Moderating heritability with genomic data

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Abstract
Environmental moderators may amplify or suppress the heritability (i.e., the proportion of genetic variation) of a phenotype. This genetic sensitivity to the environment is called gene-environment interaction (GxE). Existing GxE methods struggle to identify replicable interactions because they focus on the interaction coefficients. We propose a novel method for estimating GxE heritability using genetic marginal effects from GxE genome-wide analyses and LD Score Regression (LDSC). We demonstrate the effectiveness of our method for body mass index (BMI) treating biological sex (binary) and age (continuous) as moderators. We find robust, interpretable evidence for GxE that is not detected by existing methods.

Keywords
GxE, Marginal Effects, Heritability, LD Score Regression, BMI

Background

Gene-environment interaction (GxE) can be statistically detected when differences in an environment amplify or suppress the impact of a genotype on a phenotype. At the functional level, differences in genetic associations with a phenotype reflect differential sensitivity to an environment (1). Thus, individuals with different alleles at specific loci are predicted to respond differently depending on the characteristics of their environment. Twin and model organism studies have found pervasive evidence of GxE for a variety of traits (2–5). Model organism research strictly manipulates both the genotypes (via selecting organisms with differential genetic strains of known effect) and environments (via careful experimental manipulations) allowing the precise characterization of interaction effects. While extremely powerful, such methods do not transfer to human genetic studies. By contrast, GxE in twin studies focuses on the differences in the heritability of a trait (or the proportion of genetic variation in a phenotype) depending on the individual's or family's environment. Accordingly, it is difficult to use these results to subsequently identify alleles that are sensitive to environmental variation. Examining GxE in GWAS data provides an opportunity to identify both differences in the heritability of a phenotype at different levels of an environmental moderator, while allowing for the potential next step of identifying specific alleles that are sensitive to changes in the environment. However, relatively few studies have attempted to identify GxE in humans using genome wide association study (GWAS) data (6–12), likely due to the perception that GxE GWAS (or moderated GWAS) are plagued by low levels of statistical power and extreme multiple testing corrections (13–15).

Linkage Disequilibrium Score regression method (LDSC), and other single nucleotide polymorphism (SNP) heritability (h^2_{SNP}) methods offer a unique opportunity to address prior limitations in the detection of GxE. Specifically, LDSC regresses the χ^2 values for SNP associations identified from a GWAS onto an LD score that captures the known LD (i.e. correlations between the variants) in the sample population. The slope of this regression equation indexes the h^2_{SNP} of the phenotype (16,17). Typically, estimation of GxE from GWAS focuses on genome-wide significant SNP-moderator interaction coefficients (i.e., $p < 5 \times 10^{-8}$). LDSC, however, estimates heritability without specifying a minimum significance threshold, making it an extremely useful tool for interrogating highly polygenic phenotypes with numerous effect sizes that are not genome-wide significant. By extending these methods to test for GxE in GWAS data, we can conduct a broad examination that may identify critical environmental factors that moderate the genetic architecture of a wide variety of medical and behavioral phenotypes.

Current GxE methods struggle to accurately identify either SNP-environment interaction effects or differences in h^2_{SNP} across different moderator levels. Some approaches directly estimate h^2_{SNP} from the GxE GWAS interaction coefficient. The principle limitations of these approaches are the exclusive focus on the interaction coefficient and the assumption that the interaction coefficient uniquely indexes GxE (9,10). While this initially seems reasonable, exclusively focusing on the interaction coefficients ignores the fact that the interpretation of the interaction coefficient depends on the main effect and the level of the moderator. Accordingly, heritability estimates that focus on the interaction coefficient are analogous to random effects of the SNP and

must be interpreted with caution. Other SNP-based heritability estimation methods use a GREML-based mixed modeling approach with raw genetic data to partition the phenotypic variance into homogeneous (i.e. additive genetic), heterogeneous (i.e. GxE), and residual variation (8). GREML methods are computationally intensive (8,9).

Rather than focusing on the interaction coefficient or using GRMEL-based approaches, our method integrates the interaction coefficients and the main effects into genetic marginal effects for each SNP analyzed in a GxE GWAS (18). Genetic marginal effects simplify interpretation of GxE GWAS results so that they can be interpreted in almost the same way as standard GWAS summary statistics, just for a specific level of the moderating environment, thereby de-confounding main and interaction effects. A genetic marginal effect captures the rate at which the outcome is expected to change based upon a one allele increase in the SNP. In GxE GWAS, because the genetic association for each SNP may depend on the level of the environment, it is necessary to integrate the main effects and the interaction effects into a single interpretable value. Mathematically, this is as simple as taking the first derivative of the regression equation with respect to the SNP (See Method Eqs. 1 & 2). After calculating genetic marginal effects for characteristic values of the moderator, we can estimate heritability for each of the levels.

In this paper, we describe an extension of LDSC for estimating moderated h^2_{SNP}, using genetic marginal effects derived from GxE GWAS summary statistics (17–19) and build on several methods we have published elsewhere (18). We view moderated h^2_{SNP} as a starting point that will allow researchers to refine the search for individual variants that interact with specific moderators by focusing attention on appropriate moderators

and subsequently invest time, effort, and resources collecting data and conducting analyses that pinpoint significant locus-level genetic interactions. We demonstrate the effectiveness of our moderated h^2_{SNP} analyses using body mass index (BMI) data from the UK Biobank (20). The results identify differences in h^2_{SNP} of BMI at different levels of binary (i.e., sex) and continuous (i.e., age) moderators. However, our proposed method can be applied to GWAS summary statistics for any moderating variable that has been thoughtfully and appropriately coded, as the marginal effects calculation will not be impacted, and will be easier to interpret than other GxE heritability methods (18).

