Amplification is the Primary Mode of Gene-by-Sex Interaction in Complex Human Traits

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# Abstract

Sexual dimorphism is observed in many complex traits and diseases and is suspected to be in large part due to widespread gene-by-sex interactions (GxSex). To date, empirical evidence for GxSex in GWAS data has been underwhelming. We hypothesized that GxSex may be pervasive, but largely missed by current approaches, because it acts primarily through sex differences in the magnitude of many genetic effects (“amplification”), regulated by a shared cue such as a sex hormone, rather than differences in the identity of causal variants or the direction of their effect (“correlation”). To test this hypothesis, we inferred the genetic covariance structure between males and females across 27 traits in the UK Biobank, and decoupled GxSex signals into correlation and amplification. Across traits, amplification was a more pervasive mode of GxSex; for example, we estimate that 38% of causal variants have a greater effect on urate levels in females than males. In addition, we investigated whether testosterone levels, a continuous measure, may underlie the observed mediation by binary biological sex. For some traits, notably in body-mass-related traits, testosterone levels are associated with the magnitude of genetic effects in both males and females—but the association is different in magnitude and sign between the sexes. Finally, we developed a novel test of sexually-antagonistic viability selection linking GxSex signals and allele frequency divergence between males and females. Using independent allele frequency data from both Finnish and Ashkenazi-Jewish samples, we find subtle evidence for contemporary sexually-antagonistic selection on variants associated with several body-mass-related traits. In summary, our results suggest that the systematic amplification of genetic effects is a primary mode of GxSex that is germane for understanding the genetics and evolution of sexual dimorphism.

# Introduction

Genetic effects are not exerted in a vacuum, but in environments that mediate them. Several lines of evidence suggest large context dependency of genetic effects on polygenic (complex) human traits (Ge et al., 2017; Helgeland et al., 2022; Mostafavi et al., 2020; Patel et al., 2021; Young et al., 2019). At the same time, unlike studies in organisms and systems where the environment can be tractably manipulated (des Marais et al., 2013; Falconer & Mackay, 1996; Huang, Campbell, et al., 2020; Huang, Carbone, et al., 2020; Hudson et al., 2022; Long et al., 2013; Lynch & Walsh, 1998; MacQueen et al., 2021), there are but a few cases in which GxE models explain data—such as Genome-Wide Association Study (GWAS) data—better than parsimonious models that assume independent contributions of genetic and environmental factors (Duncan et al., 2019; Mars et al., 2020; Mostafavi et al., 2020; Patel et al., 2021; Young et al., 2018). This duality may point to a pervasive mediation of polygenic effects by the environment—alongside the inability of our current toolbox to quantify polygenic GxE (M. Mills et al., 2020; Nagpal et al., 2022; Wolak et al., 2015).

Perhaps nowhere is this duality more apparent than in the case of gene-by-sex interaction (GxSex). Sexual dimorphism is observed in many complex traits and diseases and is suspected to be in large part due to widespread GxSex involving autosomal loci (Arnqvist & Rowe, 2005; van Doorn, 2009). Sex differences in polygenic effects on traits are clearly of high importance for healthcare (Harper et al., 2021; Mokkonen & Crespi, 2015; Oliva et al., 2020; Power et al., 2013; Schroderus et al., 2010), evolution (Barson et al., 2015; Cheng & Kirkpatrick, 2016; Connallon et al., 2010; Harrison et al., 2015; Kidwell et al., 1977) and other areas in biology. But with the exception of testosterone levels (Bernabeu et al., 2021; Carole Hooven, 2021; Flynn et al., 2021; Sinnott-Armstrong et al., 2021), the genetic basis of sexual dimorphism is not well-understood (Oliva et al., 2020). To date, empirical evidence for GxSex in GWAS data—with attempts focused on identifying large GxSex effects in individual loci, or instead, with a polygenic prism, imperfect genetic correlations between the sexes—have been underwhelming.

Sex as an “environment” variable offers a methodological advantage as well. The study of context-dependency is often complicated by study participation biases, leading to genetic ancestry structure that confounds genotype-phenotype associations (Benonisdottir & Kong, 2022; Berg et al., 2019; Sohail et al., 2019; Young et al., 2019), reverse causality between the phenotype and environment variable, collider bias, gene-by-environment correlation and other problems (Coop, 2019; Coop & Przeworski, 2022; M. C. Mills & Tropf, 2020). In this sense, sex provides a useful case study for context-dependency: Reverse causality and other such “usual suspects” problems involving the phenotype causally affecting sex, are unlikely; and sex differences in ancestry composition due to study participation biases are small (Benonisdottir & Kong, 2022) (though detectable (Pirastu et al., 2021)).

In this work, we set to characterize GxSex across complex human traits. We begin by suggesting a mode of GxSex that may have gone largely undetected by previous studies: A systematic difference in the magnitude of many genetic effects, which we refer to as “amplification”. Amplification can happen for a large set of variants regulating a specific pathway if the pathway responds to a shared cue. In classic hypothesis testing approaches that test for a GxE effect separately in each variant, the signal of amplification may be crushed under the multiple hypothesis burden. On the other hand, even state-of-the-art tools designed with complex traits in mind may miss amplification signals: They often treat genetic correlation (between GWAS estimates based on samples from two environments) as a telltale of whether effects are the same in two groups (B. C. Brown et al., 2016; Bulik-Sullivan, Finucane, et al., 2015; Galinsky et al., 2019; Ni et al., 2018; Shi et al., 2017); but correlations are scaleless and thus amplification signals could be missed entirely.  To quantify the role of genetic amplification in sex differences, we developed a new approach for flexibly characterizing a mixture of male-female genetic covariance relationships, and applied it to 27 traits in the UK Biobank. We conclude that amplification is pervasive across traits, and that it is the primary mode of GxSex. We find evidence that modulators of the size of effects, or amplifiers, are shared among environmental and polygenic effects, and that together, such amplification effects help explain phenotypic sexual dimorphism. Finally, we consider an implication of pervasive amplification for sexually-antagonistic selection: many variants may be plausibly subject to sexually antagonistic selection when trait optima are very distinct—and surprisingly, even if they are very similar—for males and females. We develop a novel test for sexually-antagonistic polygenic selection, which connects GxSex signals—including amplification—to signals of contemporary viability selection. Using this test, we find subtle evidence of sexually-antagonistic selection on variation associated with body-mass-related traits.

# Results

The limited scope of single-locus analysis. We conducted GWASs stratified by sex chromosome karyotype for 27 continuous traits in the UKB using a sample of ~150K individuals with two X chromosomes and another sample of ~150K individuals with XY. While there is not a strict one-to-one relationship between sex chromosome karyotype and biological sex, we label XX individuals as females and XY individuals as males, and view these labels as capturing group differences in environments—not a dichotomy. We chose to analyze traits with SNP heritabilities over 7.5% in the combined sample of both females and males, to allow for high statistical power.

Among the 27 traits, we observed substantial discordance between males and females in associations with the trait only for testosterone and waist:hip ratio (whether or not it was adjusted for BMI; REFX **Fig. S1**). For testosterone, as noted in previous analyses, genes neighboring sex-specific associations often partake in separate pathways in males and females (Flynn et al., 2021; Sinnott-Armstrong et al., 2021). This is reflected in the small overlap of top associations in our GWAS. For example, in females, CYP3A7 partakes in the hydroxylation of testosterone, resulting in its inactivation. In males, FKBP4 plays a role in the downstream signaling of testosterone on the hypothalamus (**Fig. 1A**).

