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Supplementary Materials for

Genotype-by-environment interactions inferred from genetic effects on phenotypic variability in the UK Biobank

Huanwei Wang, Futao Zhang, Jian Zeng, Yang Wu, Kathryn E. Kemper, Angli Xue, Min Zhang, Joseph E. Powell, Michael E. Goddard, Naomi R. Wray, Peter M. Visscher, Allan F. McRae, Jian Yang*

*Corresponding author. Email: jian.yang.qt@gmail.com

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Supplementary Notes

Note S1. Theoretical derivation of vQTL as a consequence of GEI

It has been shown by Pare et al.[17] that the interaction of a genetic variant with a genetic or environmental factor for a trait (e.g., GEI) can lead to differences in variance of the trait across genotype classes of the variant. Take GEI as an example. Under a GEI model, a phenotype *y* is affected by a genetic variant x_g, an environmental factor x_E, and an interaction term $x_g x_E$, i.e.

$$y = \mu + \beta_g x_g + \beta_E x_E + \beta_{gE} x_g x_E + e$$

where μ is the intercept term, $\beta_g, \beta_E, \beta_{gE}$ are the effects of x_g, x_E and $x_g x_E$, respectively, and e is the residual. The phenotypic variance conditional on the genotype of the variant is

$$Var(y|x_g) = Var(\mu + \beta_g x_g + \beta_E x_E + \beta_{gE} x_g x_E + e)$$

$$= Var((\beta_E + \beta_{gE} x_g) x_E + \mu + \beta_g x_g + e)$$

$$= (\beta_E + \beta_{gE} x_g)^2 Var(x_E) + Var(e)$$

assuming that x_g, x_E and e are independent of each other. This equation shows that the phenotypic variance given a genotype is dependent on the genotype in the presence of GEI (i.e., $\beta_{gE} \neq 0$).

Note S2. The Bartlett's test, the FK test, and the DGLM test

We evaluated four variance quantitative trait locus (vQTL) methods by simulation. Details of the Levene's test have been described in the Methods section of the main text, and details of the other three methods are described below.

The Bartlett's test[29] is one of the earliest methods used to test the inequality of variance but known to be sensitive to the violation of normality assumption[28]. The Bartlett's test-statistic is

$$\frac{(n-k)ln(S_p^2) - \sum_{i=1}^{k}(n_i - 1)ln(S_i^2)}{1 + \frac{1}{3(k-1)}(\sum_{i=1}^{k}(\frac{1}{n_i - 1}) - \frac{1}{n-k})} \sim \chi_{k-1}^2$$

where n is the total sample size; k is the number of groups; n_i is the sample size of the i-th group, $n = \sum_{i=1}^{k} n_i$; S_i^2 is the sample variance in the i-th group; S_p^2 is the pooled estimate of the variance, $S_p^2 = \frac{1}{n-k}\sum_{i=1}^{k}(n_i - 1)S_i^2$. We used the *bartlett.test()* function in R for data analysis.

The Fligner-Killeen (median) test[32] is a rank-based method with similar performance to the Levene's test. The Fligner-Killeen test-statistic is

$$\frac{\sum_{i=1}^{k} n_i (\overline{A}_i - \overline{a})^2}{V^2} \sim \chi_{k-1}^2$$

where n is the total sample size; k is the number of groups; n_i is the sample size of the i-th group, $n = \sum_{i=1}^{k} n_i$; a is the "rank score" assigned by $\Phi^{-1}(\frac{1+\frac{j}{n+1}}{2})$ with j being the rank of all observations based on $|y_{ij} - \tilde{y}_i|$, $\tilde{y}_i$ being the median of the i-th group and Φ^{-1} being the standard normal quantile function; $\overline{A}_i$ is the mean rank score of the i-th group; $\overline{a}$ is the mean rank score of all observations; V^2 is the sample variance of rank scores of all observations. We used the *fligner.test()* function in R for data analysis.

Ronnegard et al.[33,34] proposed a double generalized linear model (DGLM)[35] that contained two linear models, one for the effect on the trait mean and the other for the effect on the trait variance

$$E(y|u, u_d) = \mu;\ \mu = Xb + Zu$$

$$var(y|u, u_d) = \phi;\ log(\phi) = X_d b_d + Z_d u_d$$

where y is the phenotype; u and u_d are the random effects on the mean and variance (dispersion), respectively; b and b_d are the fixed effects on the mean and variance (dispersion), respectively. We used "dglm" package in R for data analysis.

Note S3. Rank-based inverse-normal transformation

We used the simulated data to compare several phenotype processing strategies. Rank-based inverse-normal transformation (RINT) was conducted based on the formula below[68,69]

$$y_i^t = \Phi^{-1}\left(\frac{r_i - c}{n - 2c + 1}\right)$$

where r_i is the ordinary rank of the *i*-th observation; *n* is the total number of observations; *c* is a constant value (set to 0.5 in this study); Φ^{-1} is the standard normal quantile function; y_i^t is the transformed value for the *i*-th observation. For RINT after covariate adjustment, we first adjusted the phenotypes for covariates and then transformed the residuals by RINT.

Note S4. The effective number of independent traits

As some phenotypes were correlated with each other (Figure S2a), we used an eigendecomposition analysis to estimate the effective number of independent traits[66]. Let **y** be a vector of *p* phenotypes and **V** be the variance-covariance matrix of vector **y**. The eigen decomposition of matrix **V** is

$$\mathbf{V} = \mathbf{Q'\Lambda Q}$$

where **Q** is the matrix of eigenvectors and **Λ** is the diagonal matrix comprised of the ordered eigenvalues $\lambda_1 \ldots \lambda_p$. The effective number of *p* phenotypes can be estimated as[66]

$$\frac{(\sum_{k=1}^{p} \lambda_k)^2}{\sum_{k=1}^{p} \lambda_k^2}$$

Note S5. Definitions of the three environmental factors—PA, SB, and smoking

Physical activity (PA) was assessed based on the questions from International Physical Activity Questionnaire (IPAQ)[70], including the number of days per week of walking (DayW), the number of days per week of moderate physical activity (DayW), the number of days per week of vigorous physical activity more than 10 minutes (DayV), the duration of walking (DurW), the duration of moderate physical activity (DurM), and the duration of vigorous physical activity (DurV) (Table S1b). According to the IPAQ analysis guideline[67], the metabolic equivalents (MET)

minutes for walking (METW), moderate physical activity (METM), vigorous physical activity (METV), and the total MET (METT) minutes were calculated by

$$METW = 3.3 \times DayW \times DurW$$

$$METM = 4.0 \times DayM \times DurM$$

$$METV = 8.0 \times DayV \times DurV$$

$$METT = METW + METM + METV$$

The physical activity level was then labelled as 1) "high" (coded as 3) when "DayV≥3 and METT≥1500" or "DayW+DayM+DayV≥7 and METT≥3000"; 2) "moderate" (coded as 2) when "DayV≥3 and DurV≥20" or "DayM≥5 and DurM≥30" or "DayW≥5 and DurW≥30" or "DayW+DayM+DayV≥5 and METT≥600"; 3) "low" (coded as 1) when no activity or some activity was reported but not enough to meet the criteria above.

Sedentary behaviour (SB) was defined as the sum of the time spent driving (TimeD), non-work-related computer using (TimeC) or TV watching (TimeTV) (Table S1b). We removed outliers 5 SD from the mean; the remaining data ranged from 0 to 17 hours.

Smoking was assessed based on the answers to two questions about current tobacco smoking (CurS) and past tobacco smoking (PastS) (Table S1b). Individuals were classified as "never smoker" (coded as 0) if CurS = "no" and PastS = "tried once or twice" or "never". Individuals were classified as "ever smoker" (coded as 1) if CurS = "most days" or "occasionally", or PastS = "most days" or "occasionally".

Note S6. Expected inflation in the Levene's test statistic due to phantom vQTL effect

6.1 Two loci

Let us consider two genetic loci A and B, and let p_A and p_B denote the frequencies of the major alleles of A and B, respectively, and p_{AB} denote the haplotype frequency of the two major alleles. We know that the LD (including D, D' and r^2) between the two loci, the genotype frequencies of the two loci, and the genotype frequency of locus A conditional on locus B are a function of p_A, p_B and p_{AB}[71].

Allele and haplotype frequencies

	Locus B		
Locus A	Major allele B	Minor allele b	Allele frequency
Major allele A	p_{AB}	$p_{Ab} = p_A - p_{AB}$	p_A
Minor allele a	$p_{aB} = p_B - p_{AB}$	$p_{ab} = 1 - p_A - p_B + p_{AB}$	$p_a = 1 - p_A$
Allele frequency	p_B	$p_b = 1 - p_B$	1

p_{AB} and LD between A and B as a function of p_A and p_B

Measures	Definition	Maximum value	Minimum value
p_{AB}	-	$min[p_A, p_B]$	$p_A + p_B - 1$
D	$D = p_{AB} - p_A \times p_B$	$min[p_A(1-p_B), p_B(1-p_A)]$	$-(1-p_A)(1-p_B)$
D'	$D' = \frac{D}{\min[p_A(1-p_B), p_B(1-p_A)]}$, if D > 0	1	-1
	$D' = \frac{D}{min[p_A p_B, (1-p_A)(1-p_B)]}$, if D < 0		
r^2	$r^2 = \frac{D^2}{p_A p_B (1-p_A)(1-p_B)}$	$min[\frac{p_A(1-p_B)}{(1-p_A)p_B}, \frac{(1-p_A)p_B}{p_A(1-p_B)}]$	0

Genotype frequencies of the two loci

	Genotype BB	Genotype Bb	Genotype bb	Genotype Frequency
Genotype AA	$p_{AABB} = p_{AB}^2$	$p_{AABb} = 2p_{AB}p_{Ab}$ $= 2p_{AB}(p_A - p_{AB})$	$p_{AAbb} = p_{Ab}^2 = (p_A - p_{AB})^2$	p_A^2