Results

Method Overview. We present a method to estimate h^2_{SNP} at different, yet characteristic levels, of an environmental moderator. GxE is present if we observe significant differences in the estimate of h^2_{SNP} for the phenotype at different levels of the moderator. Our approach requires two preliminary steps before estimating h^2_{SNP}. First, it is necessary to obtain moderated, or GxE, GWAS summary statistics. At present, appropriate summary statistics are relatively rare, meaning researchers may need to conduct the GxE GWAS themselves. Then, using estimated GxE summary statistics, it is possible to calculate genetic marginal effects for each SNP at characteristic values of the moderating variable (such as categories for discrete moderators, diagnostic thresholds for medical traits used as moderators, or other notable thresholds in the distribution of a moderating variable). Genetic marginal effects are very similar to conducting stratified GWAS (separate GWAS for each level of the moderator). For continuous moderators, however, stratified GWAS analyses are infeasible, as they

would reduce the sample size in any group to such an extent that it would negate the possibility of detecting any reliable genomic signal. Our method of calculating genetic marginal effects is equally effective for continuous, ordinal, or binary moderators. These genetic marginal effects can then be used to estimate heritability at specific levels of the moderator with LDSC. The interpretation of the heritability explicitly references the level of the environment used to calculate the marginal genetic effect. To demonstrate the effectiveness of our method, we examine differences in the heritability of BMI using sex (binary: male vs female) and age (continuous: 40-70 years of age) as examples.

Gene-by-Sex Interactions for BMI (Binary Moderator). The goal of the first moderated LDSC demonstration is to illustrate how the heritability of BMI differs between males and females. Accordingly, we conducted a moderated GWAS of BMI treating biological sex (binary) as a moderator. We then calculated genetic marginal effects and standard errors for females (moderator = 0) and males (moderator = 1). Overall, the genetic architecture of BMI appears broadly similar across sex, with genetic associations appearing at similar loci. However, there are clear differences in the magnitude of the significance between females and males (Figure 1), with the associations for females achieving substantially higher levels of statistical significance. This is particularly evident for associations on chromosomes 1, 2, 3, and 18.

[Figure 1]

Figure 2 shows that BMI is more heritable in females compared with males (Females-h^2_{SNP} = 0.28, se = 0.01; Males-h^2_{SNP} = 0.21, se = 0.01; p = 5.36 x10^{-06}). Furthermore, the genetic correlation (rG_{SNP}) between males and females for BMI was estimated to be 0.94 (se = 0.03, p = 0.04), implying that a slightly different set of genetic factors

116 contributes to BMI depending on sex. This is consistent with known sexual dimorphisms
117 in body composition and body fat percentage (21).

118 **[Figure 2]**

119 *Gene-by-Age Interactions for BMI (Continuous Moderator)*. Like biological sex,
120 we observe GxE for BMI as people age (Figure 3). While the genetic associations at
121 each age point to similar loci, the level of statistical significance of genetic loci varies.

122 **[Figure 3]**

123 Specifically, we observe higher levels of h^2_{SNP} at age 40 which declines at older ages.
124 This is consistent with the possibility that individuals may begin to restrict their health
125 and eating behaviors after 40 years of age to address or prevent chronic health
126 conditions (22,23) . The h^2_{SNP} estimates for the mean age (56 years of age) remain
127 similar to previous h^2_{SNP} (24–26), even though the heritability for 40 years is higher
128 compared to other ages.

129 **[Figure 4]**

130 In contrast with sex, the rG_{SNP} across ages (rG_{SNP} ranging from 0.95 to 0.99) suggesting
131 the same genetic factors contribute to BMI across the lifespan, while the magnitudes of
132 their influence vary by age.

133

134 ## Discussion

135 We presented a method to estimate moderated h^2_{SNP} to highlight how GxE affect
136 the heritability of a phenotype. Our method is easy to interpret and adapt to a variety of
137 moderators and phenotypic outcomes. To demonstrate the effectiveness of our method,
138 we conducted analyses of BMI showing how the h^2_{SNP} of BMI varies across sex (a

binary moderator) and age (a continuous moderator). Our method detected GxE for both sex and age. Specifically, BMI is more heritable for females than males, and the heritability of BMI declines between the ages of 40 and 70. Notably, other methods for detecting GxE heritability using GWAS data have found limited evidence of genetic interactions for age (9). Below we highlight the benefits of our moderated h^2_{SNP} method, focusing on how our method works, the interpretation of the moderated h^2_{SNP} estimates, and differences from other SNP-based GxE methods.

The interpretation of moderated h^2_{SNP} follows from the interpretation of marginal genetic effects calculated from a GxE GWAS. The interpretation of marginal genetic effects is analogous to standard GWAS summary statistics. In GWAS, the beta coefficient is the expected change in a dependent variable for each additional allele and the summary statistics can be used to estimate h^2_{SNP} for the phenotype. The interpretation of a genetic marginal effects, by extension, is restricted to a particular level of the moderator. Specifically, a genetic marginal effect captures the expected change in the dependent variable for each additional allele, at the specified value of the moderator. Therefore, using GxE GWAS summary statistics, we can estimate h^2_{SNP} for the specific level of the environment that was used to calculate the marginal genetic effect, making the interpretation of GxE h^2_{SNP} straightforward. This can be repeated for any value of the moderator.

In our first example, we used biological sex as the moderator, as there are well-established sex differences in BMI (21). Male and female differences in BMI arise, in part, from differential genetic and biological pathways that affect a variety of different anthropometric factors such as fat storage, muscle development, and stature (27–30).

