{-6}$ for departure from Hardy-Weinberg and $MAF < 1 \times 10^{-3}$,
36 computed on the aforementioned subset of unrelated individuals. A stricter MAF threshold ($MAF < 1 \times$
37 10^{-1}) was set for binary traits due to the general limited number of cases available which can lead to an
38 inflation of type I error rates in association tests⁴⁸. Briefly, this is based on simulations from Loh et al's
39 work⁴⁸, where, when the case/control ratio is 0.001, a MAF filter of 10% shows no significant inflation
40 of Type I error rates for the sample sizes considered here. Furthermore, variants with a significant
41 effect ($p < 1 \times 10^{-8}$) when running a GWAS on sex for the aforementioned subset were also excluded, as
42 these could arise due to sampling bias⁴⁹. Finally, only imputed variants with no genotyped counterpart
43 and with an imputation score > 0.9 were retained. As a result, a total of 9,072,751 (602,984 genotyped

44 and 8,469,767 imputed) autosomal genetic variants and 17,364 X-chromosome genetic variants
45 remained for our analysis of non-binary traits, and 4,229,346 autosomal (244,743 genotyped and
46 3,984,603 imputed) and 7,227 genotyped X-chromosome genetic variants for our analysis of binary
47 traits.

48

49 ***Phenotypes***

50

51 In total we analyzed 530 non-sex specific traits. These included 446 binary traits, which had at least
52 400 cases in each of the sexes, relating to self-reported disease status, ICD10 codes from
53 hospitalization events, and ICD10 codes from cancer registries, as well as 84 non-binary traits
54 comprising non-scale transformed continuous and ordered integral measures.

55

56 Our starting point were the 778 traits considered in the GeneATLAS study⁴⁷. These were in turn
57 extracted from the UK Biobank June 2017 release. From these original 778 traits, we further removed
58 binary traits that had fewer than 400 traits in either sex (this thus excluded traits that were sex-
59 specific from our study). We further removed several blood measurement related traits as well as
60 others that did not pass our QC stage. The remaining 530 traits were considered in this study. For more
61 information on the treatment and filtering of the phenotype data see ⁴⁷.

62

63 **Sex-stratified parameter estimation**

64

65 To obtain genetic and environmental variance estimates for each of the sexes we used DISSECT²⁹
66 following the same methodology as described in ⁴⁷. Briefly, a partition of variance analysis was run
67 using linear mixed models (LMMs), which were fitted for each trait with a Genetic Relationship Matrix
68 (GRM) containing all common autosomal genetic variants (MAF > 5%) which passed QC.

69

70 Heritability was then calculated as

71

$$72 \quad h_g^2 = \sigma_g^2 / (\sigma_g^2 + \sigma_e^2),$$

73

74 where σ_g^2 and σ_e^2 are the estimates of the genetic and residual variance. Heritability for binary traits
75 was transformed from the observed scale to the liability scale using the sex-specific population
76 prevalence of the trait, under the assumption that there was an underlying normal distribution of
77 liability to the considered trait, as described in ⁵⁰.

78

79 Wanting to see if the sexes differ in regards to their ability to undergo adaptation, evolvability was
80 calculated for males and females separately. Evolvability, defined as the expected evolutionary
81 response to selection per unit of selection⁵¹, or the ability of populations to respond to natural or sex
82 selection⁵², was calculated as

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$$84 \quad e = \sigma_g / m^2$$

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86 where σ_g is the additive genetic variance of the trait and m is the trait mean.

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To establish differences between heritability, genetic variance, and evolvability between the sexes, we used the t statistic

$$t = \frac{X_{\text{males}} - X_{\text{females}}}{\sqrt{SE_{\text{males}}^2 + SE_{\text{females}}^2}}$$

where X represents either heritability, genetic variance or evolvability, assumed to be independent between the sexes, and SE the standard error of the aforementioned, for males and females respectively. Two-tailed p -values were then FDR corrected (using the Benjamini-Hochberg procedure) to account for multiple testing.

Sex-stratified GWAS

To test the genetic effect of each variant for each of the sexes on the 530 chosen traits we ran a sex-stratified GWAS. The procedure followed for each of the sexes is that described in ⁴⁷ using the DISSECT software²⁹. Briefly, a Linear Mixed Model (LMM) was fitted,

$$y = X\beta + g + \epsilon,$$

y being the vector of phenotypes, X the matrix of fixed effects, β the effect size of these effects, g the polygenic effect that captures the population genetic structure, and ϵ the residual effect not accounted for by the fixed and random effects. Following the procedure described in ⁴⁷, our curated genetic variants were regressed against the residuals of the LMM to assess association.