Genotype Aa	$p_{AaBB} = 2p_{AB}p_{aB}$ $= 2p_{AB}(p_B - p_{AB})$	$p_{AaBb} = 2(p_{AB}p_{ab} + p_{Ab}p_{aB})$ $= 2[p_{AB}(1 - p_A - p_B + p_{AB})$ $+(p_A - p_{AB})(p_B - p_{AB})]$	$p_{Aabb} = 2p_{Ab}p_{ab}$ $= 2(p_A - p_{AB})(1 - p_A - p_B + p_{AB})$	$2p_A(1 - p_A)$
Genotype aa	$p_{aaBB} = p_{aB}^2$ $= (p_B - p_{AB})^2$	$p_{aaBb} = 2p_{aB}p_{ab}$ $= 2(p_B - p_{AB})(1 - p_A - p_B + p_{AB})$	$p_{aabb} = p_{ab}^2$ $= (1 - p_A - p_B + p_{AB})^2$	$(1 - p_A)^2$
Genotype Frequency	p_B^2	$2p_B(1 - p_B)$	$(1 - p_B)^2$	1

Genotype frequency of locus A conditioning on locus B

Genotype	AA	Aa	aa
BB	$P(AA \mid BB) = \frac{p_{AABB}}{p_{BB}}$ $= \frac{p_{AB}^2}{p_B^2}$	$P(Aa \mid BB) = \frac{p_{AaBB}}{p_{BB}}$ $= \frac{2p_{AB}(p_B - p_{AB})}{p_B^2}$	$P(aa \mid BB) = \frac{p_{aaBB}}{p_{BB}}$ $= \frac{(p_B - p_{AB})^2}{p_B^2}$
Bb	$P(AA \mid Bb) = \frac{p_{AABb}}{p_{Bb}}$ $= \frac{p_{AB}(p_A - p_{AB})}{p_B(1 - p_B)}$	$P(Aa \mid Bb) = \frac{p_{AaBb}}{p_{Bb}}$ $= \frac{p_{AB}(1 - p_A - p_B + p_{AB}) + (p_A - p_{AB})(p_B - p_{AB})}{p_B(1 - p_B)}$	$P(aa \mid Bb) = \frac{p_{aaBb}}{p_{Bb}}$ $= \frac{(p_B - p_{AB})(1 - p_A - p_B + p_{AB})}{p_B(1 - p_B)}$
bb	$P(AA \mid bb) = \frac{p_{AAbb}}{p_{bb}}$ $= \frac{(p_A - p_{AB})^2}{(1 - p_B)^2}$	$P(Aa \mid bb) = \frac{p_{Aabb}}{p_{bb}}$ $= \frac{2(p_A - p_{AB})(1 - p_A - p_B + p_{AB})}{(1 - p_B)^2}$	$P(aa \mid bb) = \frac{p_{aabb}}{p_{bb}}$ $= \frac{(1 - p_A - p_B + p_{AB})^2}{(1 - p_B)^2}$

6.2 Causal variant (locus A) with an additive genetic effect

Let us assume that locus A is the causal variant with an additive genetic effect (b_c) on a phenotype

$$y \sim (\mu + b_c x_a, \sigma^2)$$

Genotype	Code (x_a)	$E(y\|x_a)$	$Var(y\|x_a)$	$E(y^2\|x_a)$
AA	0	μ	σ^2	$\sigma^2 + \mu^2$
Aa	1	$\mu + b_c$	σ^2	$\sigma^2 + (\mu + b_c)^2$
aa	2	$\mu + 2b_c$	σ^2	$\sigma^2 + (\mu + 2b_c)^2$

The expected phenotypic mean and variance given a genotype of locus B (marker) can be found in the tables below.

Genotype	Code (x_b)	$E(y\|x_b)$	$Var(y\|x_b)$
BB	0	$\mu + \frac{2b_c(p_B - p_{AB})}{p_B}$	$\sigma^2 + \frac{2{b_c}^2(p_B - p_{AB})p_{AB}}{p_B^2}$
Bb	1	$\mu + \frac{b_c(2p_B - p_{AB} - 2p_B^2 + 2p_B p_{AB} - p_A p_B)}{p_B(1 - p_B)}$ $= \mu + \frac{b_c[(p_B - p_{AB})(1 - p_B) + (1 - p_A - p_B + p_{AB})p_B]}{p_B(1 - p_B)}$	σ^2 $+ \frac{{b_c}^2(p_B p_{AB} - p_{AB}^2 + 2p_B p_{AB}^2 - 3p_B^2 p_{AB} + p_A p_B^2 - 2p_B^2 p_{AB}^2 + 2p_A p_B^2 p_{AB} + 2p_B^3 p_{AB} - p_A p_B^3 - p_A^2 p_B^2)}{p_B^2(1 - p_B)^2}$ $= \sigma^2 + \frac{{b_c}^2[(p_B - p_{AB})p_{AB}(1 - p_B)^2 + (1 - p_A - p_B + p_{AB})(p_A - p_{AB})p_B^2]}{p_B^2(1 - p_B)^2}$
bb	2	$\mu + \frac{2b_c(1 - p_A - p_B + p_{AB})}{1 - p_B}$	$\sigma^2 + \frac{2{b_c}^2(1 - p_A - p_B + p_{AB})(p_A - p_{AB})}{(1 - p_B)^2}$

We therefore can observe an additive effect on both mean (b_m) and variance (β_m) at the marker (locus B)

$$y \sim (\mu_m + b_m x_b, {\sigma^2}_m + \beta_m x_b)$$

where

- $\mu_m = \mu + \frac{2b_c(p_B - p_{AB})}{p_B}$
- $b_m = \frac{b_c(p_{AB} - p_A p_B)}{p_B(1 - P_B)}$

- $\sigma^2{}_m = \sigma^2 + \frac{2{b_c}^2(p_B - p_{AB})p_{AB}}{p_B^2}$
- $\beta_m = \frac{b_c^2[(1-2p_B)p_{AB}^2 + (2p_Ap_B + p_B - 1)p_Bp_{AB} + (1-p_A-p_B)p_Ap_B^2]}{p_B^2(1-p_B)^2}$

6.3 QTL test-statistics at the marker variant (locus B)

Assuming phenotypic variance of 1 (i.e., var(y) = 1), the variance explained by the marker variant (q_m^2) and the non-centrality parameter (NCP) of a chi-squared test for QTL effect at the marker can be written as

- $q_m^2 = 2p_B(1-p_B)b_m^2 = 2p_B(1-p_B)\frac{b_c^2(p_{AB}-p_Ap_B)^2}{p_B^2(1-p_B)^2} =$
- $2p_A(1-p_A)b_c^2\frac{(p_{AB}-p_Ap_B)^2}{p_A(1-p_A)p_B(1-p_B)} = q_c^2r^2$

- $\text{NCP} = \frac{nq_m^2}{1-q_m^2} = \frac{nq_c^2r^2}{1-q_c^2r^2}$

where n is the sample size, q_c^2 is the variance explained by the causal variant, and r^2 is the LD between the causal and the marker variants. This derivation is consistent with that in previous studies[72,73].

6.4 vQTL test statistic at the marker variant (locus B)

Under normality assumption, the distribution of the phenotype with respect to the marker variant can be written as

$$y \sim N(\mu_m + b_m x_b, \sigma^2{}_m + \beta_m x_b)$$

We then have

$$y - E(y|x_b) \sim N(0, \sigma^2{}_m + \beta_m x_b)$$

and $z = |y - \tilde{y}|$

$$z = |y - \tilde{y}| = |y - E(y|x_b)|$$

$$\sim \text{ Folded Normal Distribution}\left(\sqrt{\frac{2}{\pi}(\sigma^2{}_m + \beta_m x_b)}, (1 - \frac{2}{\pi})(\sigma^2{}_m + \beta_m x_b)\right)$$

Genotype	Code (x_b)	E($z|x_b$)	var($z|x_b$)	$E(z^2|x_b)$
BB	0	$\sqrt{\frac{2}{\pi}\sigma^2{}_m}$	$(1 - \frac{2}{\pi})\sigma^2{}_m$	$\sigma^2{}_m$
Bb	1	$\sqrt{\frac{2}{\pi}(\sigma^2{}_m + \beta_m)}$	$(1 - \frac{2}{\pi})(\sigma^2{}_m + \beta_m)$	$\sigma^2{}_m + \beta_m$
bb	2	$\sqrt{\frac{2}{\pi}(\sigma^2{}_m + 2\beta_m)}$	$(1 - \frac{2}{\pi})(\sigma^2{}_m + 2\beta_m)$	$\sigma^2{}_m + 2\beta_m$

$$E(z) = E(z|x_b = 0)P(x_b = 0) + E(z|x_b = 1)P(x_b = 1) + E(z|x_b = 2)P(x_b = 2)$$

$$= \sqrt{\frac{2}{\pi}\sigma^2{}_m}{p_B}^2 + \sqrt{\frac{2}{\pi}(\sigma^2{}_m + \beta_m)}2p_B(1 - p_B) + \sqrt{\frac{2}{\pi}(\sigma^2{}_m + 2\beta_m)}(1 - p_B)^2$$

$$E(z^2) = E(z^2|x_b = 0)P(x_b = 0) + E(z^2|x_b = 1)P(x_b = 1) + E(z^2|x_b = 2)P(x_b = 2)$$

$$= \sigma^2{}_m{p_B}^2 + (\sigma^2{}_m + \beta_m)2p_B(1 - p_B) + (\sigma^2{}_m + 2\beta_m)(1 - p_B)^2$$

$$= \sigma^2{}_m + 2(1 - p_B)\beta_m$$

$$var(z) = E(z^2) - [E(z)]^2 = \sigma^2{}_m + 2(1 - p_B)\beta_m - [E(z)]^2$$

The Levene's test is essentially one-way ANOVA test on the variable z (see the Methods section). We therefore have

$$E(SST) = E[\sum_{i=1}^{k}\sum_{j=1}^{n_i}(z_{ij} - z_{..})^2] = Var(z)n = (\sigma^2{}_m + 2(1 - p_B)\beta_m - [E(z)]^2)n;$$

$$E(SSE) = E\left[\sum_{i=1}^{k}\sum_{j=1}^{n_i}(z_{ij} - z_{i.})^2\right]$$

$$= (1-\frac{2}{\pi})\sigma^2{}_m n{p_B}^2 + (1-\frac{2}{\pi})(\sigma^2{}_m + \beta_m)n2p_B(1-p_B) + (1-\frac{2}{\pi})(\sigma^2{}_m + 2\beta_m)(1-p_B)^2$$