We calculated two marginal effects: one for males and one for females. We then estimated the heritability from the male and female marginal effects. Finally, we tested the difference between h^2_{SNP} for males and females by constructing confidence intervals from the standard errors. The simplicity of h^2_{SNP} in each group reduces the likelihood of misinterpretation. Our results suggest BMI is more heritable in females (Figure 2), but previous results in twin studies in the same age range are inconsistent (31). Importantly, research examining sex differences for other measures adjacent to BMI, like waist-to-hip ratio as a proxy for obesity and fat distribution, and metabolic traits, suggest more genetic loci are associated with these traits in females (29).

Our second example used continuous age as the moderator, and as such is slightly more complicated. Because age is a continuous variable, we calculated the marginal genetic effects at easily interpretable values: 40, 50, 60, and 70. The age range in the UK biobank data is approximately 40 to 70, and thus the marginal genetic effects reflect characteristic ages from the sample as people tend to think of age in decades. As the marginal genetic effects are calculated from GxE GWAS results, we could have calculated marginal genetic effects for every year of age between 40 and 70, or extrapolated age beyond the observed age range (though extreme caution would be necessary in such situations). The results suggest that the heritability of BMI decreases with age (Figure 4). These results are in line with twin studies that have examined the heritability across different ages, where the heritability of BMI was found to be higher at younger ages and progressively decrease (2,32). Interestingly, other recent methods estimating h^2_{SNP} with genome-wide GxE methods found limited evidence of an interaction between age and genetic factors underlying BMI (9,33). Nevertheless, the

results from our method show clear differences in the magnitude of genetic factors for BMI across different ages (Figure 2), which is similar to the results of Robinson *et al.*, (2017), who used GCI-GREML to examine genotype-age interactions in BMI, and Poveda *et al.*, (2017), who used a maximum likelihood-based variance component decomposition.

Caveats and Considerations. While our method to identify moderated h^2_{SNP} is an effective procedure for estimating GxE using GWAS data, several factors must be properly understood to avoid erroneously applying the method. Here we emphasize the choice of characteristic levels of the environmental moderator and the calculation of effective sample sizes for the marginal effects.

When calculating marginal genetic effects, it is possible to choose any value of the moderator even if the value is nonsensical. When choosing characteristic values of the moderator to calculate marginal genetic effects, it is necessary to keep in mind that the precision of marginal genetic effects decreases as the chosen value of the moderator diverges from its mean. The maximum precision of a marginal genetic effect is at the mean of the moderator, corresponding with estimates from standard (unmoderated) GWAS summary statistics. Genetic marginal effects calculated one standard deviation above or below the moderator's mean will be slightly less precise and the precision will decrease markedly beyond that point based upon the distribution of the moderator. As moderated h^2_{SNP} is derived from marginal genetic effects, the precision of h^2_{SNP} depends on the precision of the marginal genetic effects.

Importantly, LDSC requires users to specify the sample size. Under- or over-estimates of the sample size can have a major impact on the estimated h^2_{SNP}. This is

particularly relevant for the estimation of h^2_{SNP} from marginal genetic effects, as the effective sample size for a particular marginal genetic effect is not the total sample size. Marginal genetic effects are most precise at the mean of the moderator, in part because all observations of the moderator contribute equally to the mean value. By extension, marginal genetic effects based on values that diverge from the mean of the moderator will reduce the effective sample size. Accordingly, an effective sample size must be calculated for each marginal effect, which accounts for the fact that observations take on different weight the further the deviation from the mean. The effective sample size calculation is presented in the methods section. As proof-of-principle, when we compared the effective sample size for the sex-moderated analysis with the observed number of males and females, the numbers are extremely close (Observed: N_{males} = 179,271, $N_{females}$ = 210,169; Mean effective sample size: N_{males} = 178,684, $N_{females}$ = 209,577). The similarity between the observed and effective sample size is expected as marginal genetic effects for binary moderators are analogous to stratified analyses.

Conclusions

Moderated h^2_{SNP} will allow researchers to identify GxE in GWAS data, thereby focusing attention on moderating variables that alter the genetic architecture of medical and behavioral phenotypes. Identifying GxE in the heritability of phenotypes will allow researchers to invest time, effort, and resources into collecting the appropriate data required to pinpoint moderators that amplify or dampen the genetic associations with a phenotype. Using genetic marginal effects to estimate h^2_{SNP} provides an easily interpretable method to examine GxE that can be applied to moderated GWAS summary statistics.

Methods

Moderated Genome-Wide Association Study (moderated GWAS). The moderated GWAS model is an extension of the standard GWAS. The standard GWAS regression model is:

$$Y_i = \hat{\beta}_0 + \hat{\beta}_1 SNP_{ij} + \hat{\gamma} Covariates_i + \epsilon_i \quad \text{Eq. 1}$$

where Y_i is the outcome phenotype for the ith person, SNP_{ij} is the jth genetic variant for the ith person, and $Covariates_i$ are the standard GWAS covariates such as biological sex, age, and genetic ancestry principal components. The estimate of $\hat{\beta}_1$ is the estimate of the genetic association (which is later passed to LDSC), while $\hat{\beta}_0$ is the intercept, and $\hat{\gamma}$ is a vector of regression coefficients corresponding to the included covariates.

The GxE GWAS model extends the standard GWAS model by adding an interaction between the environment and each variant, as well as explicitly including the environmental factor (18):

$$Y_i = \hat{\beta}_0 + \hat{\beta}_1 SNP_{ij} + \hat{\beta}_2 Env_i + \hat{\beta}_3 SNP_{ij} x Env_i + \hat{\gamma} Covariates_i + \epsilon_i \quad \text{Eq. 2}$$

In the GxE GWAS model, both main effects, $\hat{\beta}_1$ and $\hat{\beta}_2$, depend on the interaction effect, $\hat{\beta}_3$. Thus, $\hat{\beta}_3$ provides a test of whether the effect of a SNP on the phenotype varies at different levels of the environment. The interaction parameter, however, is difficult to interpret directly. Therefore, it is advantageous to calculate genetic marginal effects to examine the genetic association at specific levels of an environment.