Genetic correlations

Genetic correlations between the sexes were calculated using the bivariate linkage disequilibrium score (LDSC) regression analysis software³¹, which works directly on GWAS summary data and can thus be applied to very large sample sizes. As we were using data of European origin, we used the LD scores provided by the LDSC software and limited our genetic correlation calculation to the genetic effect estimates of SNPs for which such scores were available (1,189,831 total genetic variants, of which 1,169,868 passed LDSC's QC filters and were used in the computation). These scores were computed using the 1000 Genomes European data. We furthermore restricted our binary traits to those that had at least 5000 cases in each of the sexes, as was recommended in the documentation. Note that for traits with very low heritability this computation was unsuccessful. In total, genetic correlations were obtained for 83 non-binary and 77 binary traits.

To establish which correlations differed from one, we used the t statistic

$$t = \frac{r_g - 1}{SE_{r_g}}$$

128 where r_g is the genetic correlation, and SE_{r_g} is the standard error of the genetic correlation. Two-tailed
129 p -values were FDR corrected to account for multiple testing.

130

131 **Sex differences in genetic effects**

132

133 To compare genetic effects across the genome between the sexes for all traits we considered the
134 following two-tailed t test, as used in previous sex-stratified GWAS comparison studies^{20,23}:

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$$136 \quad t = \frac{b_{\text{males}} - b_{\text{females}}}{\sqrt{SE_{\text{males}}^2 + SE_{\text{females}}^2 - 2r \cdot SE_{\text{males}} \cdot SE_{\text{females}}}}$$

137

138 where b is the estimated effect of the genetic variant considered for a given trait for males and
139 females, SE is the standard error of the effect, and r is the Spearman rank correlation between the
140 sexes across all genetic variants for a given trait. Both the SE and b were adjusted by the standard
141 deviation of the trait, for each sex, to correct for scale effects that could act as confounders in the
142 study. Some studies have opted to ignore the third term in the denominator, which estimates the
143 covariance of the error terms, assuming r to be equal to 0⁶. However, for the traits considered this
144 correlation ranged from -0.00335 (cervical spondylosis) to 0.34173 (standing height), thus our
145 decision to include it.

146

147 As this test was done for all variants and all phenotypes, this effort resulted in a total of 4,808,558,030
148 statistical tests (9,072,751 x 530). Binary traits were then filtered further as stated in the Genotypes
149 section. To account for multiple testing, we considered the commonly used genome wide significance
150 cut-off of $p < 1 \times 10^{-8}$.

151

152 In order to cluster our results into independent lead variants, we used the `--clump` option in PLINK 1.9⁵³.
153 For each individual trait, variants found to be genome-wide significant with regards to difference
154 between the sexes were clustered into lead variants, assigning them variants in LD within 10Mb, with
155 an $r^2 > 0.2$ with the lead variant. To obtain the total number of independent loci across all traits, the
156 same clustering method was used but for all variants found to be leads across traits, choosing the
157 variant with the lowest p -value if variants were found in more than one trait.

158

159 **Analysis checks**

160

161 Our replication/sanity check methods can be divided into technical (different models, sex
162 randomization, logistic mixed models using REGENIE³⁵, simulations of effect of case-control
163 imbalance on heritability estimates) and biological (comparison to the GIANT cohort). Detailed
164 information and results of these analyses can be found in the Supplementary Note.

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166 **Calculation of Polygenic Scores (PGS)**

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168 Using the subset of unrelated White British individuals from UK Biobank, we calculated PGS for our
169 traits with most evidence of GxS found using our lead sdSNPs.

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PGS are calculated as:

$$PGS_i = \sum_j^n b_j \cdot dosage_{ij}$$

Where PGS_i is the polygenic risk score estimate for individual i , b_j is the genetic effect estimate for variant j , $dosage_{ij}$ is the effect allele count (0, 1 or 2) of variant j in individual i , and n is the total number of genetic variants considered in the PGS calculation (here just the lead sdSNPs).

The genetic effects used in our PGS calculations were obtained re-running our original model using UK Biobank's unrelated White British participants, randomly selecting 150,000 women to obtain female specific genetic effects, 150,000 males to obtain male specific genetic effects, and 75,000 men and 75,000 females to obtain sex-agnostic genetic effects. This was done to match sample sizes.

We then proceeded to calculate PGS for a total of 34,928 females and 8,956 males from UK Biobank and which were self-reported white European, which had not been considered in the calculation of the genetic effects. We did this in three ways: using the genetic effects corresponding to the sex of the individual (*same* PGS), using the genetic effects corresponding to the opposite sex of the individual (*opposite* PGS) and using the genetic effects for the whole population (*agnostic* PGS). Thus, in total each of our circa 44K individuals had 3 PGS calculated.