$$= (1-\tfrac{2}{\pi})(\sigma^2{}_m + 2(1-p_B)\beta_m)n;$$

$$E(SSR) = E(SST - SSE) = [\tfrac{2}{\pi}(\sigma^2{}_m + 2(1-p_B)\beta_m) - [E(z)]^2]n;$$

$$F_{\text{Levene}} = \frac{(n-3)E(SSR)}{(3-1)E(SSE)} \approx \frac{n}{2}\frac{E(SSR)}{E(SSE)} = \frac{n}{2}\frac{\frac{2}{\pi}(\sigma^2{}_m + 2(1-p_B)\beta_m) - [E(z)]^2}{(1-\frac{2}{\pi})(\sigma^2{}_m + 2(1-p_B)\beta_m)}$$

$$= \frac{n}{\pi-2}(1 - \frac{[\sqrt{\sigma^2{}_m}{p_B}^2 + \sqrt{\sigma^2{}_m + \beta_m}2p_B(1-p_B) + \sqrt{\sigma^2{}_m + 2\beta_m}(1-p_B)^2]^2}{\sigma^2{}_m + 2(1-p_B)\beta_m})$$

where F_{Levene} is the Levene's *F*-statistic; *SST*, *SSR* and *SSR* are the total sum of squares, regression sum of squares and error sum of squares, respectively, as defined in an ANOVA analysis.

Given that var(y) = 1, we can replace b_c^2 with $\frac{q_c^2}{2p_A(1-p_A)}$, and σ^2 with $1 - q_c^2$

$$\beta_m = \frac{q_c^2[(1-2p_B)p_{AB}^2 + (2p_Ap_B + p_B - 1)p_Bp_{AB} + (1-p_A-p_B)p_Ap_B^2]}{2p_A(1-p_A)p_B^2(1-p_B)^2}$$

$$\sigma^2{}_m = 1 - q_c^2 + \frac{(p_B - p_{AB})p_{AB}}{p_A(1-p_A)p_B^2}q_c^2$$

F_{Levene}

$$= \frac{n}{\pi-2}(1 - \frac{[\sqrt{\sigma^2{}_m}{p_B}^2 + \sqrt{\sigma^2{}_m + \beta_m}2p_B(1-p_B) + \sqrt{\sigma^2{}_m + 2\beta_m}(1-p_B)^2]^2}{\sigma^2{}_m + 2(1-p_B)\beta_m})$$

Therefore, the phantom vQTL test statistic is a function of sample size n, variance explained by the causal variant q_c^2, allele frequency of the causal variant p_A, allele frequency of the marker variant p_B, and the haplotype frequency p_{AB}. This formula has been confirmed by simulation (Figure S7a). We then computed F_{Levene} given a number of parameters including p_{AB} (equivalent to D' ranging from -1 to 1), p_a (ranging from 0.001 to 0.5, equivalent to p_A from 0.999 to 0.5), p_b (ranging from 0.05 to 0.5, equivalent to p_B from 0.95 to 0.5), q_c^2 (= 0.005, 0.01 or 0.02) and n (= 350,000) (Figure S7b-d).

Note S7. Acknowledgments

This study has been conducted using the UK Biobank resource under Application Number 12505. The UK Biobank was established by the Wellcome Trust medical charity, Medical Research Council, Department of Health, Scottish Government and the Northwest Regional Development Agency. It has also had funding from the Welsh Assembly Government, British Heart Foundation and Diabetes UK.

Supplementary Figures

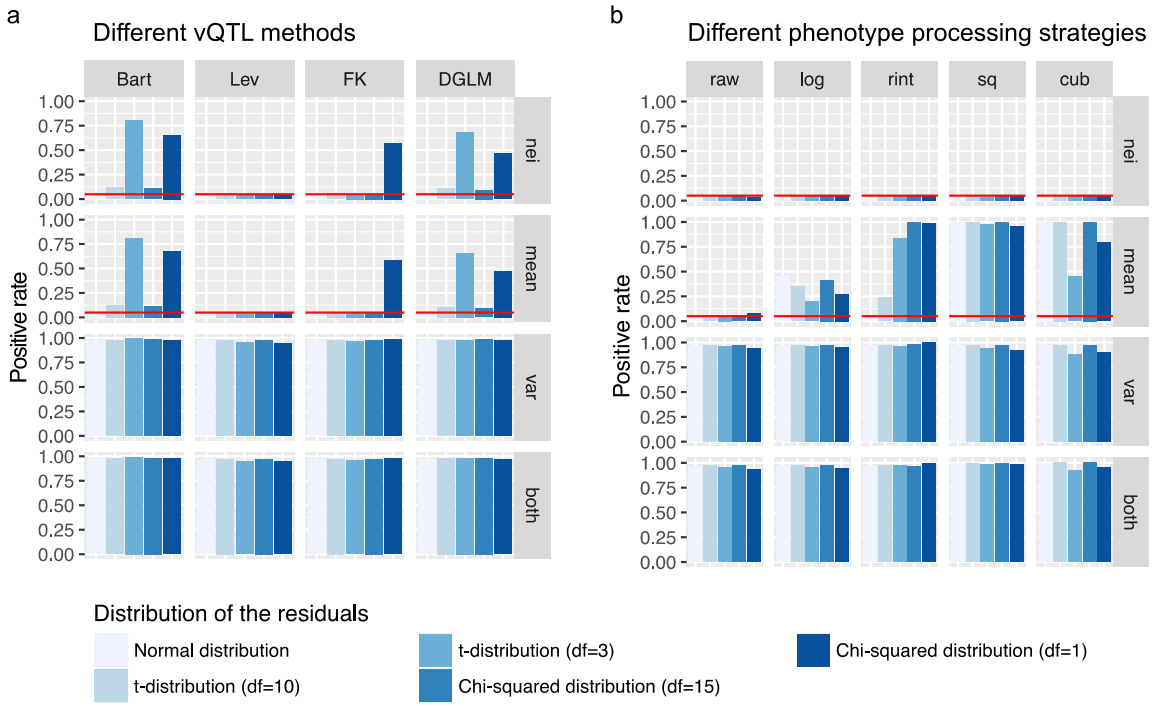


Fig. S1. Evaluation of statistical methods and phenotype processing strategies for the vQTL analysis by simulation based on a single-SNP model. Evaluation of statistical methods (a) and phenotype processing strategies (b) for vQTL analysis by simulation based on a single-SNP model. Phenotypes of 10,000 individuals were simulated based on one SNP and one error term in a single-SNP model (Methods). The SNPs effects were simulated under four scenarios: 1) effect on neither mean nor variance (nei), 2) effect on mean only (mean), 3) effect on variance only (var), or 4) effect on both mean and variance (both). The error term was generated from 5 different distributions: normal distribution, *t*-distribution with degree of freedom (df) = 10 or 3, or χ^2 distribution with df = 15 or 1. Four statistical test methods, i.e. the Bartlett's test (Bart), the Levene's test (Lev), the Fligner-Killen test (FK) and the DGLM, were used to detect vQTLs. In panel b, the Levene's test was used to analyse phenotypes processed using five strategies, i.e. raw phenotype (raw), raw phenotype adjusted for covariates (adj), rank-based inverse-normal transformation after adj (rint), logarithm transformation after adj (log), square transformation after adj (sq), and cube transformation after adj (cub). Positive rate is defined as the number of vQTLs with $p < 0.05$ divided by the total number of tests across 1,000 simulations, which is the FPR under the null ("nei" and "mean") and power under the alternative ("var" and "both"). The red horizontal line represents an FPR of 0.05.