Calculating Genetic Marginal Effects. Summary statistics from the moderated GWAS are used to calculate genetic marginal effects. Genetic marginal effects are the association between the SNP and a phenotype at a specific level of an environment. In

a standard GWAS model, the genetic marginal effect of the SNP is the regression coefficient ($\hat{\beta}_1$). This is the effect of the SNP on the phenotype at the mean level of the moderating environment. In the moderated GWAS model, the genetic marginal effect is a function of both genetic and environmental factors (18). To calculate genetic marginal effects ($\hat{\beta}_{ME}$), we take the first derivative of the GxE GWAS model with respect to the SNP, leaving:

$$\hat{\beta}_{ME} = \hat{\beta}_1 + \hat{\beta}_3 Env \quad \text{Eq. 3}$$

We can then use this equation to calculate a genetic marginal effect for any value of the environment by inserting a characteristic value for *Env*.

We can calculate the standard errors of the genetic marginal effects (SE_{ME}) using parameters from the variance-covariance (vcov) matrix of the moderated GWAS model:

$$SE_{ME} = \sqrt{\sigma^2_{\beta_1} + \sigma^2_{\beta_3} \mathrm{Env}^2 + 2\sigma_{(\beta_1,\beta_3)} \mathrm{Env}} \quad \text{Eq. 4}$$

inserting the corresponding value of *Env* that was used to calculate the genetic marginal effects. After calculating the marginal effect and the standard error, the z-statistic and p-value are easily calculated for use in subsequent analyses. This process is then repeated for each SNP that is analyzed. This process is automated in GW-SEM (35), which is the only software platform that currently stores the $\sigma_{(\beta_1,\beta_3)}$ statistic necessary to calculate the standard error of the marginal effects.

Effective Sample Size. Users must supply accurate sample sizes for estimate h^2_{SNP} using LDSC to avoid over- or under-estimating heritability, but the total sample size for the GxE GWAS analysis does not reflect the effective sample size for a marginal effect. The effective sample size used to estimate h^2_{SNP} must be calculated for each marginal effect. The effective sample size is calculated in two steps, based on the

assumption that the standard error of a parameter estimate is equal to the ratio of the standard distribution of the parameter and the square root of the sample size. Thus, using the standard error of the genetic marginal effects for the mean level of the moderator (which has the highest level of statistical precision) and the overall sample size from the GWAS which is the effective sample size at the mean of the moderator, we calculate the standard deviation of the marginal effect (SD).

$$SD = \sqrt{N}\ x\ SE_{ME.MEAN} \quad \text{Eq. 5}$$

Then assuming the SD is homoskedastic, we can calculate the effective sample size, N_{eff}, for any marginal effect by solving for N, using the calculated SE_{ME}.

$$N_{eff} = \left(\frac{SD}{SE_{ME}}\right)^2 \quad \text{Eq. 6}$$

N_{eff} can then be used calculate h^2_{SNP}.

Estimating h^2_{SNP}. LDSC requires GWAS summary statistics to calculate h^2_{SNP}. After 1) conducting the GxE GWAS or obtaining GxE GWAS summary statistics, 2) calculating genetic marginal effects, and 3) calculating the effective sample size for the marginal effects, users will have all the necessary information to use LDSC to estimate h^2_{SNP} (17). As genetic marginal effects can be interpreted in the same ways as other GWAS summary statistics, h^2_{SNP} for a particular value of a marginal effect can be interpreted in the same way as standard h^2_{SNP}.

Sample for the Demonstration Analyses. We used data from the UK Biobank (application number 57923) to conduct the demonstration analyses. The UK Biobank is a large, phenotypically rich dataset, containing information pertaining to general demographics to detailed health information (20). We used data from individuals of European ancestry and selected body mass index (BMI) as our outcome variable.

Subsequently we selected two moderators known to influence BMI: biological sex (28,29) and age (34).

As GxE summary statistics were unavailable, we first conducted GxE GWAS in GW-SEM (35). Age, sex, and the first ten genetic principal components were included as covariates, as were interactions between the moderator (i.e., sex or age depending on the model) and the first ten PCs (36). Following the GxE GWAS, genetic marginal effects, standard errors, z-statistics, and p-values were calculated. For the sex moderated GWAS, marginal effects were calculated for males and females, and for the age moderated GWAS, genetic marginal effects were calculated for ages 40, 50, 60, and 70. Finally, h^2_{SNP} was estimated for each level for the genetic marginal effects.

Software Requirements: The following software tools are required: R Core Team (2023). _R: A Language and Environment for Statistical Computing_. R Foundation for Statistical Computing, Vienna, Austria. (https://www.R-project.org/); OpenMx (https://CRAN.R-project.org/package=OpenMx); GW-SEM (https://github.com/jpritikin/gwsem); and LDSC (https://github.com/bulik/ldsc).

References

1. Mather K, Jinks JL. Biometrical Genetics [Internet]. Boston, MA: Springer US; 1982 [cited 2024 Apr 30]. Available from: http://link.springer.com/10.1007/978-1-4899-3406-2

2. Korkeila M, Kaprio J, Rissanen A, Koskenvuo M. Effects of gender and age on the heritability of body mass index. Int J Obes. 1991 Oct;15(10):647–54.

3. Hallmayer J, Cleveland S, Torres A, Phillips J, Cohen B, Torigoe T, et al. Genetic Heritability and Shared Environmental Factors Among Twin Pairs With Autism. Archives of General Psychiatry. 2011 Nov 1;68(11):1095–102.