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**Figure 1: Inferring polygenic covariance structure between males and females. (A)** Our analysis of the polygenic covariance between males and females is based on sex-stratified GWAS. Shown for illustration, is a “Miami plot” for testosterone. Highly-associated SNPs were annotated with the gene with the closest transcription start site less than 5 kbp away.  **(B)** We modelled the sex-stratified GWAS estimates as sampled, with error, from true effects arising from a mixture of hypothesized covariance relationships between female and male genetic effects; see examples in red frames. Each box shows the weight (± SE) we infer for one hypothesis matrix, corresponding to the probability that a variant’s effects adhere to that covariance relationship. The boxes are shown along axes indicating the relative magnitude (amplification) and correlation between males and females, which together fully specify the covariance relationship.  **(C)** The x and y axis are a condensed version of the x and y axes from (B) for testosterone, as well as the condensed version for diastolic blood pressure. The weights are the percentage of non-null weights, i.e. the weight divided by the sum of all weights except for the weight on the all-zeros matrix corresponding to no effect in either sex. For example, the square in purple sums over all 12 weights for matrices corresponding to larger effects on testosterone in males that are negatively correlated with effects in females, 5.1%, divided by the total weight on matrices with nonzero effects, 32%.

For waist:hip ratio, we saw multiple genes associated with females only, such as ADAMTS9, a gene involved in insulin sensitivity (Lumish et al., 2020). As previous work established (Bernabeu et al., 2021; Flynn et al., 2021; Sinnott-Armstrong et al., 2021), testosterone and waist:hip ratio are the exception, not the rule: Most traits did not display many sex differences in top associations. For instance, arm fat-free mass, a highly heritable dimorphic trait, showed near-perfect concordance in significant loci (**Fig. S1**). Previous studies (Bernabeu et al., 2021) examining top SNPs between males and females have found few uniquely-associated SNPs (<20) across the 84 continuous traits they studied apart from waist:hip ratio. Considering overwhelming evidence on the vast polygenicity of additive genetic variation affecting complex traits (Boyle et al., 2017; Sella & Barton, 2019; Shi et al., 2016), it stands to reason that a look beyond lead associations, through a polygenic prism, can aid in the characterization of non-additive effects (such as GxSex) as well.

The limited scope of analyzing GxSex via heritability differences and genetic correlations. We therefore turned to consider the polygenic nature of GxSex; first, by employing commonly-used approaches. We used LD Score Regression (LDSC) (Bulik-Sullivan, Finucane, et al., 2015; Bulik-Sullivan, Loh, et al., 2015) to estimate sex-specific SNP heritabilities and the genetic correlation between the sexes for each trait. In most traits (17/27), males and females had a genetic correlation greater than 0.9. Testosterone had the lowest genetic correlation of 0.01, which suggests very little sharing of signals between males and females.

For the majority of traits (18/27), male and female heritabilities were both greater than the heritability in a sample that included both sexes. For instance, in arm-fat free mass (right), the heritability in the both-sex sample was 0.232 (± 0.009), while the heritabilities for male and female were 0.279 (± 0.012) and 0.255 (± 0.011), respectively. In particular, all body mass-related traits, excluding BMI-adjusted waist:hip ratio, had greater sex-specific heritabilities.

Application

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**Table 1. Polygenic Models of GxSex.** We examine different models of the nature of GxSex in complex traits that link to previous studies and motivations. Each model leads to different expectations from the analysis of heritability and genetic correlations (**Fig. 2**). The illustration depicts examples of directions and magnitudes of genetic effects as described by the model. , and denote narrow-sense heritabilities in males, females and a combined sample, respectively.

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**Figure 2: Heritabilities and Genetic Correlations Cannot Fully Distinguish Models of GxSex.** **(A)** Genetic correlations between the male and females, estimated using bi-variate LD Score Regression, are shown in descending order. **(B)** The x-axis represents the relative heritability, i.e. the SNP heritability divided by the SNP heritability estimated in the both-sex sample. Therefore, the purple values, indicating relative both-sex heritability all fall on the 1 line. Traits marked with red asterisks indicate body-mass related traits with greater sex-specific than both-sex heritabilities.

In addition, we noticed a trend in which as genetic correlation decreased, the difference between the heritabilities within each sex relative to the both-sex heritability tended to increase (Pearson r = -0.88, paired t-test p = 10-10, **Fig. 2**). However, several traits with genetic correlation above 0.9, such as diastolic blood pressure and arm fat free mass (left), also present relatively large heritability sex differences of 5.2% (two-sample z-test p=) and 3.4% (two-sample z-test p = 0.04), respectively. Such discrepancies are incompatible with a model of pervasive uncorrelated genetic effects driving sex-specific genetic contributions to variation in the trait (**Table 1**, second model). We therefore considered two other alternative hypotheses under a simple additive model of variance in a trait within each sex,

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where represent the trait value, additive effect, and environmental effect (including all non-genetic context aside from sex) in sex , respectively. Under this model, the sex-specific heritability is

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and therefore, sex differences in heritability may be due to sex differences in genetic variance, environmental variance, or a combination of the two. If genetic effects are similar, differences in environmental variance alone may explain heritability differences entirely (**Table 1**, first model). But as we show in the **Methods** section, under such a model, the heritability in the combined sample cannot be smaller than both sex-specific heritabilities.

Therefore, the observation of higher sex-specific heritabilities for most traits suggests that the genetic variance must differ between males and females. Given the random segregation of autosomal alleles independently of an individual’s sex chromosomes, and assuming, further, that there is little-to-no interaction of sex and genotype affecting participation in the UKB (Benonisdottir & Kong, 2022), UKB allele frequencies in males and females are expected to be very similar and thus this suggests that causal genetic effects differ between males and females for most traits we analyzed.

A less appreciated possibility for pervasive GxSex is that the identity and direction of effects may often be shared (leading to high genetic correlation), but there are nonetheless pervasive differences in the magnitude of genetic effects—e.g., systematically larger genetic effects on blood pressure in females—which in turn lead to large differences in genetic variance (**Table 1**, third model). To evaluate the evidence for systematic amplification and compare it with evidence for uncorrelated effects as a main mechanism of GxSex, we next set to infer the genome-wide covariance of genetic effects among the sexes.

Amplification of genetic effects is the primary mode of GxSex. We jointly assessed amplification and correlation of genetic effects between males and females using multivariate adaptive shrinkage (*mash*) (Urbut et al., 2019), a tool that allows the inference of genome wide frequencies of genetic covariance relationships (**Table 1**, fourth model). Namely, we model marginal SNP effects as sampled (with SNP-specific, sex-specific noise) from a mixture of zero-centered Normals with various covariance relationships (2x2 Variance-Covariance matrices for male and female effects). We pre-composed hypothesis covariance matrices that span a wide array of amplification and correlation relationships, and use *mash* to estimate the mixture weights. These weights can be roughly interpreted as the proportion of variants that follow the pattern specified by the covariance matrix (**Fig. 1B, C**). Our hypothesis covariance matrices ranged from -1 to 1 in correlation, and 9 levels of male greater, female greater, and equal magnitude. We also included a matrix representing no effect in either sex (**Fig. 1B**).

We first examined testosterone as a positive control, in the sense that previous research sets our expectation for polygenic male-female covariance: In terms of magnitude, the vast majority of effects should have much greater effect in males. In terms of correlation, we expect a class of genetic effects acting through largely independent and uncorrelated pathways alongside a class of effects through shared pathways (Sinnott-Armstrong et al., 2021). Independent pathways include the role of hypothalamic-pituitary-gonadal axis in male testosterone regulation and the contrasting role of the adrenal gland in female testosterone production. Shared pathways were found to involve sex hormone-binding globulin (SHBG), which decreases the amount of bioavailable testosterone in both males and females. Indeed, we found that mixture weights for testosterone concentrated on greater magnitudes in males and largely uncorrelated effects. Out of the 32% total weights on matrices with an effect in at least one sex, 98% of the weights were placed on matrices representing larger effects in males, including 20.4% (± 0.7%) having no effect in females (**Fig. 1B**).

While testosterone is unusual in the relative lack of correlation and the extent of male lob-sided amplification, about half (13/27) of the traits analyzed had the majority of weights placed on either female-greater or male-greater magnitudes (**Fig. 3**). For instance, BMI-adjusted waist:hip ratio displayed higher percentages for greater effects in females (64%; **Fig. S3AA**) and arm fat-free mass (right) showed higher percentages of greater effects in males (92%; **Fig. S3C**). Both traits had weights concentrated on highly correlated effects.