In order to assess predictive power, the phenotypes of our 44K individuals (corrected by all the covariates in our original model to account for population structure and other effects) were then either regressed on the *same*, *opposite* and *agnostic* PGSs respectively in the case of non-binary traits, and in the case of binary traits the area under the curve (AUC) was calculated for the ROC curve for the three PGS groups. Statistical significance of AUCs was assessed using the two-tailed Mann Whitney U test⁵⁴. To assess differences between PGS-phenotype correlations, these were transformed using Fisher's Z transformation⁵⁵, and then compared using the resulting Z scores (two-tailed Z test). AUCs were compared using the `roc.test` function from the `pROC` R-package⁵⁶. Correlation, AUC and comparison statistics and p -values are reported in Supplementary Table 11.

An important caveat of this methodology is that there is an overlap between the discovery (the population used to declare variants as sexually different) and the replication (for which genetic effects were re-calculated and/or PGS were obtained) populations. As a way of checking whether the overlap could potentially be influencing our results, we repeated this step by obtaining the genetic effects for the circa 408K individuals of White British ethnicity in UK Biobank, repeating the steps described in the "Sex differences in genetic effects" section, to establish genetic effect differences across the genome. Then we calculated the different PGSs for the remaining circa 42K individuals of white ethnicity, again regressing on the phenotype, for our most representative trait: waist-hip circumference ratio. This, however, only serves as a validation for a single trait, meaning that caution should be taken when interpreting the predictive power of the PGSs calculated.

Heritability explained by sdSNPs

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In order to put our prediction analysis into context, we obtained the proportion of sex-specific heritability explained by the sex-specific genetic effect estimates of the sdSNPs found for each trait. To do this, for each trait with i sdSNPs, the heritability of sdSNPs was calculated, for males and females separately, as

$$h_{\text{sdSNP}}^2 = \frac{\sum_i 2p_i(1 - p_i)b_i^2}{\sigma_g^2 + \sigma_e^2}$$

where b is the sex-specific genetic effect for each of the i lead sdSNPs for a given trait, p is the frequency of the reference allele, and σ_g^2 and σ_e^2 are the sex-specific genetic and residual variance estimates for each trait respectively. The proportion of the sex-specific heritability explained by sdSNPs was then calculated for each sex as h_{sdSNP}^2 / h^2 .

Masking analysis

To evaluate potential masking across traits in the UK Biobank, we compared the results from sex-stratified models to those from a non-stratified model, across the 530 traits in our study. Genetic effects across the genome were assessed for significant association in males and females, and were deemed to be potentially masked if significance was reached in either at a $p < 1 \times 10^{-8}$ threshold, but not in a sex-agnostic model. 209 traits were found to have at least one potentially masked genetic variant, with a total of 127/446 (28.48%) binary and 82/84 (97.62%) non-binary traits (Supplementary Table 13).

We also performed this analysis by LD-clumping the results from our sex-stratified models prior to assessing significance in a sex-agnostic model across traits in order to account for the effects of random fluctuation (Supplementary Table 14). Using this methodology, a total of 176 traits, 98/446 (21.97%) binary and 78/84 (92.86%) non-binary, were found to present at least one potentially masked genetic variant. While we found a high correlation with our original results ($r = 0.96$, $p = 4.59 \times 10^{-299}$, Supplementary Table 14, Figure S8), numbers of potentially masked variants found decreased by around half for each trait (regression slope = 0.49, Figure S8). To be conservative, these are the results considered in the main text.

Gene level analysis

We performed a gene-level analysis to translate our SNP data into a more manageable and interpretable form. This was done for the subset of traits that presented at least one sdSNP for a total of 103 traits.

As we wanted to obtain genes relevant to each of the sexes, we began by partitioning our two-tailed p -values (p_{2T}) from the genetic effect (b) comparison between the sexes into two one-tailed p -values. For genetic variants where b_F was greater than b_M , one tailed p -values were calculated as:

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$$p_F = \frac{p_{2T}}{2} \text{ and } p_M = 1 - \left(\frac{p_{2T}}{2}\right)$$

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257 On the other hand, when the genetic effect was greater in males, the p -values were calculated as

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259
$$p_M = \frac{p_{2T}}{2} \text{ and } p_F = 1 - \left(\frac{p_{2T}}{2}\right).$$

260

261 This process led to the creation of two additional distinct sets of p -values for each phenotype,
262 corresponding to sites where the genetic effect was significantly greater in males or females.