4. Zadro JR, Shirley D, Pinheiro MB, Sánchez-Romera JF, Pérez-Riquelme F, Ordoñana JR, et al. Does educational attainment increase the risk of low back pain when genetics are considered? A population-based study of Spanish twins. Spine J. 2017 Apr;17(4):518–30.

5. Knigge A, Maas I, Stienstra K, de Zeeuw EL, Boomsma DI. Delayed tracking and inequality of opportunity: Gene-environment interactions in educational attainment. NPJ Sci Learn. 2022 May 4;7(1):6.

6. Tahmasbi R, Evans LM, Turkheimer E, Keller MC. Testing the moderation of quantitative gene by environment interactions in unrelated individuals [Internet]. bioRxiv; 2017 [cited 2023 Aug 9]. p. 191080. Available from: https://www.biorxiv.org/content/10.1101/191080v1

7. Roy-Gagnon MH. Investigating Gene–Gene and Gene–Environment Interactions in the Association Between Overnutrition and Obesity-Related Phenotypes. Frontiers in Genetics. 2019;10:10.

8. Dahl A, Nguyen K, Cai N, Gandal MJ, Flint J, Zaitlen N. A Robust Method Uncovers Significant Context-Specific Heritability in Diverse Complex Traits. American Journal of Human Genetics. 2020 Jan 1;106(1):71.

9. Shin J, Lee SH. GxEsum: a novel approach to estimate the phenotypic variance explained by genome-wide GxE interaction based on GWAS summary statistics for biobank-scale data. Genome Biology. 2021 Jun 21;22(1):183.

10. Werme J, van der Sluis S, Posthuma D, de Leeuw CA. Genome-wide gene-environment interactions in neuroticism: an exploratory study across 25 environments. Transl Psychiatry. 2021 Dec;11(1):180.

11. Miao J, Song G, Wu Y, Hu J, Wu Y, Basu S, et al. Reimagining Gene-Environment Interaction Analysis for Human Complex Traits [Internet]. Genetics; 2022 Dec [cited 2023 Aug 17]. Available from: http://biorxiv.org/lookup/doi/10.1101/2022.12.11.519973

12. Srivastava AK, Williams SM, Zhang G. Heritability Estimation Approaches Utilizing Genome-Wide Data. Current Protocols. 2023 Apr;3(4):e734.

13. Gauderman WJ, Mukherjee B, Aschard H, Hsu L, Lewinger JP, Patel CJ, et al. Update on the State of the Science for Analytical Methods for Gene-Environment Interactions. American Journal of Epidemiology. 2017 Oct 1;186(7):762–70.

14. McAllister K, Mechanic LE, Amos C, Aschard H, Blair IA, Chatterjee N, et al. Current Challenges and New Opportunities for Gene-Environment Interaction Studies of Complex Diseases. American Journal of Epidemiology. 2017 Oct 1;186(7):753–61.

15. Brandes N, Weissbrod O, Linial M. Open problems in human trait genetics. Genome Biology. 2022 Jun 20;23(1):131.

16. Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: A Tool for Genome-wide Complex Trait Analysis. Am J Hum Genet. 2011 Jan 7;88(1):76–82.

17. Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J, Schizophrenia Working Group of the Psychiatric Genomics Consortium, et al. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet. 2015 Mar;47(3):291–5.

18. Verhulst B, Pritikin JN, Clifford J, Prom-Wormley E. Using Genetic Marginal Effects to Study Gene-Environment Interactions with GWAS Data. Behav Genet. 2021 May;51(3):358–73.

19. Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh PR, et al. An atlas of genetic correlations across human diseases and traits. Nat Genet. 2015 Nov;47(11):1236–41.

20. Allen NE, Sudlow C, Peakman T, Collins R, on behalf of UK Biobank. UK Biobank Data: Come and Get It. Sci Transl Med [Internet]. 2014 Feb 19 [cited 2021 Nov 4];6(224). Available from: https://www.science.org/doi/10.1126/scitranslmed.3008601

21. Bredella MA. Sex Differences in Body Composition. Adv Exp Med Biol. 2017;1043:9–27.

22. Morley JE. Decreased Food Intake With Aging. The Journals of Gerontology: Series A. 2001 Oct 1;56(suppl_2):81–8.

23. Drewnowski A, Shultz JM. Impact of aging on eating behaviors, food choices, nutrition, and health status. J Nutr Health Aging. 2001;5(2):75–9.

24. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature. 2015 Feb 12;518(7538):197–206.

25. Yengo L, Sidorenko J, Kemper KE, Zheng Z, Wood AR, Weedon MN, et al. Meta-analysis of genome-wide association studies for height and body mass index in ~700000 individuals of European ancestry. Hum Mol Genet. 2018 Oct 15;27(20):3641–9.

26. Marderstein AR, Davenport ER, Kulm S, Van Hout CV, Elemento O, Clark AG. Leveraging phenotypic variability to identify genetic interactions in human phenotypes. Am J Hum Genet. 2021 Jan 7;108(1):49–67.

27. Randall JC, Winkler TW, Kutalik Z, Berndt SI, Jackson AU, Monda KL, et al. Sex-stratified Genome-wide Association Studies Including 270,000 Individuals Show Sexual Dimorphism in Genetic Loci for Anthropometric Traits. PLoS Genet. 2013 Jun 6;9(6):e1003500.

28. Rawlik K, Canela-Xandri O, Tenesa A. Evidence for sex-specific genetic architectures across a spectrum of human complex traits. Genome Biology. 2016 Jul 29;17(1):166.