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**Figure 3. Phenotypic variance strongly correlates with amplification.** The x-axis represents the amplification of polygenic effects, and is calculated by taking the difference between the sum of weights on matrices with male effects greater in magnitude than female effects (M>F) and sum of weights of M<F matrices. The solid gray line depicts the linear regression of the phenotypic variance ratio on amplification of polygenic effects.

In addition, none of the 27 traits we studied had more than 10% of the non-zero weights on matrices with negative correlation, save for testosterone, which had 17%. Most weights were rather on perfect or high positive correlation matrices. For example, diastolic blood pressure and eosinophil percentage had 66% (**Fig. 1C**) and 68%, respectively, of the non-zero weights on matrices representing perfect correlation. Overall, the low weights on matrices representing negative correlation do not support opposite directions of effects being a major mode of GxSex (**Fig. S7**).

We also found that, across traits, the difference between male and female amplification weights correlates strongly with male-to-female phenotypic variance ratio (Pearson r = 0.873, p = 610-9 after removing testosterone as an outlier; **Fig. 3**). This observation is consistent with our hypothesis of amplification GxSex leading to differences in genetic variance and thereby contributing substantially to sex differences in phenotypic variance. Together, these observations point to amplification, rather than uncorrelated effects, as a primary mode of polygenic GxSex.

Low utility of sex-specific models for complex phenotype prediction. The pervasiveness of GxSex that we infer, alongside the plurality of covariance relationships across the genome for each trait, may mean that GxSex is important to consider in phenotypic prediction. To test this possibility, we compared the prediction accuracy of three polygenic scores (PGS) for various traits, together with covariates (**Fig. 4; Methods**):

1. Additive PGS, assuming no GxSex
2. Sex-specific, but M-F covariance-naïve PGS: Based on stratified GWAS independently for each sex.
3. Sex-specific, covariance-aware: Using *mash*, we refine marginal SNP effect estimated, by modelling them as sampled from the mixture of covariance metrices with the weights we estimated previously (**Methods**).

Timeline

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**Figure 4. The predictive utility of G-by-Sex aware polygenic scores.** We compare the incremental squared correlation (incremental R2) of the phenotypic values and a predictor for three predictors. Incremental R2 is obtained by taking the difference in R2 between a prediction with covariates and the polygenic score and a prediction with only covariates. For each of the three models, we choose the highest incremental R2 across four p-value thresholds (Methods). The additive (red) and sex-specific, covariance-naïve (yellow) models were calculated from effect estimates generated in GWAS, with the latter in sex-stratified samples. The sex-specific, covariance aware model (blue) refers to a polygenic score constructed using mash posterior effect estimates, which considers the covariance in genetic effects between the sexes. Sex-specific models contained a median sample size of around 123k males and 147k females, whereas the additive model retained the full training set of around 271k individuals. Incremental R2 values and ±3 SE-wide error bars were computed using 5-fold cross-validation.

In almost all cases (25/27), the sex-specific, covariance-naïve PGS model had the lowest predictive power—measured as the squared correlation between the predictor () and trait value. For some traits, like testosterone, height, arm fat-free mass, and hip circumference, the sex-specific covariance-aware PGS outperformed the additive PGS by a slight margin (significant at p < 0.05 level in a two-sample t-test for only height and arm fat-free mass (right)). However, for most traits (22/27), the covariance-aware PGS model did not predict better than the additive model (**Fig. 4**), including a significantly better (two-sample t-test p < 0.05) performance of the additive model in 14 of the 22 traits.

Based on these results, there was little improvement in prediction accuracy even with a detailed consideration of polygenic GxSex. We can hypothesize that the persistent advantage of the additive model is due to the reliance on double the sample size, outweighing the utility of refined, covariance-aware sex-specific effect estimates. We chose not to match sample sizes for the additive model to mimic the competition between prediction models in practice. At this stage, we find little utility for sex-specific models in complex trait prediction; yet it seems plausible that future approaches—that better make up for the loss of accuracy in capturing the additive effect because of higher model complexity—could surpass the performance of additive models.

Testosterone as a regulating factor. Thus far, we treated the genetic interaction we observe as discretely mediated by biological sex. One mechanism that may underlie our observation is a cue or exposure that modulates the magnitude (and less often, the direction) of genetic effects, and varies in its distribution between the sexes. One natural candidate is testosterone. Testosterone may be a key instigator since the hormone is present in distinctive pathways and levels between the sexes, and a known contributor to the development of male secondary characteristics, and therefore could modulate genetic causes on sex-differentiated traits.

For each sex, we first binned individuals by their testosterone levels. Then, for each trait, we quantified the amplification of total genetic effect as the linear regression coefficient, within the bin, of phenotypes to the additive PGS for the trait (**Methods**; see **Fig. S10** for results obtained using sex-specific PGS).

There was a strong correlation between the testosterone (mean per bin) and the magnitude of genetic effect, for both males and females and for multiple traits–especially ones related to body mass (**Fig. 5**). BMI (**Fig. S9**) and whole body fat mass (**Fig. 5A**) showed significant correlations (Pearson p < 0.05) for both sexes. For all the body-mass-related traits, there was a negative correlation between the magnitude of genetic effect and testosterone for males, and a positive correlation for females.  For example, Pearson's correlation coefficient for whole body fat mass in males was -0.86 (Pearson p = 0.001) and 0.76 for females (Pearson p = 0.011). For these traits, since the relationship with testosterone is clearly not continuous across the sexes, a model of testosterone as a continuous underlier of the binary sex mediator would be false. These observations may help explain previous reports of positive correlations between obesity and free testosterone in women, and negative correlations in men (Pasquali, 2006). Therefore, in body-mass related traits, testosterone may be modulating genetic effects in a sexually antagonistic manner.

Additionally, we considered the effect of reverse causation or potential confounders in the association between testosterone and total genetic effect. We performed a mendelian randomization study using the sex-specific PGS for testosterone as the instrumental variable associated with testosterone levels (**Methods**, **Fig. S11**). We found that the results did not neatly replicate findings using testosterone levels (**Fig. 5B**) and all traits apart from weight and BMI-adjusted waist:hip ratio had non-significant correlations. However, this could be possibly due to low power in estimation since PGS may explain a low proportion of testosterone levels.

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**Figure 5. Amplification of total genetic effect in relation to testosterone levels.** **(A)** The relationship between testosterone level bins and genetic effect—measured as the slope from the regression of phenotypic values to polygenic scores in that bin—is depicted for three different traits. The hollow data points signify a testosterone level bin with overlapping range between males and females, and are based on fewer individuals (~800 compared to ~2200 in other bins). **Figs. S9** show all other traits analyzed. **(B)** The correlation coefficient for each sex (90% CI) is plotted for all 27 traits. Traits are ordered in descending order of male-female differences in R.

A model of shared polygenic and environmental amplification. If polygenic amplification is a common mechanism, an immediate question of interest is whether environmental effects are amplified across the sexes via modulators shared with polygenic effects. Consider the example of human skeletal muscle. The impact of resistance exercise varies between males and females. Resistance exercise can be considered as an environmental effect since it upregulates multiple skeletal muscle genes present in both males and females such as IGF-1, which is in turn involved in muscle growth (Liu et al., 2010). However, after resistance exercise at similar intensities, males experienced sustained upregulation of such genes, while in females, levels returned sooner to the resting state (**Fig. S12**). It is plausible that shared modulators, such as sex hormones, drive a difference in the magnitude of effect of core genes such as IGF-1 and thus all its genetic and environmental regulators.

To generalize this intuition into a model: If amplification mechanisms are shared, then the genetic and environmental effect may be modeled as having the same scalar multiplier effect on genetic and environmental effects. Next, we specify the details of a null model of shared amplification, present a prediction that it yields and test this prediction across the 27 traits analyzed.