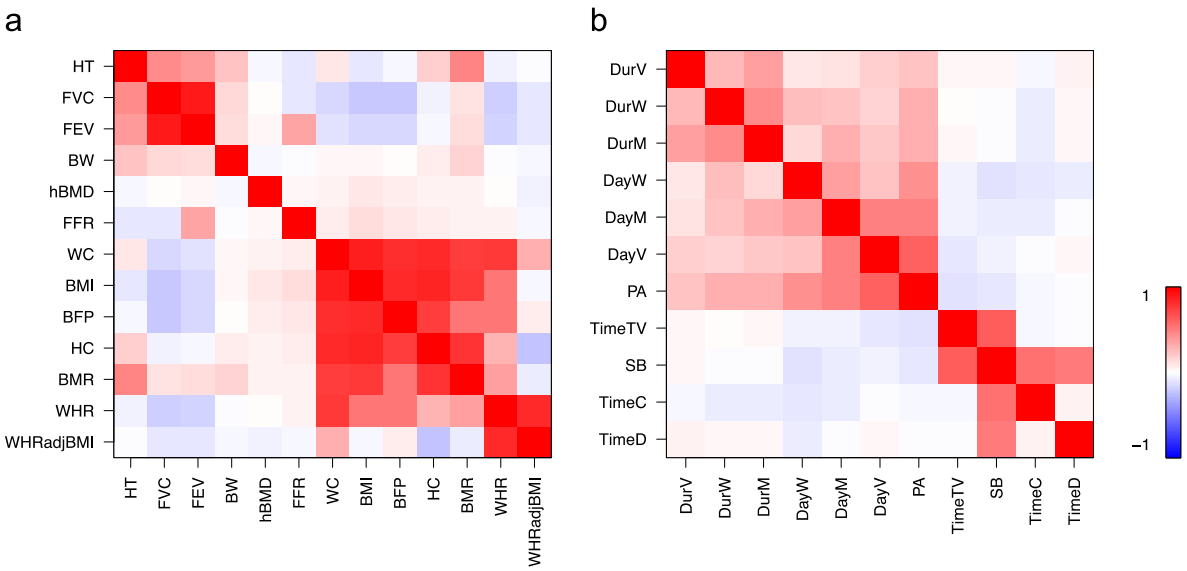
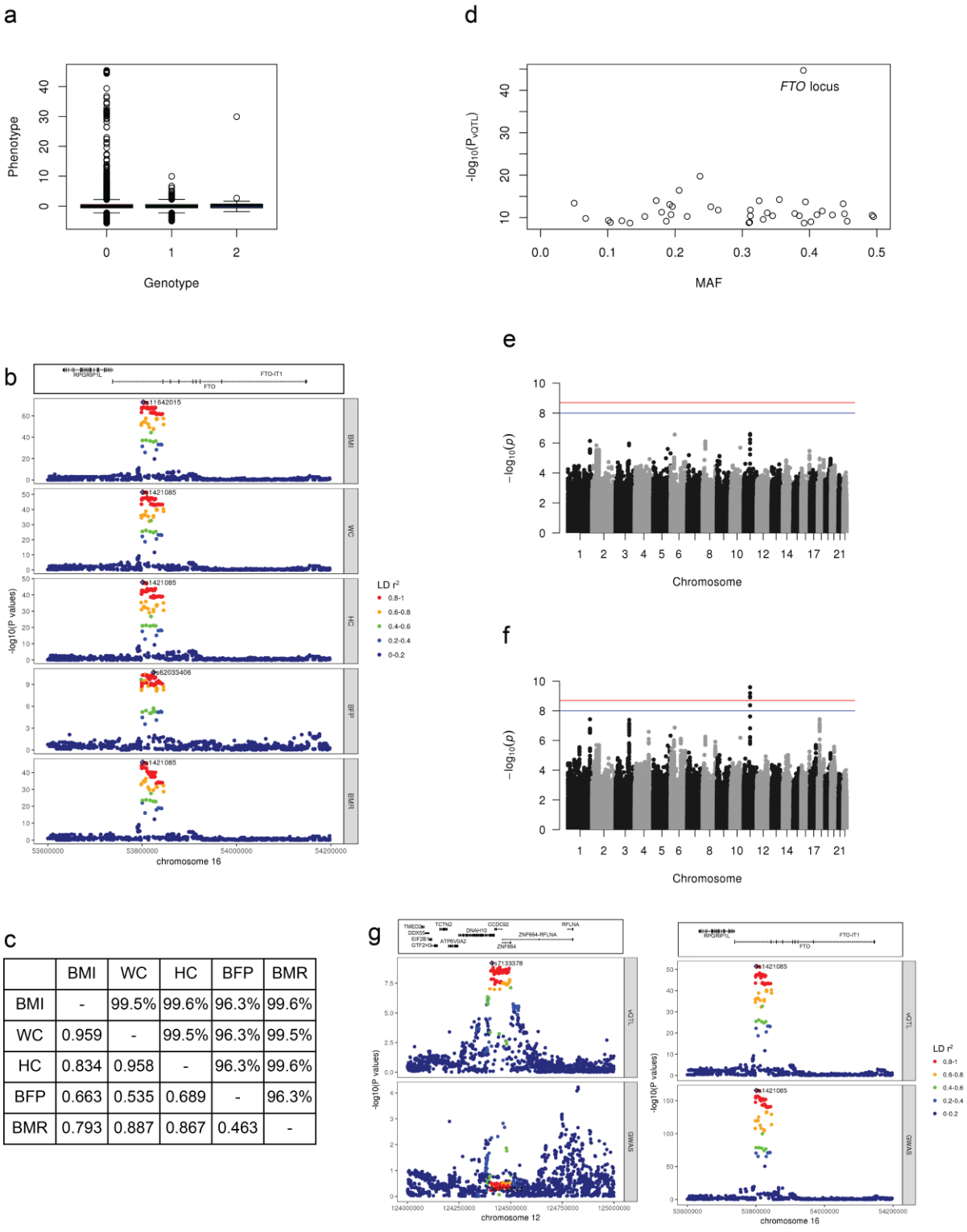


Fig. S2. Phenotypic correlations among 13 quantitative traits, and PA and SB measures in the UKB. Phenotypic correlations among (a) 13 quantitative traits and (b) PA and SB measures in the UKB. The Pearson's correlation coefficient was calculated between each pair of (a) the processed phenotypes or (b) the PA and SB measures. The order shown on the plot above was determined by hierarchical cluster analysis using the R function *hclust().*

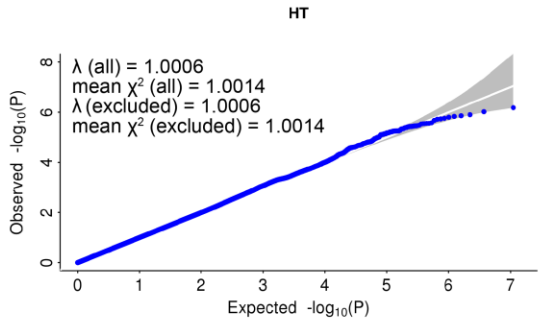


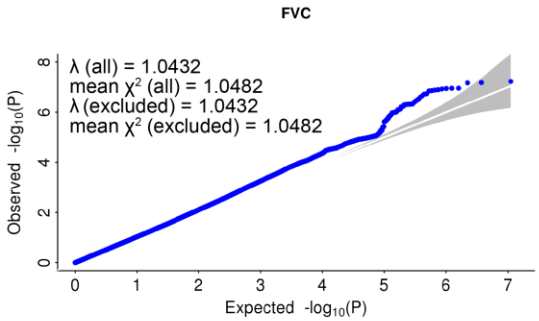
c

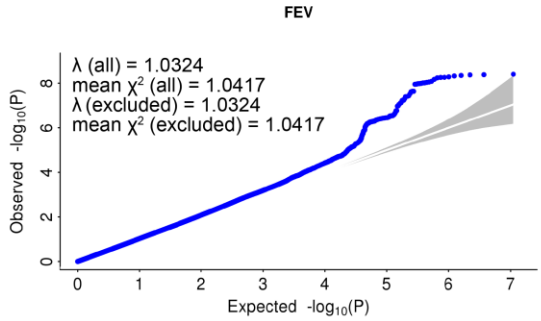
	BMI	WC	HC	BFP	BMR
BMI	-	99.5%	99.6%	96.3%	99.6%
WC	0.959	-	99.5%	96.3%	99.5%
HC	0.834	0.958	-	96.3%	99.6%
BFP	0.663	0.535	0.689	-	96.3%
BMR	0.793	0.887	0.867	0.463	-

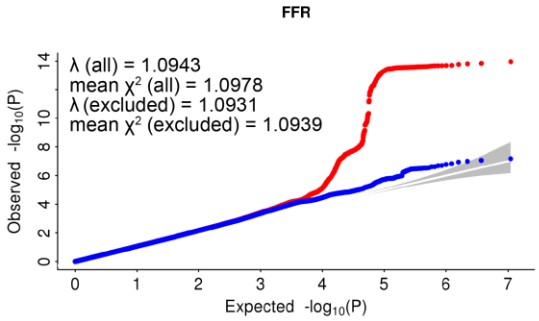
Fig. S3. Genome-wide vQTL and QTL analyses for 13 traits in the UKB. (a) Spurious vQTL association due to the coincidence of a minor allele with a phenotypic outlier. This is an example that a spurious vQTL signal (P_{vQTL} = 4.48×10^{-9}) at a low-MAF variant (MAF = 0.012) is caused by the coincidence of a minor allele with a phenotypic outlier for FVC. The variance of the phenotype (after covariates adjustment and standardisation) are 1.00, 0.83 and **20.20** in the three genotype groups of rs11102024 respectively. Note that for all the other vQTL results

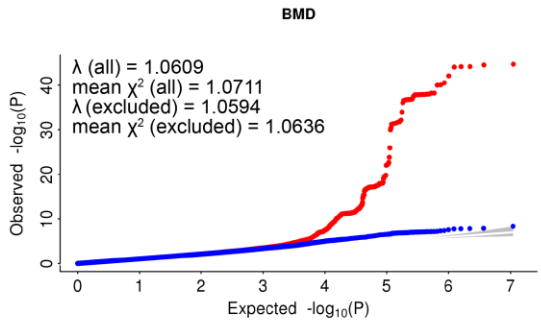
presented in this paper are from analyses excluding individuals with adjusted phenotypes more than 5 SD from the mean and SNPs with MAF < 0.05. (b) vQTL regional plot at the *FTO* locus for 5 traits. For each of the 5 traits for which the phenotypic variance is significantly associated with the *FTO* locus, vQTL test statistics ($-\log_{10}(P_{vQTL})$) are plotted against SNP positions surrounding the top vQTL SNP (represented by a purple diamond) at the *FTO* locus. SNPs in different levels of LD with the top vQTL SNP are shown in different colours. The RefSeq genes in the top panel are extracted from the UCSC Genome Browser (URLs). (c) Colocalization and HEIDI tests for the vQTL associations at the *FTO* locus for the 5 traits. We used the COLOC[74] method implemented in *R* and the HEIDI method[75] implemented in SMR (URLs) to test whether the vQTL associations at the *FTO* locus for the 5 traits as shown in panel (b) are due to the same underlying causal variant. The COLOC and HEIDI analyses were performed for each pair of traits. Note that we convert vQTL p-values to vQTL effect sizes and standard errors using the method described in Zhu et al.[75] (with the direction of each vQTL effect determined by comparing the phenotypic variance among the genotype classes of a SNP) for the HEID analysis. The COLOC PP4 values (up-right off-diagonal), the posterior possibility for hypothesis 4 (i.e., association signals at a locus for two traits are driven by a shared causal variant), were all greater than 80%, and the HEIDI p-values (down-left off-diagonal), testing against the null hypothesis that the association signals for two traits at a locus are driven by the same set of causal variants, were all larger than 0.05. (d) A plot of test statistic ($-\log_{10}(P_{vQTL})$) against MAF for the 41 independent vQTLs across traits. (e-f) Manhattan plots of genome-wide vQTL analysis for height squared (e) and cubed (f) in the UKB. Test statistics ($-\log_{10}(P_{vQTL})$) of all common (MAF≥0.05) SNPs from the vQTL analysis are plotted against their physical positions. The blue horizontal line represents the genome-wide significance level 1.0×10^{-8} and the red horizontal line represents the experiment-wise significance level 2.0×10^{-9}. (g) QTL and vQTL regional plots at the *CCDC92* or *FTO* locus for waist circumference. The QTL and vQTL test statistics (i.e., $-\log_{10}$(P values)) for waist circumference are plotted against SNP positions surrounding the top vQTL SNP at the *CCDC92* (panel a) or *FTO* locus (panel b). The top vQTL SNP is represented by a purple diamond. SNPs in different levels of LD with the top vQTL SNP are shown in different colours. The RefSeq genes in the top panel are extracted from the UCSC Genome Browser (URLs).