29. Link JC, Reue K. The Genetic Basis for Sex Differences in Obesity and Lipid Metabolism. Annu Rev Nutr. 2017 Aug 21;37:225–45.

30. Rosa-Caldwell ME, Greene NP. Muscle metabolism and atrophy: let's talk about sex. Biology of Sex Differences. 2019 Aug 28;10(1):43.

31. Elks CE, den Hoed M, Zhao JH, Sharp SJ, Wareham NJ, Loos RJF, et al. Variability in the Heritability of Body Mass Index: A Systematic Review and Meta-Regression. Front Endocrinol (Lausanne). 2012 Feb 28;3:29.

32. Min J, Chiu DT, Wang Y. Variation in the Heritability of Body Mass Index Based on Diverse Twin Studies: A Systematic Review. Obes Rev. 2013 Nov;14(11):871–82.

33. Poveda A, Chen Y, Brändström A, Engberg E, Hallmans G, Johansson I, et al. The heritable basis of gene–environment interactions in cardiometabolic traits. Diabetologia. 2017 Mar 1;60(3):442–52.

34. Robinson MR, English G, Moser G, Lloyd-Jones LR, Triplett MA, Zhu Z, et al. Genotype–covariate interaction effects and the heritability of adult body mass index. Nat Genet. 2017 Aug;49(8):1174–81.

35. Pritikin JN, Neale MC, Prom-Wormley EC, Clark SL, Verhulst B. GW-SEM 2.0: Efficient, Flexible, and Accessible Multivariate GWAS. Behav Genet. 2021 May;51(3):343–57.

36. Keller MC. Gene × Environment Interaction Studies Have Not Properly Controlled for Potential Confounders: The Problem and the (Simple) Solution. Biological Psychiatry. 2014 Jan;75(1):18–24.

Figures and Figure Captions

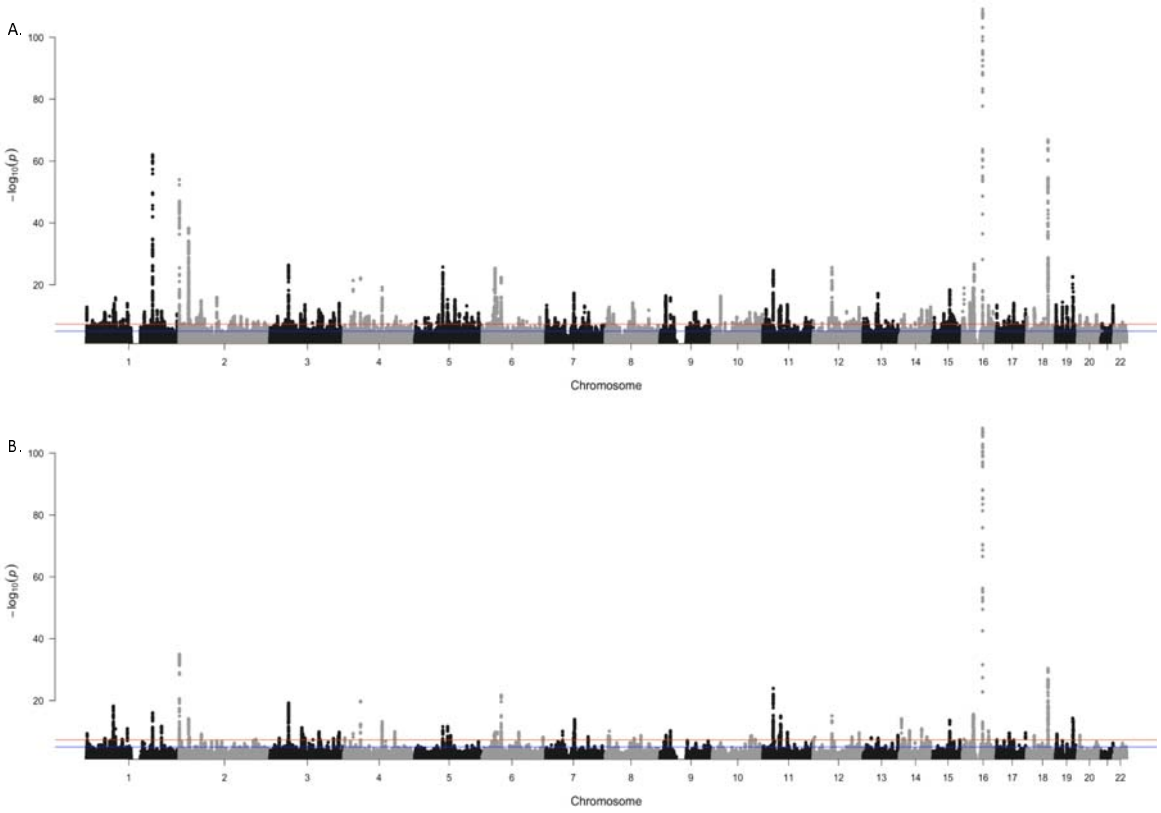
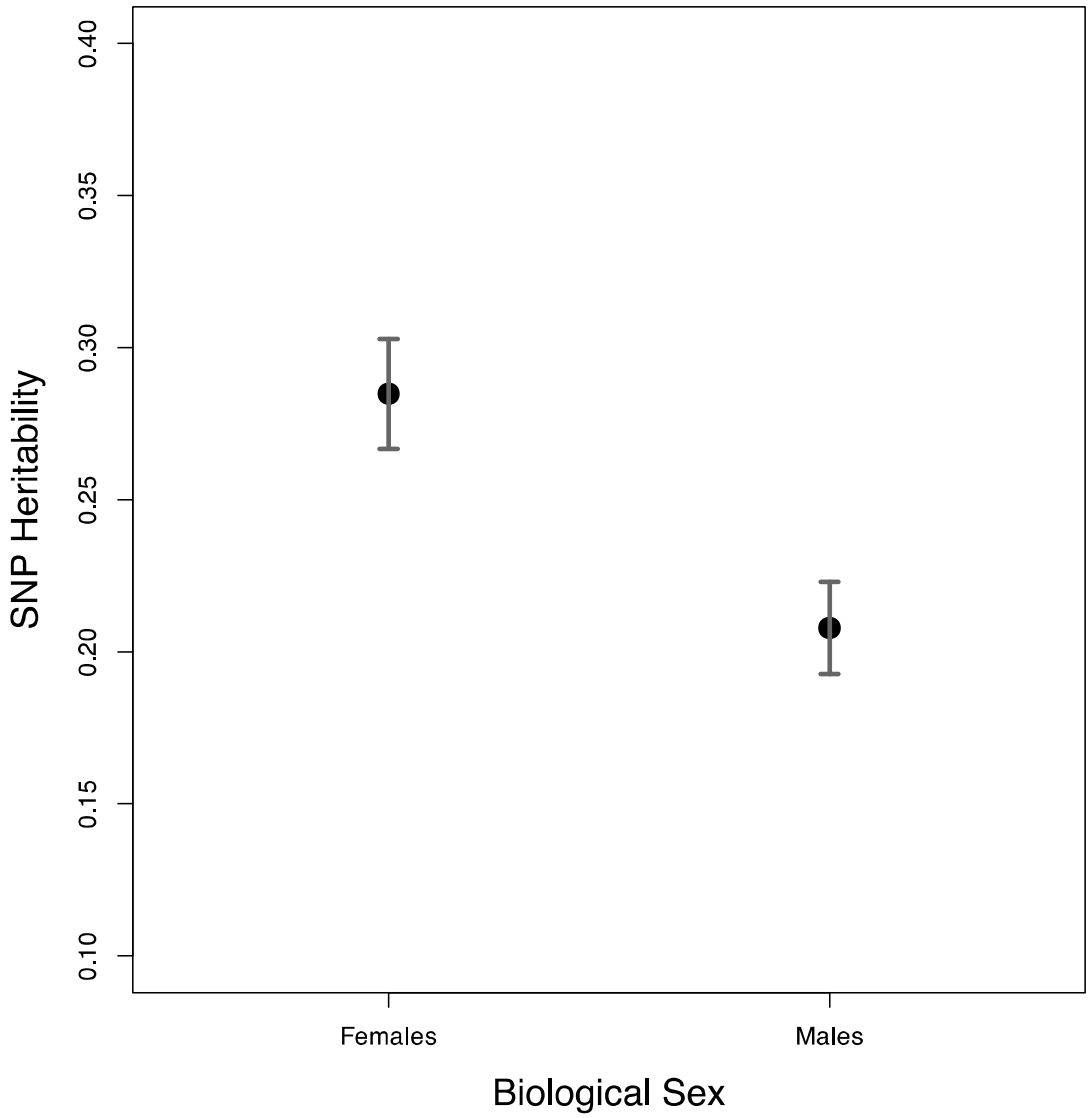