Consider the within-sex additive model of [**Eq. 1**](#eq1) in the section “The limited scope of analyzing GxSex via heritability differences and genetic correlations” above. For a phenotype value in sex

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where is the environmental effect and

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is the polygenic effect where is the effect of an allele at site (say the minor allele) and  is the number of copies of the allele (Harpak & Przeworski, 2021). We assume here for simplicity that male genetic effects relate to female effects solely through a shared polygenic amplification constant, α,

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Allele frequencies are once again assumed to be close to equal between males and females, since due to random segregation of alleles during meiosis, genotype frequencies at autosomal sites are independent of sex; and further assuming no substantial interaction between genotype and sex affecting participation in UKB (Benonisdottir & Kong, 2022). Consequently, differences in polygenic effect distributions between males and females are solely based on GxSex, and thus:

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The model we would like to test is one where the amplification of environmental effects can also be simplified to the same scalar multiplier,

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| , and  . | (7) |

Hence, with equal amplification,

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|  | (8) |

To test the fit of this theoretical prediction to our data, we used our estimates of sex-specific phenotypic variance and SNP heritabilities to estimate the ratios of genetic and environmental variances (**Methods**). We note that environmental variance is proxied here by all variance not due to additive genetic effects, and caution should be taken with interpretation of this proxy.

20 of the 27 traits were consistent with the null model of equal amplification (within 90% CI; **Fig. 6B**). This may suggest a sharing of pathways between polygenic and environmental effects for these traits (**Fig. 6A**). Interesting exceptions include BMI-adjusted waist:hip ratio, creatinine, arm fat-free mass, and systolic and diastolic blood pressure—which was the strongest outlier (p = 3.06e-12 from one-sample z-test), excluding testosterone.

Chart

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**Figure 6. Testing a model of shared amplification between environmental and polygenic effects**. **(A)** A model of equal amplification of genetic (G) and environmental (E) effect, that produces the dimorphism shown in the phenotype, Y. G and E both act through a core gene that is amplified in a sex-specific manner. **(B)** The blue 1:1 line depicts the theoretical expectation under a simple model of equal amplification of genetic and environmental effects in males compared to females. Error bars show 90% confidence intervals. Traits in blue are consistent (within 90% CI) with the prediction of a 1:1 relationship.

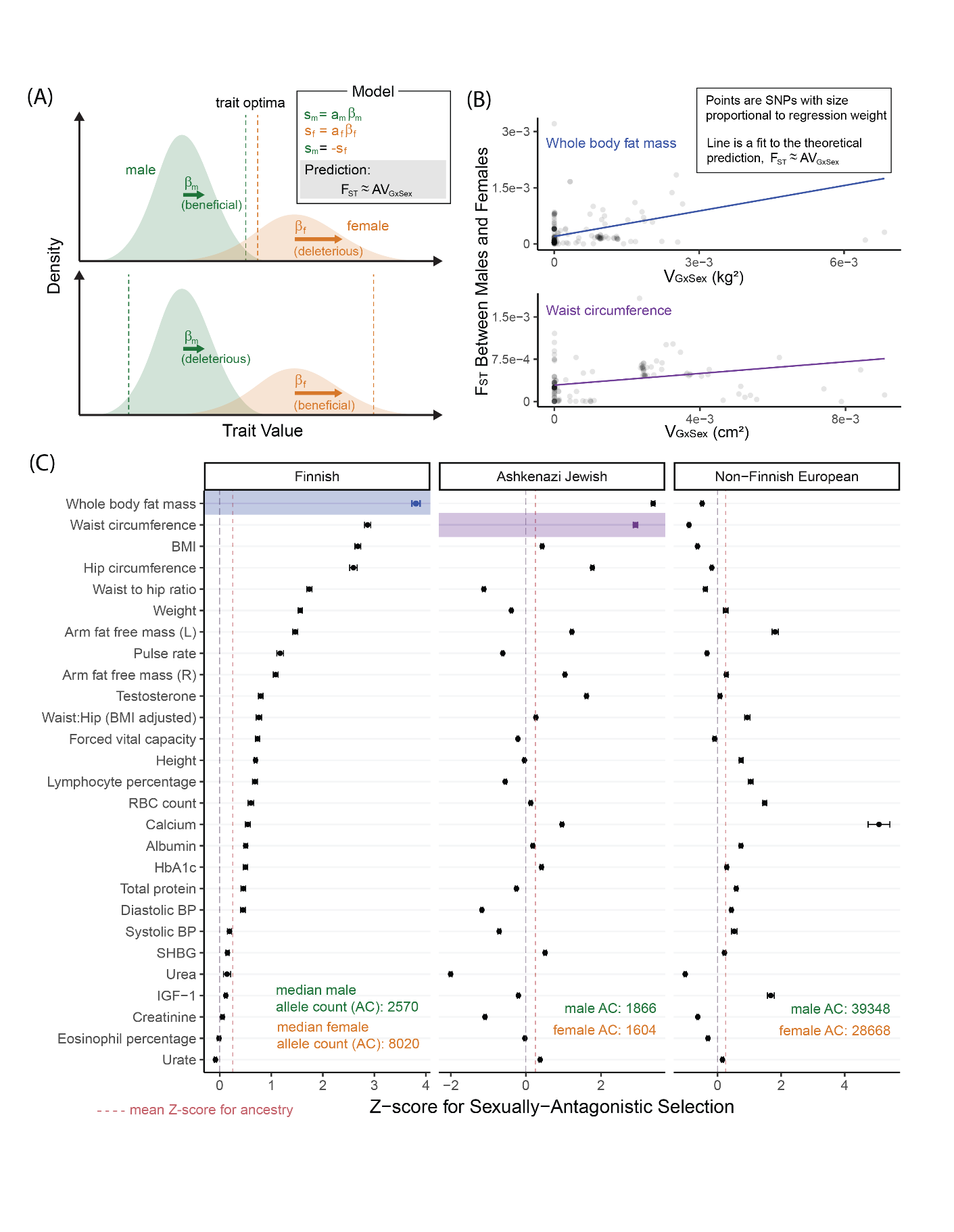
Sexually-antagonistic selection. A hypothesized driver of sexual dimorphism is sexually-antagonistic selection, where some alleles are beneficial in one sex yet deleterious in the other (Cheng & Kirkpatrick, 2016; Connallon et al., 2010; Kasimatis et al., 2021; Kidwell et al., 1977; Ryan, 2020). Sexually-antagonistic selection is difficult to study using traditional population genetics methods because Mendelian inheritance equalizes autosomal allele frequencies between the sexes at conception in each generation, thereby erasing informative signals. One way around this limitation is to examine allele-frequency differences between the sexes in the current generation, known as “selection in real time” (Cheng & Kirkpatrick, 2016; Ruzicka et al., 2020, 2021). In this section, we consider a model of sexually-antagonistic selection acting on a polygenic trait and use it to estimate the strength of contemporary viability selection acting on the 27 traits we analyzed.

Our findings on pervasive amplification suggest that variant effects tend to have concurrent signs, and still set the stage for substantial sexual dimorphism. Taken together, these results suggest the somewhat-surprising intuition that alleles affecting a trait under stabilizing selection may frequently experience sexually antagonistic selection—both in the case where trait optima for males and females are very distinct and for the case that they are similar, as we illustrate in **Fig. 7A**.

We developed a theoretical model of sexually-antagonistic viability selection on a single trait which extends on this intuition. The model ties sex-specific effects on a complex trait and the divergence in allele frequency between males and females (measured as (Weir & Cockerham, 1984; Wright, 1951)) due to viability selection “in real time”, i.e., acting between conception and the age at the time of sampling. We derive the expected relationship for each site ,

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where is the genetic variance due to GxSex at site . is a constant shared across all variants and can therefore be interpreted as the effect of sexually-antagonistic selection on male-female divergence at polymorphic sites associated with variation in that trait (**Methods**). We estimated for all sites across subsamples of various ancestry groups in the gnomAD dataset (Karczewski et al., 2020). To estimate at each site and for each trait, we used our previous sex-stratified GWAS. Since there is large heterogeneity in uncertainty of GxSex-genetic variance estimates, we use a variance-weighted linear regression to estimate A (see **Methods** for the derivation of the variance of estimates and for further details on the estimation procedure.)