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264 Each of these sets of p -values (p_{2T} , p_M and p_F) was subsequently used to identify gene level associations
265 using MAGMA⁵⁷. First, we annotated every gene (i.e. defined which SNPs were in the gene region)
266 considering a range of 1kb upstream and downstream. MAGMA was then run for each phenotype and
267 each set of one tailed p -values separately, considering two distinct SNP-wise models (SNP mean and
268 top SNP), using a random sample of 1,000 unrelated white British individuals from the UK Biobank, 500
269 males and 500 females, as a base population for LD and MAF correction. The analysis provides three
270 distinct p -values for each gene, one for the SNP mean model, one for the SNP top model, and a
271 combined p -value. For subsequent analyses, we considered the combined p -value for each gene.
272 Genes were declared significantly dimorphic and female or male dominant if an FDR corrected
273 combined p -value (q) < 0.01 was obtained when considering p_F or p_M respectively.

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275 The set of genes that reached our threshold were then used in the gene set and enrichment analyses
276 using the GENE2FUNC tool in FUMA⁵⁸. The GENE2FUNC tool in FUMA was run for the top 10 traits with
277 the largest number of significant genes when considering a two-tailed p -value. As a result, FUMA was
278 run for 10 traits for both male and female dominant genes.

279

280 Briefly, FUMA takes our list of candidate genes and checks for enrichment across: (1) differentially
281 expressed genes (DEG) for different tissues (tissue enrichment analysis was conducted considering
282 the GTEx V6 database⁵⁹), and (2) biological pathways/functional categories (considering MSigDB v7,
283 WikiPathways and GWAS Catalog⁶⁰). Enrichment is assessed using a hypergeometric test. In this study
284 we have focused on just biological pathways/functional categories. Significantly differentially
285 enriched gene sets between female and male dominant genes were assessed using a Fisher's exact
286 test, and p -values were FDR corrected.

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288 As a background, the same procedure as is described in this section was followed using sex-agnostic
289 GWAS results for the 10 traits of interest. Using MAGMA, genes associated to each of the traits were
290 obtained, and sets enriched for genes associated to each trait were obtained using FUMA. Significantly
291 differentially enriched gene sets between our background and our female and male dominant genes
292 were obtained using a Fisher's exact test, and p -values were FDR corrected.

293

294 Heatmaps of the scaled $-\log_{10} q$ -values per set were created for each phenotype and sex. Heatmaps
295 for gene sets were limited to those both significantly differentially enriched in at least one sex versus
296 our background (Fisher's exact test $q < 0.05$), as well as significantly differently enriched between
297 female and male dominant genes (Fisher exact test $q < 0.05$).

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299 **GTEx data**

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301 In order to assess whether differences in genetic architecture, as established by our analysis of the
302 UK Biobank data, lead to differences in gene expression, we proceeded to complete an expression
303 quantitative trait loci (eQTL) analysis looking for GxS interactions in gene expression. The data from
304 the Genotype-Tissue Expression Project (GTEx) V6p release was used, which consists of samples and
305 genotypes from 449 human donors (292 males and 158 females) and 39 non-sex specific and non-
306 diseased tissue types. Each tissue type holds a different number of samples (minimum of 70, median
307 of 149), with a male-bias present in all of them (the percentage of female samples ranging from 25% to
308 44%).

309

310 Processed, filtered and normalized RNA-seq data was downloaded from the GTEx portal for both the
311 autosomal genome as well as for the X chromosome, the number of transcripts varying across tissues
312 due to tissue-specific expression, with a median of 23,538 autosomal transcripts and 793 X-linked
313 transcripts per tissue. Covariates were also downloaded for each of the considered tissues. Further
314 information regarding the treatment of the data can be found in the GTEx v6p analysis methods
315 documentation. Genotype data was also obtained for all the donors from dbGaP, and which included a
316 total of 11,607,846 genetic variants, from genotyping efforts with Illumina OMNI 5M and 2.5M SNP
317 Arrays and imputation from the 1000 Genomes Project Phase I version 3 reference panel. For more
318 information regarding the processing of the genotype data see the GTEx v6p analysis methods
319 documentation.

320

321 **eQTL analysis**

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323 To assess whether our sdSNPs had different effects on the expression of nearby genes depending on
324 sex, we assigned our lead sdSNPs nearby genes (1Mb window) using *Granges*⁶¹ and the Biomart
325 resource⁶². The total number of sdSNP-gene pairs were 6,591 when considering our autosomal hits for
326 non-binary traits, 4,533 when considering our autosomal hits for binary traits, and 95 when
327 considering our X-chromosome hits for non-binary traits.