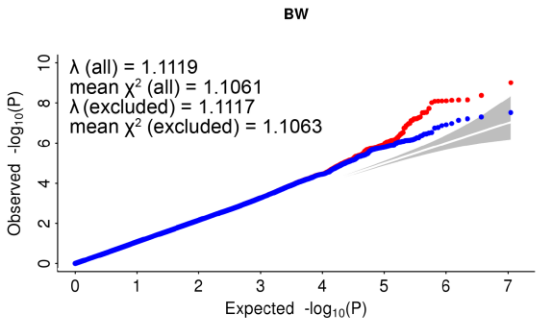

HT
λ (all) = 1.0006
mean χ² (all) = 1.0014
λ (excluded) = 1.0006
mean χ² (excluded) = 1.0014
Observed -log10(P)
Expected -log10(P)

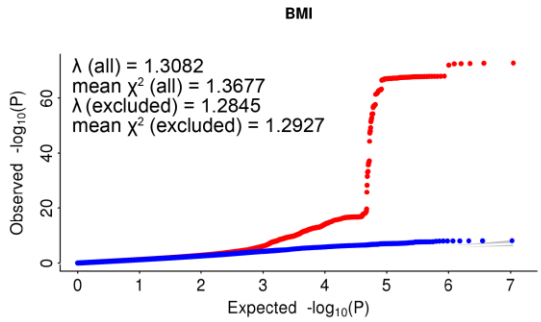

FVC
λ (all) = 1.0432
mean χ² (all) = 1.0482
λ (excluded) = 1.0432
mean χ² (excluded) = 1.0482
Observed -log10(P)
Expected -log10(P)

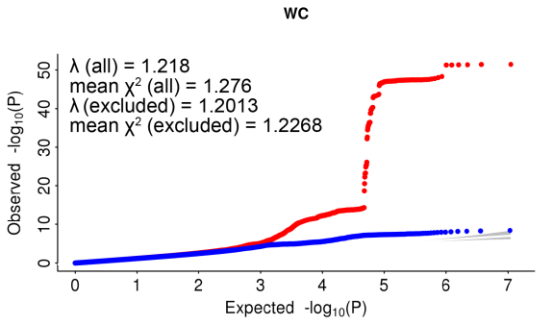

FEV
λ (all) = 1.0324
mean χ² (all) = 1.0417
λ (excluded) = 1.0324
mean χ² (excluded) = 1.0417
Observed -log10(P)
Expected -log10(P)


FFR
λ (all) = 1.0943
mean χ² (all) = 1.0978
λ (excluded) = 1.0931
mean χ² (excluded) = 1.0939
Observed -log10(P)
Expected -log10(P)


BMD
λ (all) = 1.0609
mean χ² (all) = 1.0711
λ (excluded) = 1.0594
mean χ² (excluded) = 1.0636
Observed -log10(P)
Expected -log10(P)


BW
λ (all) = 1.1119
mean χ² (all) = 1.1061
λ (excluded) = 1.1117
mean χ² (excluded) = 1.1063
Observed -log10(P)
Expected -log10(P)


BMI
λ (all) = 1.3082
mean χ² (all) = 1.3677
λ (excluded) = 1.2845
mean χ² (excluded) = 1.2927
Observed -log10(P)
Expected -log10(P)


WC
λ (all) = 1.218
mean χ² (all) = 1.276
λ (excluded) = 1.2013
mean χ² (excluded) = 1.2268
Observed -log10(P)
Expected -log10(P)

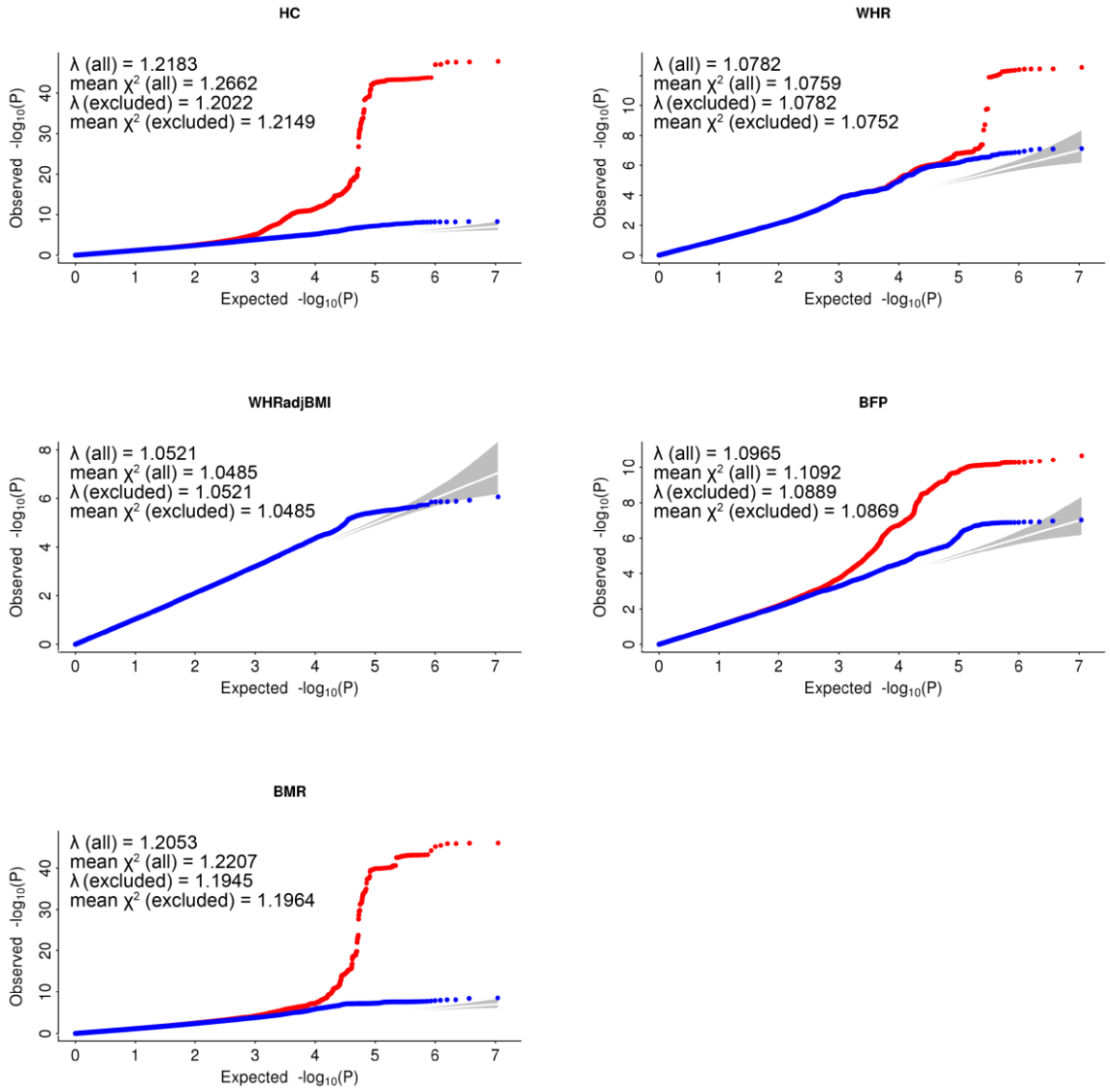


Fig. S4. Quantile-quantile plots of vQTL associations for the 13 UKB traits. For each trait, we shown the QQ plots for all SNPs including (red) or excluding (blue) the top vQTLs and SNPs in LD with them (determined by GCTA-LDF[65]). The area highlighted in grey is the 95% confidence interval.