**Figure 7. Testing for sexually-antagonistic selection. (A)** A model of sexually-antagonistic selection where selection coefficients, and , are linear with the additive effect on the trait and sexually-antagonistic selection such that . The model yields the prediction of [**Eq. 9**](#eq9)**.** In the top figure, the allele’s effect, on average, drives trait values towards the optimum in males, and away from the optimum in females. In the bottom example, the fitness optima are farther in males and females; In both examples, selection on acts antagonistically (in opposite directions). **(B)** Two examples of the weighted least-squares linear regression preformed to estimate the strength of sexually-antagonistic selection on variants associated with a trait ( in panel A and [**Eq. 9**](#eq9)). **(C)** Z-scores (90% non-parametric CI) estimated through 1000 resampling iterations of the weighted linear regression of panel B for each trait. The two colored estimates match the corresponding examples in panel B.

In two of three gnomAD subsamples that are the closest in their genetic ancestry to our UKB sample (Privé et al., 2022; results for other ancestry groups are shown in **Table. S5**), we find marginally significant evidence for sexually-antagonistic selection on body-mass-related traits: The three highest Z-scores (for the null hypothesis **in** [**Eq. 9**](#eq9)) in the Ashkenazi-Jewish sample are whole-body fat mass (Z=3.4±0.0), waist circumference (Z=2.9±0.1) and hip circumference (Z=1.8±0.0; **Fig. 7C**); for the Finnish samples the three top traits are whole-body fat mass (Z=3.8±0.1), waist circumference (Z=2.9±0.1) and BMI (Z=2.7±0.1; **Fig. 7C**). For Non-Finish Europeans—the largest subsample—these signal of selection on body fat related traits does not replicate and the only trait with significant signal is calcium (Z=5.1±0.3; **Fig. 7C**).

# Discussion

Departing from previous studies identifying GxSex (or GxE more broadly) through single loci or heritability analysis, we examine GxSex through a polygenic lens and modelled it using a mixture of relationships across the genomes. Our analysis supports pervasive context-dependency of genetic effects on complex traits. Not only is GxSex pervasive, but it also largely acts through the systematic amplification of effects, an underappreciated mode of GxE. Surprisingly, even some traits such as red blood cell count, previously considered non-sex-specific because of high genetic correlations a concordance in significantly-associated loci, we find instead substantial GxSex through amplification. The strong relationship between amplification and phenotypic values further suggests amplification plays a primary role in sexual dimorphism. Future efforts localizing amplification in the genome may provide clues to the modulation mechanisms underlying GxSex. Here, we proposed one such modulator, testosterone, and found a strong (but discrepant in the two sexes) correlation between testosterone and polygenic effect on multiple body-mass-related traits such as BMI and whole body fat mass. These results, with polygenic effect increasing in females and decreasing in males with increasing testosterone levels, may reflect the discrepant relationship between testosterone and these traits at the phenotypic level.

With this in consideration, we examined whether amplification due to a modulator also applied to environmental effects. We found that most traits were consistent with a model of equal amplification of polygenic and environmental effects. Co-amplification may point to a shared biological pathway mediated by the same amplifier. We draw intuition from the example with muscle mass, in which the effect of resistance exercise (environmental effect) is amplified in males—along with genetic regulators for muscle mass—by affecting a core gene, IGF-1. Further research into specific biological pathways may provide more concrete understanding of potential amplifiers and the interaction between polygenic and environmental effects.

In our analysis, however, the utility of a refined inference of polygenic GxSex did not carry over to improved predictive ability. Out of our three models—additive; sex-specific, covariance naïve; and sex-specific covariance aware—the additive model still had the highest predictive value for most of the traits. Given that the additive model had approximately twice the sample size (both-sex vs one sex), we hypothesized that at this point, the advantage in accurate estimation of the additive effect is still greater than the benefit of improved estimates of non-additive effect.

Finally, we developed a model implicating GxSex as a possible fuel for sexually-antagonistic selection in contemporary populations. Over long evolutionary timescales, the two scenarios depicted in Fig. 7A lead to different predictions about the maintenance of GxSex genetic variance; distinct optima suggest this variance would be maintained while similar optima act to purge GxSex variance. But interestingly, in both cases alleles may experience sexually-antagonistic selection.

In samples of two of three ancestry groups, we found subtle signals of selection on body-mass-related traits such as whole-body fat mass, BMI, and waist and hip circumference. Body-mass-related traits have been implicated as leading to decreased life expectancy in both males and females (Mostafavi et al., 2017). A recent study also indicated an association between body fat percentage and male-female estimated in the UKB White British sample (Ruzicka et al., 2021). We note that the values we estimated are in an independent (gnomAD) samples, and can therefore be considered as independent evidence. The signal for our inference of selection is adult male-female allele-frequency differences which we presume to be due to modern-day viability selection. These signals may therefore point to a related disease that differentially affects lifespan, such as diabetes, cardiovascular disease, cancers, or hypertension (C. D. Brown et al., 2000; Khan et al., 2018; Ning et al., 2010; Vazquez et al., 2007).

In this work we have shown that amplification of the magnitude of polygenic effects plays a primary role in the genetics and evolution of sexual dimorphism. Our approach included the flexible modelling of effect covariance, as well as various subsequent analyses exploring the implications of the inferred covariance structure. We hope this study can inform for future work on the context-specifity of genetic effects on complex traits.

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# Methods

UK Biobank sample characteristics. The UK Biobank is an extensive database that contains a wide variety of phenotypic and genotypic information of around half a million participants aged 40-69 at recruitment (Bycroft et al., 2018).

In this study, we considered 337,111 individuals who passed quality control (QC) checks, which included the removal of samples identified by the UK Biobank with sex chromosome aneuploidy or self-reported sex differing from sex determined from genotyping analysis. We excluded related individuals (3rd degree relatives or closer) as identified by the UK Biobank in data field 22020. To reduce potential population structure confounding, we further limited our sample to individuals identified by the UK Biobank as “White British” in data field 22006. These are individuals who both self-identified as white and as British and were additionally very tightly clustered in the genetic principal component space (Bycroft et al., 2018; Haworth et al., 2019). Individuals who had withdrawn from the UK Biobank were removed by the time of this study. For each phenotype, we also removed individuals who had missing data for the specified phenotype. These procedures left us with between 255,426 to 336,551 individuals included in the analysis for each trait.

Genotype data. We focused on autosomal bi-allelic SNPs with an INFO score greater than 0.8. Using *plink 2.0 alpha* (Chang et al., 2015; Graffelman & Moreno, 2013; Graffelman & Weir, 2016; Purcell et al., 2007; Purcell & Chang, n.d.; Wigginton et al., 2005), we further retained variants with calling rate > 0.95, Hardy-Weinberg equilibrium test p-value > 10-9, minor allele frequency (MAF) > 0.001 and MAF < 0.999, following a QC procedure used by the Neale Lab on version 2 of UK Biobank (Abbot et al., 2017). These were computed on the aforementioned quality-controlled sample set and resulted in 9,607,691 SNPs.

Phenotype data. Our analysis consisted of 27 continuous traits for their relatively high SNP heritability estimates, based on LD Score regression (Abbot et al., 2017; Bulik-Sullivan, Loh, et al., 2015). BMI-adjusted waist:hip ratio (WHR) was calculated by regressing WHR on BMI and obtaining the residuals, as obtained using the following commands in R:



GWAS. We performed all GWAS using *plink 2.0 alpha*, adjusting for birth year, sex, and the first 10 principal components (PC) provided by the UK Biobank as covariates. Covariates were standardized to mean 0, variance 1 (using the flag --covar-variance-standardize). We generated sex-specific GWAS summary statistics for each trait by separating the sample by males and females and applying the same regression model for each sex independently. Any variants with missing values in the summary statistics were removed from further analysis.