328

329 For each of the 39 tissues, we tested for GxS in gene expression for each variant-gene pair using a
330 linear regression model in PLINK 1.9, which was adjusted for three genotyping principal components
331 (PCs) and PEER factors, the number of which included in the model depended on the sample size
332 (sample sizes < 150 had 15 PEER factors, sample sizes between 150 and 250 had 30 PEER factors, and
333 sample sizes over 250 had 35 PEER factors), as indicated in ⁶³. In the end, our gene expression model
334 for each gene within 1Mb of a sexually dimorphic variant, and each tissue was formulated as

335

$$336 \quad y = \mu + \beta_1 \cdot \text{sex} + \beta_2 \cdot \text{SNP} + \beta_3 \cdot \text{SNP} \cdot \text{sex} + \text{PC}_{1-3} + \text{PEER} + \epsilon$$

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338 where y is the gene expression of the given gene in a given tissue, μ is the mean expression levels, β_1
339 and β_2 are the regression coefficients for sex and genotype of the sexually dimorphic variant
340 respectively, β_3 is the regression coefficient for the interaction of the genotype with sex, PC_{1-3} and PEER

341 are the principal components and PEER factor covariates, and ϵ is the residual. FDR correction was
342 applied to account for multiple testing.

343

344 When running our eQTL analysis we found that two tissues returned missing values across all tests
345 performed with PLINK, the brain anterior cingulate cortex BA24 and the small intestine terminal ileum
346 tissues. These are the two tissues with the smallest number of samples, therefore this absence of
347 results is likely due to not enough variation being present in the phenotype.

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349 **eQTL enrichment**

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351 To assess whether our sexually dimorphic genetic variants were enriched for GxS interactions versus
352 those not presenting sex differences, we proceeded to re-run our eQTL model using genetic variants
353 significant for the whole population ($p < 1 \times 10^{-8}$) but that had no evidence of being sexually dimorphic
354 (t-statistic comparing genetic effects between the sexes with $p > 0.5$). Using contingency tables and
355 Fisher's exact test, we considered whether the number of significant variant-gene GxS terms (at a $p <$
356 1×10^{-3} threshold) was enriched for our sexually dimorphic variants for each of the tissues.

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358 **DATA AVAILABILITY**

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360 This research has been conducted using the UK Biobank Resource under project 788. Data from the
361 Genotype Tissue Expression (GTEx) project V6p release was also employed, protected genotype data
362 accessed via dbGaP, and processed gene expression data downloaded from the GTEx portal, which is
363 openly available: <https://gtexportal.org>. The GIANT cohort's summary statistics were employed to
364 compare findings to (openly available: <https://portals.broadinstitute.org/collaboration/giant/>), as well
365 as Pulit et al's (Human Molecular Genetics, 2019) summary statistics pertaining to a GIANT-UKB meta-
366 analysis (openly available: <https://github.com/lindgrengroup/fatdistnGWAS>). The authors declare that
367 the data supporting the findings of this study are available within the paper and its supplementary
368 information files. The GWAS summary statistics of both autosomal and X-chromosome variants from
369 sex-stratified models are openly available from the University of Edinburgh DataShare repository
370 within the following collection: <https://datashare.ed.ac.uk/handle/10283/3908> (clinical binary traits
371 DOI: 10.7488/ds/3046, non-clinical binary traits DOI: 10.7488/ds/3047, non-binary traits:
372 10.7488/ds/3048, and logistic mixed model results DOI: 10.7488/ds/3049).

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374 **CODE AVAILABILITY**

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376 We used DISSECT (v1.15.2c, May 24, 2018), which is publicly available at <http://www.dissect.ed.ac.uk/>
377 under GNU Lesser General Public License v3), PLINK (v1.9 and v2.0, freely available online at
378 <https://www.cog-genomics.org/plink2/>), BGENIX (v1.0 freely available online at
379 <https://bitbucket.org/gavinband/bgen>), LD Score Regression (v.1.0.1, freely available online at
380 <https://github.com/bulik/ldsc>), MAGMA (v1.06, freely available online at
381 <https://ctg.cncr.nl/software/magma>), FUMA (freely available online at <https://fuma.ctglab.nl/>), GCTA
382 (v. 1.91.4, freely available at <https://cnsgenomics.com/software/gcta/>) and REGENIE (v.1.0.7, freely
383 available online at <https://github.com/rgcgithub/regenie/tree/v1.0.7-latest>). Custom code created to

384 perform the analysis is openly available (<https://zenodo.org/record/4844680>), with DOI:
385 10.5281/zenodo.4844680.

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