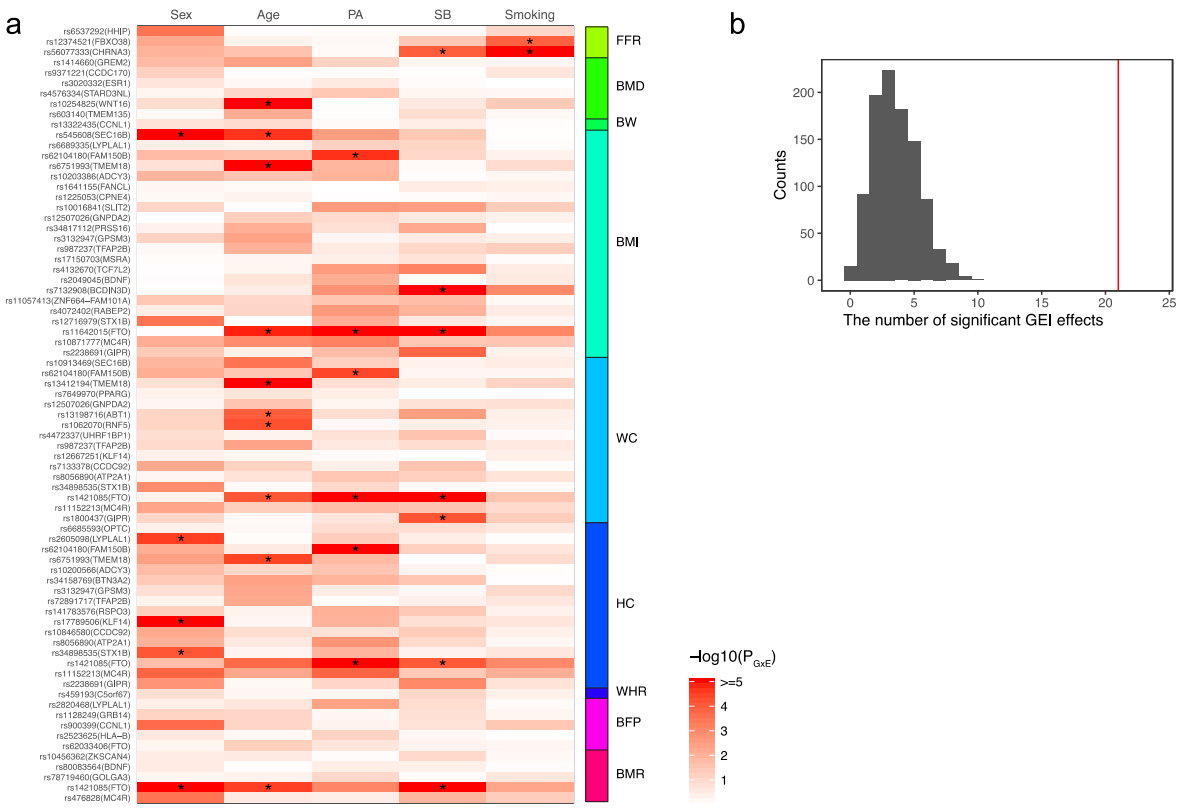


Fig. S5. Enrichment of GEI effects among the 75 vQTLs compared with a random set of QTLs using the raw phenotypic values. Five environmental factors, i.e., sex, age, physical activity (PA), sedentary behaviour (SB), and smoking, were used in the GEI analysis. (a) The heatmap plot of GEI test statistics ($-\log_{10}(P_{GEI})$) for the 75 top vQTL SNPs. "*" denotes significant GEI effects after Bonferroni correction ($P_{GEI} < 1.33\times10^{-4} = 0.05/75/5$). (b) The distribution of the number of significant GEI effects for 75 top QTL SNPs randomly selected from all the top QTL SNPs with 1000 repeats (mean 3.56 and SD 1.76). The red line represents the number of significant GEI effects for the 75 top vQTL SNPs (i.e., 21).

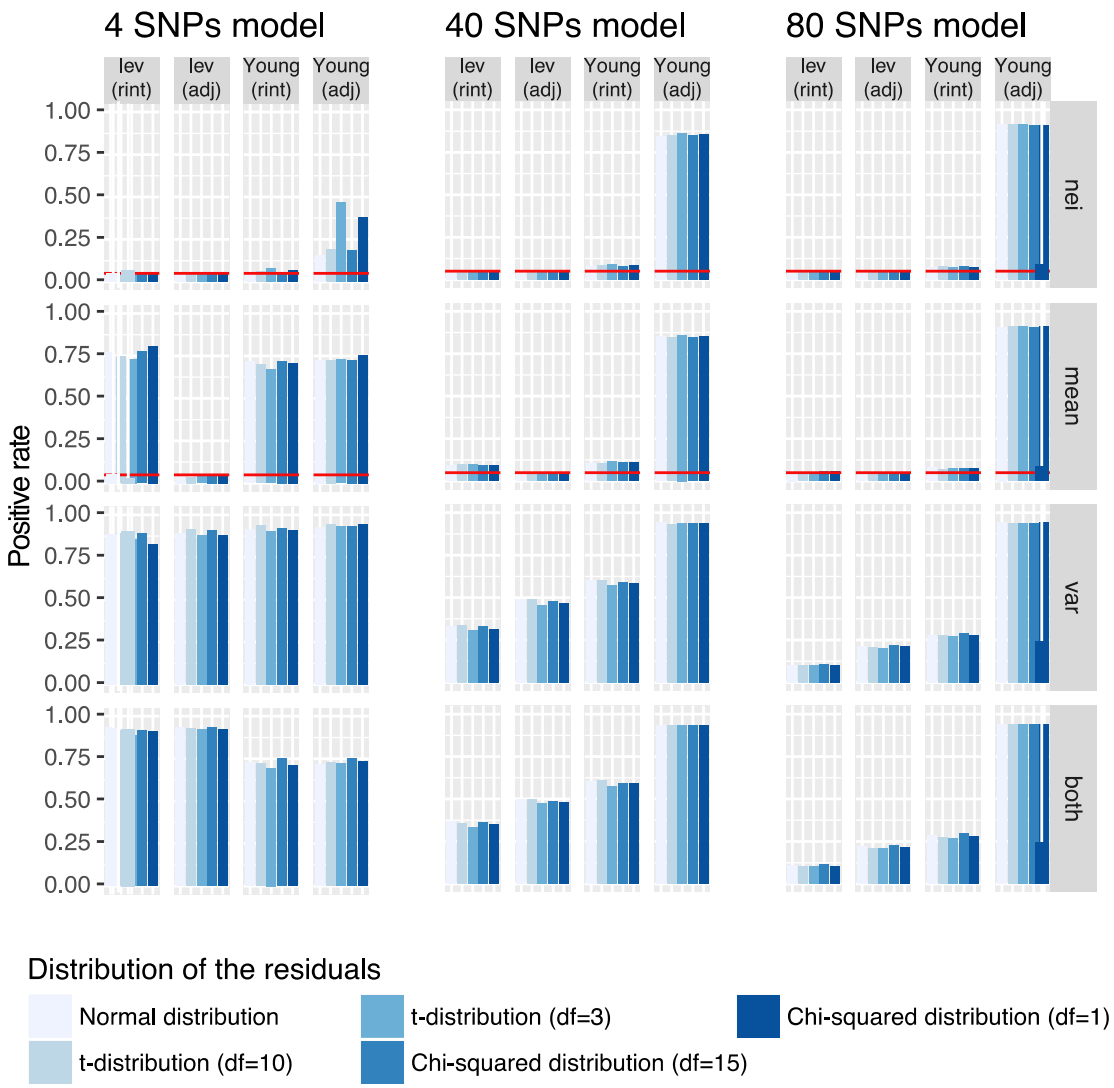


Fig. S6. Comparison of the Young *et al.* method with the Levene's test by vQTL simulation. While we were preparing the manuscript, a very recent study from Young et al.[40] developed an efficient algorithm for fitting DGLM (called heteroskedastic linear mixed model or HLMM) and proposed a dispersion effect test (DET) to remove the impact of the QTL effects on the vQTL signals. We used our multiple-SNP simulation setting (Figure 2 and Methods) to quantify the FPR and power of the Young et al. method (HLMM + DET) in comparison with the Levene's test based on the phenotype after 1) covariate adjustment ("adj") or 2) covariate adjustment followed by rank-based inverse-normal transformation ("rint"). For the Levene's test, the positive rate (FPR or power) was computed as the number of vQTLs with $p < 0.05$ divided by the total number of tests across 1,000 simulations. For the analysis with the Young et al. method, the positive rate (FPR or power) was computed as the number of vQTLs with DET $p < 0.05$ divided by the total number of tests across simulations.

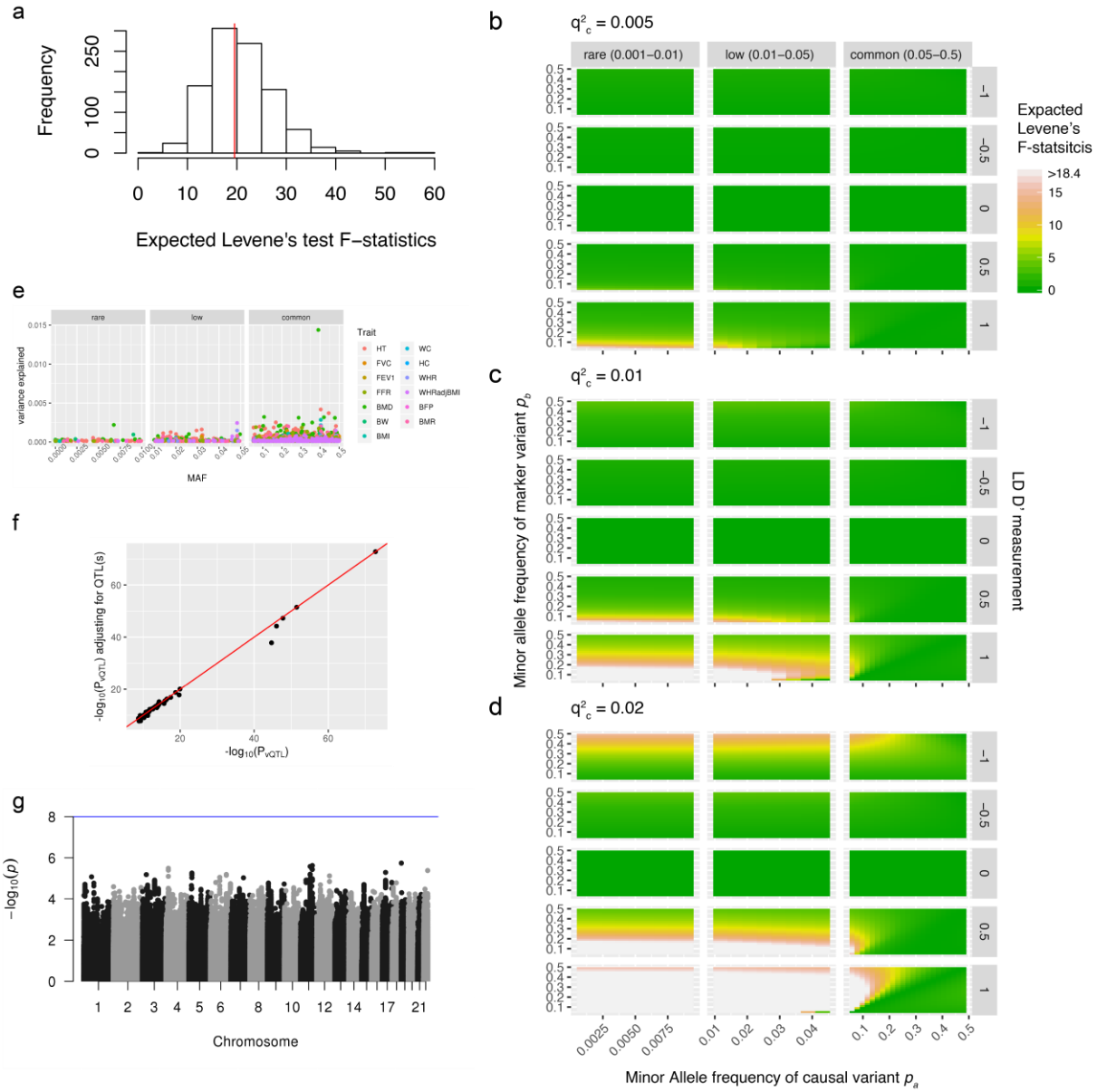


Fig. S7. Excluding two alternative explanations for vQTL signals: Phantom vQTLs and epistasis. (a) Verification of the expected Levene's test *F*-statistic due to phantom vQTL effect by simulation. We simulated two variants A (p_A = 0.7) and B (P_B = 0.6) in LD (P_{AB} = 0.6, LD r^2 = 0.64, and LD D' = 1) from multinomial(2, (P_{AB}, P_{Ab}, PaB, Pab)) and a phenotype based on the causal variant A explaining 5% variance in 350,000 individuals. Shown is the distribution of *F*-statistics from the Levene's test using the simulated data with 1,000 replicates. The red line indicates the theoretical value based on the formula in Note S6.4. (b-d) Expected phantom vQTL *F*-statistics from the Levene's test. We calculated the expected phantom vQTL *F*-statistics given a number of parameters including p_{AB} (equivalent to LD D' from -1 to 1), p_a (ranging from 0.001 to 0.5), p_b (ranging from 0.05 to 0.5), q_c^2 (= 0.005, 0.01 or 0.02) and n (= 350,000) (Note S6 for more details). An F value of 18.4 is equivalent to a genome-wide significant p-value of 1×10^{-8}. (e) Estimated variance explained by top QTL SNPs for the 13 UKB traits. Note that because the