Miami plots. We used the *Ensembl Variant Effect Predictor (VEP)* (McLaren et al., 2016) based on the GRCh38 genome build to annotate SNPs with p < 5x10-8 in Miami plots (**Figs S1**). Using the --nearest flag, we retrieved the gene with the closest protein-coding transcription start site within 5,000 bp up- and down-stream each SNP.

Heritability and genetic correlation estimation using LD Score Regression. We estimated the SNP heritability of each trait for both-sex, female-specific, and male-specific GWAS, as well as the genetic correlation between sexes using LD Score Regression (Bulik-Sullivan, Finucane, et al., 2015; Bulik-Sullivan, Loh, et al., 2015). Since our GWAS summary statistics were based on White British individuals of primarily European ancestry, we used the precalculated LD scores computed by Bulik-Sullivan et al. (Bulik-Sullivan, Loh, et al., 2015).

Expectations for sex-specific heritabilities with no GxSex.In the section “The limited scope of analyzing GxSex via heritability differences and genetic correlations” we report our observation that, for most traits examined, sex-specific heritabilities, and are both higher than the heritability in the combined sample, . Here, we provide a short explanation for why this observation is inconsistent with a simple model in which genetic effects are the same across the sexes.

Denote the phenotype again by the polygenic effect by , the environmental effect by and the sex by . We assume as before that allele frequencies are similar enough between males and females. Since genetic effects are equal, this implies

For the environmental variance, we have that

|  |  |
| --- | --- |
|  | (10) |

where the second equality we have assumed that there are no mean sex differences in the environmental effects (or, in the more practical empirical case, have been corrected for via the correction for the mean phenotypic difference between the sexes, giving

.

**Eq. 10** we have that the environmental variance must be less than the maximal sex-specific environmental variance. It follows that the heritability in the combined sample must be larger than at least one of the sex-specific heritabilities,

|  |  |
| --- | --- |
|  | (11) |

Multivariate adaptive shrinkage (mash). We used multivariate adaptive shrinkage (*mash*) to examine correlation and differences in magnitude of SNP effects between males and females (Urbut et al., 2019). *mash* is an adaptive shrinkage method (Stephens, 2016) that improves upon previous methods of estimating and comparing effects across multiple conditions by flexibly allowing for a mixture of covariance patterns between conditions and requiring only summary statistics from each condition (including a point estimate of the effect and corresponding standard error for each SNP and condition). The method adapts to patterns of sparsity, sharing, and correlation among the conditions to compute improved effect estimates.

In this study, we set two conditions, male and female, and provided effect estimates and corresponding standard errors from our male-specific and female-specific GWAS. *mash* learns from the data by estimating mixture proportions of various predefined covariance matrices representing different patterns in effects. Using maximum-likelihood, mash assigns low weights to matrices that capture less patterns in the data, and vice versa.

Mixture weights for covariance structure between male and female effects. To interpret patterns of SNP effects between males and females, we input 66 hypothesis-based covariance matrices (**Fig. S2**) spanning a range of correlations and relative magnitudes of effects between males and females. We used a random subset of all SNPs for mash to learn the covariance mixture weights. In order for the random subset to contain approximately independent SNPs and capture the weight of SNPs with no effect (**Fig. S2**), we created a subset of SNPs for each trait by taking a random SNP from each of 1703 approximately independent LD blocks estimated for Europeans (Berisa & Pickrell, 2016). *mash* can also generate data-driven covariance matrices that capture SNP effects in the data, but we did not use this feature since the data-driven matrices had negligible differences from our hypothesis matrices and were less interpretable.

For each trait, we repeat this weight-learning step 100 times, sampling the SNPs from the 1703 LD blocks without replacement to fit the mash model and generate mixture proportions. We then take the average proportion for each covariance matrix as an estimate of its weight, effectively treating each of the 100 samples as iid draws.

Choice of SNPs used to estimate male-female effect covariance. We examined the effect of using a random subset taken from different p-value thresholds [1, 5e-2, 1e-5, 5e-8] while selecting from LD blocks. By doing so, we can examine differences in the distribution of weights across the p-value thresholds. We performed this test on height, BMI, testosterone, and BMI-adjusted waist:hip ratio. For each trait, weight placed on the no-effect matrix decreased as we reduced the p-value threshold (**Fig. S3**). Patterns of weights for non-null effect matrices varied across the traits (**Fig. S3**). Since *mash* considers the proportion of null effects and sex-specific, SNP-specific noise; together with the fact that for complex traits, less significant SNPs may still reflect important signal, we decided on using the whole set of SNPs to sample from when estimating mixture proportions.

Posterior estimates of sex-specific effect sizes. *mash* can also apply adaptive shrinkage after learning patterns in effect sizes to improve marginal point estimates—estimated using the posterior mode—and measures of significance. These posterior estimates could reduce noise by shrinking effects towards zero and possibly reveal greater or lesser variation in effect sizes between males and females. Therefore, using the average of the fitted mixture model over 100 repetitions (See section “Mixture weights for covariance structure between male and female effects”), we computed posterior estimates for each trait (**Table S7**) to be used in further analysis (See section “Evaluating the performance of sex-specific polygenic scores”). *mash* calculates a local false sign rate (lfsr) for each effect, which is similar to a local false discovery rate and is defined as the cumulative density of the posterior distribution of values with a sign that differs from that of the posterior mean. We mapped lfsr to “pseudo p-values” by ranking the SNPs according to lfsr values, and then ascribing the p-value of the same rank (**Fig. S5**).

Environmental variance simulation for mash. To ensure that *mash* was not mistaking sex differences in environmental variance to be differences in the magnitude of genetic effects, we performed a simulation study where, in short, samples of males and females are generated under the model in [**Eq. 1**](#eq1), where genetic effects are exactly the same but the environmental variance differs across the sexes; we then perform a GWAS on both samples and input the simulated GWAS results into *mash*, and test whether *mash* identifies no GxSex in the data. We performed this simulation with various levels of heritability in males [0.05, 0.5], female to male environmental variance ratio [1, 1.5, 5], and numbers of causal SNPs [100, 1K, 10K].

First, we created a sample of 300K individuals with randomly assigned sex. We then created a matrix of genotypes for all individuals consisting of 20K SNPs by sampling from a binomial distribution of allele frequencies from UK Biobank’s imputed data (Sudlow et al., 2015). From the 20K SNPs, we portioned out the predetermined number of causal SNPs and assigned effect sizes by sampling from a Normal distribution with mean 0, standard deviation 1. We estimated the male environmental variance for each causal SNP using the equation,

|  |  |
| --- | --- |
|  | (12) |

where is a vector of the genetic effects, is the heritability in males and andare the effect size and allele frequency at site . We multiplied by the environmental variance ratio to obtain the environmental variance for females, . Afterwards, for each individual, we sampled environmental effects from a Normal distribution with mean zero, and variance set as or according to the sex of the individual. Phenotypes were then simulated using the following,

|  |  |
| --- | --- |
|  | (13) |

where represents the phenotype for individual and represents the genotype of the causal SNP for the individual. With the phenotype, genotype and environmental effect, we obtained the estimated effect sizes, , using least squares simple linear regression for all 20K SNPs and used the estimated effect sizes and corresponding standard errors as input into *mash*.

For nearly all parameters, out of the weights on matrices with effect, the vast majority was placed on the matrix for perfect correlation, equal magnitude (**Fig S6**). As the number of causal SNPs increased, the weight on the no-effect covariance matrix decreased accordingly. These results suggest that *mash* was not grossly mistaking differences in environmental variance as amplification.

Evaluating the performance of sex-specific polygenic scores. We calculated polygenic scores (PGS) for three models to test differences in prediction:

1. Additive model based on both-sex GWAS summary statistics
2. Sex-specific, additive model based on sex-specific GWAS summary statistics
3. sex-specific, covariance aware model based on posterior sex-specific effect estimates (Section “Posterior estimates of sex-specific effect sizes”)

The estimation, prediction and evaluation pipeline are illustrated in **Fig. S8**, and, for models (a) and (b), parallels the procedure described in (Choi et al., 2020).