Figure 1: Manhattan Plots of BMI moderated by biological sex. Manhattan plots showing the statistical significance of biological sex for each SNP on BMI, where A. is biological females and B. is biological males. The red line represents genome-wide significance ($5x10^{-8}$), and the blue line represents nominal significance (0.05).



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412 **Figure 2: h^2_{SNP} of BMI moderated by biological sex**. h^2_{SNP} for biological females and males with 95%

413 confidence intervals represented by the grey bars.

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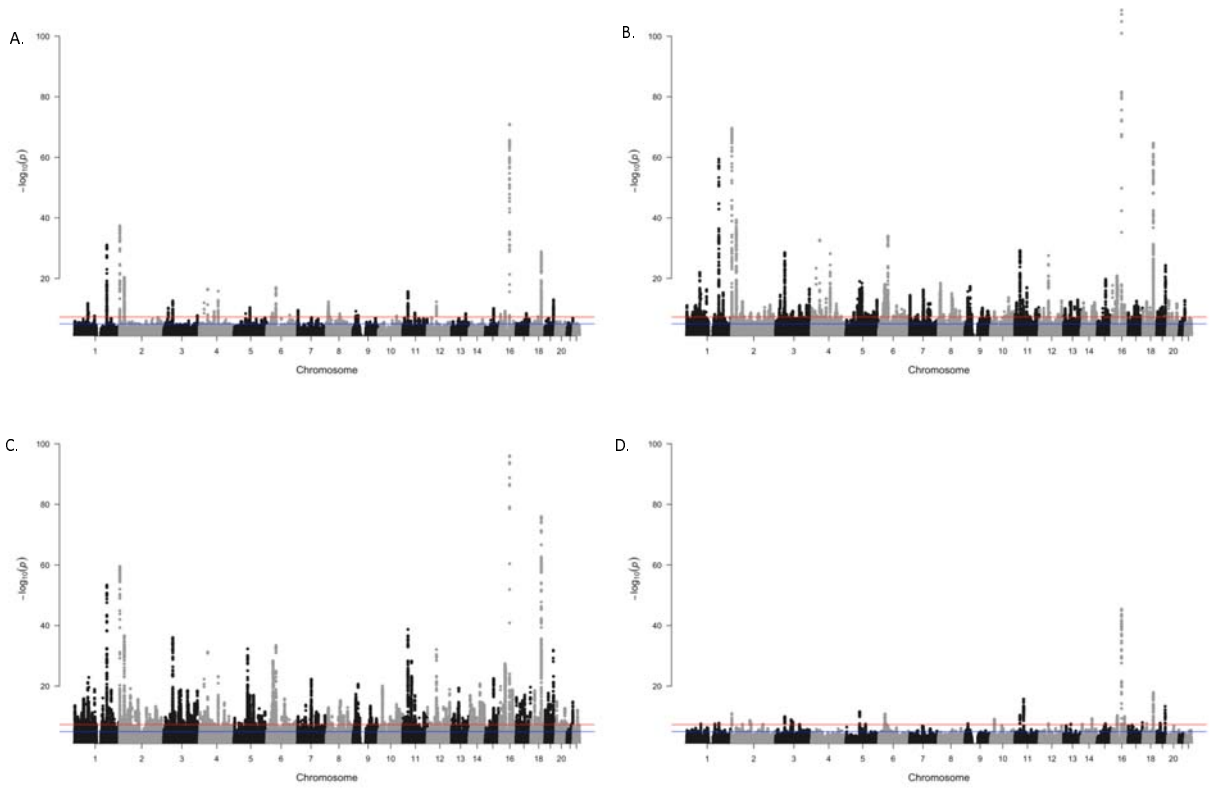