phantom vQTL signals at common SNPs can be induced by rare (MAF≤0.01) or low-frequency (0.01≤MAF<0.05) variants, we extended our GWAS analysis to all 44,741,800 imputed variants (MAF<0.05). The estimated variance explained by each GWAS top SNP is plotted against its MAF. (f) vQTL test statistics ($-\log_{10}(P_{vQTL})$) from analyses with and without adjusting the phenotype for the QTL effect(s) of the top GWAS SNP(s) within 10Mb of the top vQTL SNP. The red line represents the line with slope 1 and intercept 0. (g) Manhattan plot of epistasis analysis for one of top vQTL SNPs. We conducted epistasis analysis between each of 75 top vQTL SNPs and any other SNPs in more than 10 Mb distance or on a different chromosome for the relevant trait using PLINK2[63] (--epistasis option). The blue horizontal line represents the genome-wide significance level (i.e., p-value = 1×10^{-8}). Shown are the results from the epistasis analysis with the top vQTL SNP rs10913469 for waist circumference (WC).

Supplementary Tables

Table S1. Descriptive summary of (A) the quantitative traits and (B) the environmental data used in this study from the UKB.

(a) 13 quantitative traits

Trait	Description	Sample size	UDI[a]
HT	Standing height	347,086	50-0.0
FVC	Forced vital capacity	317,222	3062-0.0
FEV1	Forced expiratory volume in 1-second	317,285	3063-0.0
FFR[b]	FEV1 and FVC ratio	316,614	NA
BMD	Heel bone mineral density T-score, automated	197,261	78-0.0
BW	Birth weight	197,758	20022-0.0
BMI	Body mass index (BMI)	346,393	21001-0.0
WC	Waist circumference	347,158	48-0.0
HC	Hip circumference	346,781	49-0.0
WHR[c]	Waist to Hip Ratio	347,134	NA
WHRadjBMI[d]	WHR adjusted for BMI	346,535	NA
BFP	Body fat percentage	341,632	23099-0.0
BMR	Basal metabolic rate	341,584	23105-0.0

(b) Environmental data used in the GEI analysis.

Item	Description	UDI[a]
Sex	Sex	31-0.0
Age	Year of birth	34-0.0
DayW	Number of days/week walked 10+ minutes	864-0.0
DurW	Duration of walks	874-0.0
DayM	Number of days/week of moderate physical activity 10+ minutes	884-0.0
DurM	Duration of moderate activity	894-0.0
DayV	Number of days/week of vigorous physical activity 10+ minutes	904-0.0
DurV	Duration of vigorous activity	914-0.0
TimeD	Time spent driving	1090-0.0
TimeC	Time spent using computer	1080-0.0
TimeTV	Time spent watching television (TV)	1070-0.0

CurS	Current tobacco smoking	1239-0.0
PastS	Past tobacco smoking	1249-0.0

Note: a) UDI, the Unique Data Identifier in the UKB dataset; b) FFR is the ratio of FEV1 to FVC; c) WHR is the ratio of waist circumference to hip circumference; d) WHRadjBMI is the residual after adjusting WHR for BMI.

Table S2. Seventy-five experiment-wise significant vQTLs for nine UKB traits.

(a) The vQTL and QTL tests.

Trait	CHR	SNP	bp	Nearest Gene	MAF	vQTL p-value	QTL p-value	Phenotypic variance in each genotype group	Phenotypic mean in each genotype group
FFR	4	rs6537292	145469968	HHIP	0.394	1.97E-14	3.58E-122[a]	1.0217,0.9936,0.9561	-0.0453,0.0091,0.0787
	5	rs12374521	147836880	FBXO38	0.456	7.10E-10	1.60E-58	1.0223,0.9978,0.97	-0.039,0.0055,0.0417
	15	rs56077333	78899003	CHRNA3	0.325	1.09E-14	2.11E-06	0.9757,1.0107,1.0588	0.0072,-0.0019,-0.0225
BMD	1	rs1414660	240586695	GREM2	0.192	7.83E-14	1.28E-94	0.977,1.0362,1.0452	-0.0322,0.0523,0.1304
	6	rs9371221	151885986	CCDC170	0.101	4.59E-10	1.30E-76	1.0097,0.9502,0.9408	0.02,-0.0817,-0.1479
	6	rs3020332	152008924	ESR1	0.45	5.42E-14	8.94E-130	0.966,0.997,1.0429	-0.074,0.0126,0.0795
	7	rs4576334	38153747	STARD3NL	0.196	2.36E-13	2.60E-86	0.9784,1.0308,1.0684	-0.0325,0.0511,0.1152
	7	rs10254825	120956440	WNT16	0.391	2.01E-45	0	0.9279,1.0107,1.057	-0.1455,0.05,0.1903
	11	rs603140	86884615	TMEM135	0.312	1.61E-12	4.48E-98	1.0149,0.9924,0.9333	0.0417,-0.0204,-0.1142
BW	3	rs13322435	156795468	CCNL1	0.402	9.71E-10	6.21E-48	1.0287,0.9847,0.9742	0.0376,-0.0072,-

									0.0585
BMI	1	rs545608	177899121	SEC16B	0.206	3.88E-17	1.97E-63	0.9801,1.0251,1.0835	-0.0202,0.0282,0.0847
	1	rs6689335	219628682	LYPLAL1	0.419	2.86E-12	4.73E-08	1.0249,0.9907,0.972	0.0106,-0.0013,-0.0167
	2	rs62104180	466003	FAM150B	0.05	1.22E-11	3.57E-51	1.0054,0.9461,0.8598	0.0083,-0.075,-0.1488
	2	rs6751993	635864	TMEM18	0.167	3.50E-18	3.31E-65	1.0155,0.9707,0.9188	0.0197,-0.0361,-0.0912
	2	rs10203386	25136866	ADCY3	0.452	1.33E-11	8.45E-43	0.9768,0.9994,1.0333	-0.0272,3e-04,0.0404
	2	rs1641155	58965211	FANCL	0.311	1.25E-09	4.42E-17	0.9872,1.0092,1.0266	-0.0141,0.0108,0.0266
	3	rs1225053	131642852	CPNE4	0.264	1.69E-12	2.85E-17	0.9863,1.009,1.0577	-0.0109,0.0073,0.0444
	4	rs10016841	20213781	SLIT2	0.133	1.95E-09	2.11E-13	0.9898,1.0272,1.0621	-0.007,0.0187,0.0468
	4	rs12507026	45181334	GNPDA2	0.434	1.84E-11	6.78E-41	0.9762,0.9998,1.0381	-0.0243,-6e-04,0.0435
	6	rs34817112	27176628	PRSS16	0.134	8.48E-17	3.51E-08	0.9857,1.0416,1.0635	-0.0054,0.0154,0.026
	6	rs3132947	32176782	GPSM3	0.218	2.36E-13	8.53E-15	0.9834,1.0214,1.0563	-0.0096,0.0119,0.038
	6	rs987237	50803050	TFAP2B	0.18	2.18E-16	7.51E-43	0.9842,1.0249,1.0845	-0.0148,0.0247,0.0833
	8	rs17150703	9745798	MSRA	0.104	1.38E-09	2.05E-11	0.9925,1.0243,1.1486	-0.0053,0.0196,

	10	rs4132670	114767771	TCF7L2	0.312	3.88E-11	2.75E-15	1.0205,0.986,0.9606	0.0583 0.0133,-0.0084,-0.0263
	11	rs2049045	27694241	BDNF	0.187	6.91E-10	8.20E-42	1.0115,0.9794,0.9461	0.0162,-0.0288,-0.0563
	12	rs7132908	50263148	BCDIN3D	0.385	3.73E-11	3.94E-32	0.9791,1.0024,1.0429	-0.0211,0.0046,0.0392
	12	rs11057413	124489162	ZNF664-FAM101A	0.334	1.05E-10	6.30E-09	0.981,1.0071,1.0456	-0.0104,0.0064,0.0173
	16	rs4072402	28937259	RABEP2	0.337	5.55E-12	2.72E-28	0.9802,1.0076,1.0463	-0.0185,0.0081,0.0393
	16	rs12716979	31011821	STX1B	0.375	1.40E-16	7.30E-24	1.031,0.9897,0.9517	0.0186,-0.0053,-0.0328
	16	rs11642015	53802494	FTO	0.404	1.73E-73	7.43E-217	0.9398,1.0013,1.1095	-0.0555,0.005,0.1062
	18	rs10871777	57851763	MC4R	0.236	1.73E-19	3.01E-81	0.9767,1.0232,1.0751	-0.0248,0.0262,0.0897
	19	rs2238691	46179043	GIPR	0.194	3.46E-15	2.31E-32	1.0176,0.9706,0.9309	0.0142,-0.0231,-0.0537
WC	1	rs10913469	177913519	SEC16B	0.205	3.80E-14	4.50E-44	0.9848,1.0189,1.0695	-0.0166,0.0229,0.0724
	2	rs62104180	466003	FAM150B	0.05	3.93E-14	4.02E-44	1.0061,0.9417,0.8124	0.0077,-0.0689,-0.1472
	2	rs13412	65324	TMEM	0.1	9.76E	1.39E-	1.0134,0.972	0.0176,-