First, for each phenotype, we split the sample of unrelated White British individuals into a test set of 25K individuals randomly sampled from each sex and a training set with the remaining individuals. Second, we re-ran GWAS on the training set following the same procedure above (“GWAS”), generating both-sex, female-specific, and male-specific summary statistics. Third, to obtain posterior estimates, we input the effect sizes and standard errors from the male-specific and female-specific GWAS into *mash*, and took the average of 100 resampling estimates of mixture proportion vectors and fed them to *mash* to perform the refined, covariance-aware estimation of effects. The output from *mash* included posterior mean and a local false sign rate (lfsr) for each SNP. We then sorted SNPs by lfsr and matched it to a sorted list of p-values taken from the same GWAS summary statistics.

Afterwards, we performed clumping three times for the additive model (both-sex, male-specific, and female-specific GWAS) and two times for the covariance-aware model (male and female posterior estimates) to produce a subset of SNPs that are relatively independent using *plink 1.9 beta*’s --clump command, removing SNPs with pairwise LD threshold or within 250kb. To estimate pairwise LD values, we used a sample of 187 unrelated European (population code: GBR and CEU) individuals from 1000 Genomes phase 3 (Auton et al., 2015).

Using the resulting subset of SNPs, we estimate PGS for the individuals in the test set by summing the number of effect alleles an individual has weighted by the allelic effect sizes. We use *plink 2.0 alpha’s* --score command along with the --q-score-range flag to repeat the PGS computation over a range of p-value thresholds [1, 0.01, 1e-5, 1e-8]. Therefore, a total of 20 PGS runs are performed for each trait over the combination of five models and four p-value thresholds (**Fig. S8B**).

Finally, to assess the prediction accuracy, we computed for the following,

|  |  |
| --- | --- |
|  | (14) |

The covariates used for the regression are the same as those used in our GWAS: sex, birth year, and the first 10 PCs of the genotype matrix (UKB data field 22009). We performed regressions both separately by sex and together with both sexes in the test set. For each of the three predictors—additive model, sex-specific additive model, and sex-specific covariance aware model—we selected the p-value threshold with the greatest . We also calculated the incremental , which is the increment in after adding the PGS to a null model with only the covariates. (**Fig. S8**).

We performed five-fold cross validation for our PGS procedure. Each prediction was performed on a different randomly sampled 25K female and 25K male test set, with the remaining used at the training set. For each model, we averaged the greatest from the p-value thresholds over the five folds for comparison across all models.

Testosterone as a Regulating Factor and Mendelian Randomization. We tested a model of testosterone as a modulator of magnitude differences in males and females. We first split individuals by sex and for each sex, created 10 bins of testosterone levels. We adjusted one of the 10 bins to have testosterone levels overlap between males and females. The overlapping testosterone bin was based on fewer individuals (~800) compared to the other bins (~2200). Then for each trait, using polygenic scores based on both-sex summary statistics (“Evaluating the performance of sex-specific polygenic scores”), we regressed the phenotype values to the additive PGS within each bin. The resulting linear regression coefficient represents the amplification of total genetic effect. We compared the mean of each testosterone level bin to the linear regression coefficient and obtained the Pearson’s correlation coefficient for each sex.

We then assessed the causal relationship between testosterone levels and amplification of total genetic effect using mendelian randomization, which reduces the effect of confounding or reverse causation. We compare the association between PGS based on additive GWAS summary statistics for all phenotypes to the PGS based on both-sex summary statistics, this time binning individuals into 10 bins of PGS based on sex-specific summary statistics for testosterone (**Fig. S11**). PGS for testosterone is associated with testosterone levels, and we cautiously assume that it is not associated with the amplification of genetic effect in other ways aside from testosterone levels. Again, each trait, we estimate the Pearson’s correlation coefficient by sex.

Model of Shared Amplification. To test the model of shared amplification between environmental and polygenic effects ([**Eq. 8**](#eq8)) we obtained the genetic and environmental variance for males and females based on the following relationships,

|  |  |
| --- | --- |
| , and  , | (15) |

where , and refers to the additive genetic, environmental, and phenotype variances, respectively. The sex-specific heritabilities, , were obtained from previous estimates using LD Score Regression (“Heritability and genetic correlation estimation").

Representing male genetic or environmental variance as , and the corresponding female variance as , we derived standard errors for the ratio of male to female variance using the Taylor approximation for the standard error of a ratio of statistics,

|  |  |
| --- | --- |
|  | (16) |

assuming independence between and since they are statistics of independent sampling distributions (independent samples of males and females). The standard errors of the genetic and environmental variance were estimated using the law of total variance for a product of two random variables, and ,

|  |  |
| --- | --- |
|  | (17) |

and plugging in and as estimates of and , respectively,

|  |  |
| --- | --- |
|  | (18) |

In this case, represents the phenotypic variance, and represents for estimation of genetic variance or for estimation of environmental variance. Lastly, to obtain the standard error of the phenotypic variance, we used bootstrapping with 100 samples (with replacement) of estimates of the phenotypic variance in sex ,

|  |  |
| --- | --- |
|  |  |

Finally, for each trait, we estimated , the ratio of the two male-female ratios (environmental and genetic, y and x axes in Figure 6, respectively), and its standard error, , using the same method as in **Eq. 16**. Under the null hypothesis of equal environmental and genetic amplification (**Eq. 8**),

|  |  |
| --- | --- |
|  | (19) |

where

|  |  |  |  |
| --- | --- | --- | --- |
| . |  |  | (19) |

In **Fig. 6** we approximate 90% confidence intervals on by treating it as a Z score, i.e. further treating as a Standard Normal.

Sexually Antagonistic Selection

The relationship between male-female allele frequency divergence at adulthood and GxSex. We developed a model relating sex differences in additive effects on a trait at a biallelic locus (and ) and divergence in allele frequencies. Our model resembles that of Cheng and Kirkpatrick (Cheng & Kirkpatrick, 2016) who developed a similar model relating allele frequency differences and sex bias in gene expression. In short, we model sexually-antagonistic, post-conception viability selection on a focal complex trait. We assume allele frequencies in adult males, , and adult females, , are at equilibrium. Under these conditions, we derive the relationship

|  |  |
| --- | --- |
|  |  |

where (Wright, 1951) is the fixation index with respect to the male and female subpopulations, i.e. the proportion of heterozygosity in the population that is due to allelic divergence between the sexes. is the contribution to phenotypic variance due to GxSex,

|  |  |
| --- | --- |
|  | (20) |

where is the mean allele frequency at adulthood. is parameter that, importantly, is shared across all variants affecting the trait and can be thought of as the potential for sexually antagonistic selection acting on genetic variation for the trait in question.

Allele frequencies at the autosomal locus are assumed to be equal in males and female zygotes. at adulthood takes the form

|  |  |
| --- | --- |
|  | (21) |

Sexually-antagonistic selection acting on viability will cause divergence in allele frequencies between adult males and females. We write the relative viabilities of the homozygote for the reference allele, the heterozygote and the homozygote for the effect allele as for each sex . The selection coefficient and dominance coefficient can be frequency-dependent, in which case these coefficients take their values at equilibrium. We can write the additive selection coefficient of the effect allele as

|  |  |
| --- | --- |
|  | (22) |

Assuming that zygotes are at Hardy-Weinberg equilibrium, the allele frequency in each sex at adulthood is

|  |  |
| --- | --- |
|  | (23) |

where we neglected terms of order (Gillespie, 2004). Plugging **Eq. 23** into [**Eq. 21**](#eq19), the divergence between males and females post-selection is

|  |  |
| --- | --- |
|  | (24) |

We model the strength of viability selection acting on males and females as linear with the additive effect on a focal trait in each sex,

|  |  |
| --- | --- |
|  | (25) |

and recalling the simplifying assumption that allele frequencies are at equilibrium under sexually-antagonistic viability selection at the locus, such that selection favoring an allele in one sex is balanced by selection against that allele in the other sex,

|  |  |
| --- | --- |
|  | (26) |

If , then **Eq. 24** simplifies to

|  |  |
| --- | --- |
|  | (27) |

where

|  |  |
| --- | --- |
|  | (28) |

is the additive genetic variance. However, when does not strictly equal , [**Eq.**](#eq23) **25,** [**26**](#eq24) together imply

|  |  |
| --- | --- |
|  | (29) |

Finally, using [**Eq.**](#eq23) **25***,*

|  |  |
| --- | --- |
|  | (30) |

which together with **Eq. 29** gives

|  |  |
| --- | --- |
|  | (31) |

We denote the heritability due to GxSex at the locus as and the parameter relating this contribution to the differentiation in allele frequencies as

|  |  |
| --- | --- |
|  | (32) |

and plug **Eq. 31** into **Eq. 24**, we get

|  |  |
| --- | --- |
|  | (33) |

as given by **Eq. 9** in **Results**.