Figure 3: Manhattan Plots of BMI moderated by age. Manhattan plots showing the statistical significance of the selected marginal effects for each SNP on BMI, where A. is 40 years of age, B. is 50 years of age, C. 60 years of age, and D. 70 years of age. The red line represents genome-wide significance ($5x10^{-8}$), and the blue line represents nominal significance (0.05).

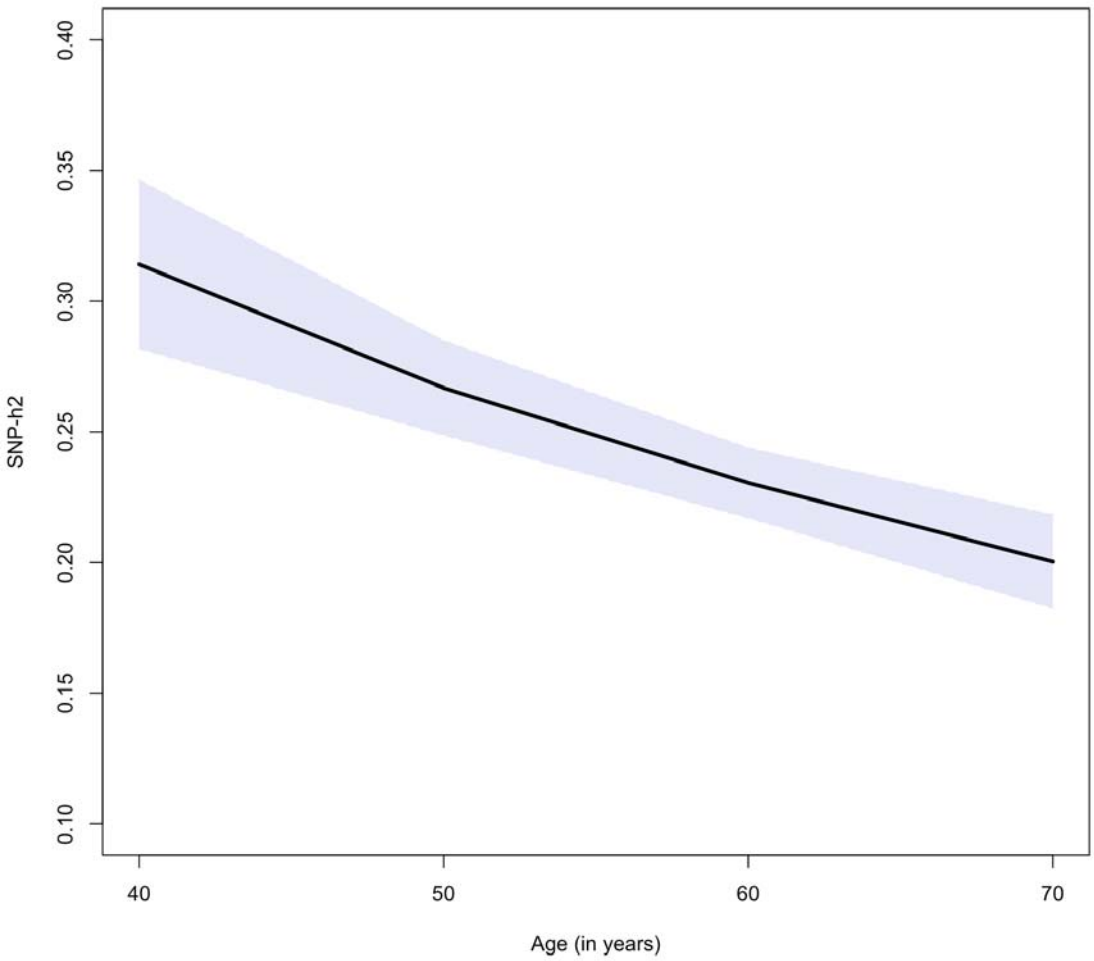

Figure 4: h^2_{SNP} of BMI moderated by age. h^2_{SNP} for ages 40, 50, 60 and 70 with 95% confidence intervals represented by the purple shaded region.

Declarations

Ethics approval and consent to participate

Not Applicable

Consent for publication

Not Applicable

Availability of data and materials

Data from the UKB was accessed using application 57923 and is subject to restrictions by the UKB and so is not publicly available.

Competing interests

Not Applicable

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Authors' contributions

BV designed the study. SB conducted all moderated GWAS. SB and BV conducted moderated heritability analyses and interpreted the results. BV and EPW developed the moderated heritability methodology. All authors contributed in writing the manuscript. All authors read and approved the final manuscript.

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Not Applicable