Gathering and Filtering Allele Frequency Data. We downloaded allele frequency data from the gnomAD dataset (Karczewski et al., 2020) a consortium of several ongoing global research projects. Specifically, we used *gnomAD v3.1.2* which consists of 76,156 whole genome sequences mapped to the GRCh38 reference. This data is labeled by gnomAD and available for download with information about the sample demographics. The data is divided into ten ancestry groups: African/African American samples (abbreviated “afr” in the gnomAD files); Amish (“ami”); Latino/Admixed American (“amr”); Ashkenazi Jewish (“asj”); East Asian (“eas”); Finnish (“fin”); Non-Finnish European (“nfe”); Middle Eastern (“mid”); South Asian (“sas”); and samples not assigned to any population, designated Other (“oth”). The data is also separately divided into two chromosomal sexes, labeled XX and XY, based on coverage of X and Y chromosomes for the given individual. Aneuploid individuals (e.g., X or XXY) are not included in the dataset. For the purposes of this study, we again refer to XX as female and XY as male. Total numbers of individuals sampled can be found on the gnomAD website’s help page (<https://gnomad.broadinstitute.org/help>).

We downloaded gnomAD VCF files from the gnomAD browser (browser (https://gnomad.broadinstitute.org/downloads) for all autosomes and used *VCFTools* (Danecek et al., 2011) to parse the file. We filtered the data to exclude insertions or deletions, and only kept bi-allelic SNPs. We further removed missing data (3,698 sites). These filtering steps resulted in 2,285,169 remaining sites. In an effort to avoid confounding results that could arise from population substructure, we split the data into the different ancestry groups labeled by gnomAD and worked with the data in each subpopulation separately from this point forward. We removed sites with less than 1,000 alleles in each ancestry group independently. The number of loci we removed at this step depended on the sample size of each group, as we removed fewer loci from large populations and removed more loci in small populations (**Table S1**). This step resulted in the complete removal of the Amish and Middle Eastern populations because their low sample sizes.

Estimating Male-Female FST. We estimated Male-Female for every site remaining in our dataset following **Eq. 21**. We note that this is an upward biased estimator—especially for low levels of , as it only takes non-negative values. To get and , we could directly use the AF\_XX column for each subpopulation. To get , we use (AC\_XX + AC\_XY) / (AN\_XX + AN\_XY), such that is given as the number of alternate alleles in the sample divided by the total number of alleles in the sample.

We removed any sites which resulted in “NA”, indicating that there were no samples with the male or female tag with the alternative allele for that site. This step resulted in a significant reduction in sample size by one or two orders of magnitude, depending on the ancestry (**Table S2**).

Integrating with GWAS Data and Calculating VGxSex. We removed sites that were not found in both the gnomAD dataset and the UKB GWAS dataset. The number of sites removed through this step varied greatly across ancestry groups (**Table S3**).

We used the point estimates and the standard errors of the sex-stratified GWAS (**Table S6**) for 27 physiological or physical traits. We also got an estimate of using **Eq. 20**, where and are the GWAS effect estimates and is the total alternate allele frequency as above.

Our final step of filtering involved filtering sites by GWAS p-value. To investigate the contribution of on a trait, we used four different p-value thresholds at 1e-3, 1e-5, 1e-8 and 1 (i.e., all SNPs; see **Table S4** for the number of sites remaining for each p-value threshold). In the main text, we arbitrarily focus on the 1e-5 threshold reasoning that it strikes a reasonable middle ground between sample size and noise. Results for other p-value thresholds are shown in **Table. S5**.

Estimating the potential for sexually-antagonistic selection acting on variation in a trait (). For each trait and population, we estimated using weighted least squares linear regression of to , with weight inversely proportional to our site-specific estimate of noise in the estimate of .

|  |  |
| --- | --- |
|  | (34) |

To simplify the estimation of we treat the allele frequency as perfectly estimated, and as independent of the allele frequency in the GWAS sample—as different data are used in the GWAS (UK Biobank) and in the allele frequency estimation (gnomAD). Under these assumptions,

|  |  |
| --- | --- |
|  | (35) |

and thus the task at hand is estimating . Using the law of total variance,

|  |  |
| --- | --- |
|  | (36) |

We begin with the argument of the first term,

|  |  |
| --- | --- |
|  | (37) |

where we denoted

|  |  |
| --- | --- |
|  | (38) |

for each sex Plugging **Eq. 37** into the first term of **Eq. 36**,

|  |  |
| --- | --- |
|  | (39) |

where the first and second step follow from the fact that is a constant. We can take note of the fact that is Normally distributed around , and in particular that it has no skewness. Therefore,

|  |  |
| --- | --- |
|  | (40) |

where is the skewness of . We can also note that

|  |  |
| --- | --- |
|  | (41) |

where we defined

|  |  |
| --- | --- |
|  |  |

and therefore is a Standard Normal and therefore is Chi-squared with one degree of freedom. **Eq. 41** now gives

|  |  |
| --- | --- |
|  | (42) |

Plugging **Eq. 40** and **Eq. 42** into **Eq. 39**, we find

|  |  |
| --- | --- |
|  | (43) |

We now turn to the second term of **Eq. 36**. First,

|  |  |
| --- | --- |
|  | (44) |

**Eq. 40** and **42** again give us

|  |  |
| --- | --- |
|  | (45) |

which then gives

|  |  |
| --- | --- |
|  | (46) |

Plugging **Eq. 43** and **Eq. 46** into **Eq. 36**, we get

|  |  |
| --- | --- |
|  | (47) |

Finally, we estimate with the GWAS-derived point estimate of the effect and with its standard error, . Plugging back into **Eq. 35**, we get

|  |  |
| --- | --- |
|  | (48) |

To perform this estimation of A on the GWAS and data, we used paired and points for all sites which passed all previous stages of filtering. Weights were set by **Eq. 34** and follow **Eq. 48** where and are the GWAS effect estimates as above, and and are the GWAS standard errors (SE) estimates for each locus’ effect size per trait.

To minimize the possibility of LD between sites used in the analysis as much as possible used the approximately independent LD blocks in Europeans (Berisa & Pickrell, 2016) as in Section “Mixture weights for covariance structure between male and female effects”. Namely, we subdivided the genome into 1703 LD blocks such that we expect sites from different LD blocks will have little to no LD between them. We iterated over the 1703 blocks and identified all post-filtering sites which fell within each block; we then randomly sampled one of these sites within each LD block and used this sample of (up to) 1703 sites to perform the weighted linear regression of on The slope and SE of this regression line was our estimate of A. We replicated this estimation process 1,000 times to generate 1,000 estimates of A. We then used the estimates of slope divided by the SE of these estimates to generate 1,000 Z-scores for A. The point estimate Z-score presented in **Fig. 7B** is the mean of the 1,000 replicates, and the error bar is the middle 90% (i.e., the 5th to 95th quantile) of those replicates. In the main text, we focus on the results performed this estimation for Ashkenazi Jewish, Finnish, and Non-Finnish European populations as the other ancestry groups in gnomAD are more genetically diverged from the UKB White British sample and the GWAS estimates are expected to be less portable (Privé et al., 2022; Wang et al., 2020), similar to the UK Biobank sample.

## Code and Data Availability

All code and sex-specific GWAS summary statistics are available at REFX XXX.

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