	194	5	18	72	-15	55	6,0.9343	0.0341,-0.0761
3	rs7649970	12392272	PPARG	0.121	5.60E-10	5.30E-10	0.9915,1.0245,1.0873	-0.0057,0.0186,0.0314
4	rs12507026	45181334	GNPDA2	0.434	2.39E-11	9.40E-31	0.9757,1.0016,1.0355	-0.0207,-8e-04,0.0377
6	rs13198716	26582035	ABT1	0.109	4.89E-15	0.0305	0.99,1.0363,1.0714	-0.002,0.0078,0.0046
6	rs1062070	32148031	RNF5	0.199	7.20E-12	6.06E-10	0.9862,1.0221,1.043	-0.0079,0.0132,0.0217
6	rs4472337	34769765	UHRF1BP1	0.155	5.60E-11	1.78E-23	0.9893,1.0237,1.0573	-0.0105,0.024,0.0493
6	rs987237	50803050	TFAP2B	0.18	5.43E-12	1.09E-34	0.9874,1.0199,1.0669	-0.0137,0.0239,0.0663
7	rs12667251	130449458	KLF14	0.436	6.82E-12	1.91E-05	1.025,0.9962,0.9637	0.0096,-0.0023,-0.0109
12	rs7133378	124409502	CCDC92	0.318	6.25E-10	0.506	0.9845,1.0071,1.0384	0.001,1e-04,-0.0034
16	rs8056890	28897452	ATP2A1	0.355	5.57E-15	8.85E-40	0.9759,1.009,1.0433	-0.0234,0.0094,0.0433
16	rs34898535	31025641	STX1B	0.378	1.11E-11	6.24E-22	1.0246,0.991,0.9616	0.0173,-0.0047,-0.0316
16	rs1421085	53800954	FTO	0.404	3.27E-52	3.21E-166	0.9501,1.0048,1.0807	-0.0481,0.0038,0.0936
18	rs11152213	57852948	MC4R	0.236	5.62E-15	1.39E-70	0.9828,1.0153,1.0646	-0.0224,0.0224,0.0898

	19	rs1800437	46181392	GIPR	0.194	2.05E-11	1.19E-24	1.0137,0.9791,0.93	0.0124,-0.0203,-0.0445
HC	1	rs6685593	203516075	OPTC	0.495	5.99E-11	2.47E-12	0.9682,1.0032,1.0238	-0.016,-3e-04,0.0181
	1	rs2605098	219643649	LYPLAL1	0.338	1.11E-20	3.87E-38	0.9723,1.0085,1.0687	-0.0209,0.0081,0.0483
	2	rs62104180	466003	FAM150B	0.05	1.58E-09	5.56E-45	1.0054,0.9447,0.9202	0.0078,-0.07,-0.1422
	2	rs6751993	635864	TMEM18	0.167	3.84E-12	1.43E-58	1.0142,0.9714,0.932	0.0186,-0.0337,-0.0883
	2	rs10200566	25130462	ADCY3	0.451	2.32E-10	2.29E-18	0.9811,0.9976,1.0342	-0.0171,0,0.026
	6	rs34158769	26336572	BTN3A2	0.104	5.06E-15	4.20E-13	0.9881,1.0436,1.0925	-0.0061,0.0238,0.0417
	6	rs3132947	32176782	GPSM3	0.218	5.34E-11	2.52E-24	0.9851,1.019,1.049	-0.0132,0.0176,0.0429
	6	rs72891717	50858235	TFAP2B	0.169	6.03E-10	1.10E-36	0.9869,1.0226,1.0786	-0.0134,0.0247,0.0784
	6	rs141783576	127439897	RSPO3	0.067	1.57E-10	4.72E-32	1.0064,0.9482,0.994[b]	0.0079,-0.0512,-0.0833
	7	rs17789506	130445574	KLF14	0.493	2.80E-11	1.87E-18	0.9676,1.0001,1.0321	-0.0189,-0.0019,0.0234
	12	rs10846580	124415453	CCDC92	0.337	7.64E-12	9.27E-17	0.9793,1.0122,1.0302	-0.016,0.0106,0.0209
	16	rs8056890	28897452	ATP2A1	0.355	1.27E-09	1.71E-41	0.9762,1.0105,1.0362	-0.0239,0.0096,0.0444
	16	rs34898	31025	STX1B	0.3	2.57E	1.58E-	1.0248,0.994	0.0198,-

		535	641		78	-12	27	5,0.9502	0.0054,-0.0352
	16	rs14210 85	53800 954	FTO	0.4 04	1.65E -48	2.05E-152	0.9486,1.002 9,1.0909	-0.0462,0.0039, 0.0893
	18	rs11152 213	57852 948	MC4R	0.2 36	2.39E -16	1.44E-72	0.98,1.0189,1 .0704	-0.0237,0.0257, 0.0817
	19	rs22386 91	46179 043	GIPR	0.1 94	4.52E -11	9.80E-20	1.0162,0.972 7,0.9364	0.0105,-0.0164,-0.0467
W HR	5	rs45919 3	55806 751	C5orf6 7	0.2 53	2.86E -13	1.75E-19	0.9859,1.010 2,1.0584	-0.0128,0.0129, 0.0354
BF P	1	rs28204 68	21967 3705	LYPLA L1	0.3 45	3.76E -11	3.46E-21	0.9824,1.006 3,1.0364	-0.0164,0.0066, 0.0328
	2	rs11282 49	16552 8624	GRB14	0.3 92	1.93E -09	2.32E-18	0.9819,1.004 5,1.0279	-0.0165,0.0039, 0.0275
	3	rs90039 9	15679 8732	CCNL1	0.3 97	1.82E -09	0.0001 21	1.0198,0.993 2,0.9746	0.0065,-4e-04,-0.0138
	6	rs25236 25	31315 648	HLA-B	0.3 31	2.69E -10	0.0215	0.9852,1.007 1,1.0331	-0.0049,0.0039, 0.0041
	16	rs62033 406	53824 226	FTO	0.4 11	2.15E -11	1.44E-91	0.9806,0.999 1,1.0359	-0.0367,0.0025, 0.0677
BM R	6	rs10456 362	28221 816	ZKSCA N4	0.1 61	1.48E -09	1.63E-09	0.99,1.0252,1 .0064	-0.0069,0.0163, 0.0186
	11	rs80083 564	27733 143	BDNF	0.1 36	1.15E -09	2.32E-22	0.9895,1.027 3,1.0718	-0.0092,0.0242, 0.0657
	12	rs78719 460	13339 5038	GOLGA 3	0.3 1	1.66E -09	1.92E-12	0.984,1.0063, 1.0467	-0.0108,0.0054,

16	rs1421085	53800954	FTO	0.404	8.95E-47	9.23E-154	0.9561,1.0008,1.0805	0.0289 - 0.0469,0.0041, 0.09
18	rs476828	57852587	MC4R	0.237	1.87E-20	1.35E-148	0.9775,1.0195,1.0716	- 0.0351,0.0388, 0.1125

Note: a) p values smaller than 2.0×10^{-9} are highlighted in pink; b) vQTLs with non-additive genetic effect on variance are highlighted in yellow.

(b) Testing for the variance effects of the BMI, WHR and FFR vQTLs on $1/HT^2$, 1/HC and 1/FVC respectively.

vQTL test	SNP	vQTL p-value
BMI - 1/HT2	rs545608	4.42E-01
	rs6689335	2.00E-01
	rs62104180	4.31E-02
	rs6751993	2.97E-01
	rs10203386	6.71E-03
	rs1641155	6.74E-01
	rs1225053	1.90E-01
	rs10016841	3.98E-01
	rs12507026	9.08E-01
	rs34817112	2.08E-01
	rs3132947	3.90E-01
	rs987237	7.39E-01
	rs17150703	1.24E-01
	rs4132670	7.29E-01
	rs2049045	6.00E-01
	rs7132908	9.29E-01
	rs11057413	1.71E-01
	rs4072402	1.99E-01
	rs12716979	1.73E-01
	rs11642015	7.65E-01
	rs10871777	8.46E-01
	rs2238691	9.75E-01

WHR - 1/HC	rs459193	9.98E-01
FFR - 1/FVC	rs6537292	5.82E-01
	rs12374521	5.89E-01
	rs56077333	5.11E-06

(c) GEI analyses with five environmental factors/covariates in the UKB.

Trait	CHR	SNP	BP	Nearest Gene	P values of GEI analyses with				
					Sex	Age	PA	SB	Smoking
FFR	4	rs6537292	145469968	HHIP	3.13E-02	7.20E-01	5.91E-01	6.39E-01	8.14E-02
	5	rs12374521	147836880	FBXO38	9.46E-02	1.43E-01	2.63E-01	4.79E-02	2.88E-04
	15	rs56077333	78899003	CHRNA3	2.36E-02	2.52E-02	9.88E-01	3.02E-04	4.55E-25
BMD	1	rs1414660	240586695	GREM2	7.60E-01	7.09E-05	1.45E-01	4.26E-01	4.55E-01
	6	rs9371221	151885986	CCDC170	9.81E-01	7.05E-01	8.33E-01	7.69E-01	1.28E-01
	6	rs3020332	152008924	ESR1	2.08E-01	4.76E-01	3.28E-01	9.46E-01	9.53E-01
	7	rs4576334	38153747	STARD3NL	2.85E-01	9.08E-02	1.17E-01	4.58E-01	4.45E-01
	7	rs10254825	120956440	WNT16	3.06E-04	1.16E-07	4.02E-01	7.83E-01	1.59E-03
	11	rs603140	86884615	TMEM135	1.07E-03	2.75E-02	5.74E-01	4.58E-02	7.51E-01
BW	3	rs13322435	156795468	CCNL1	8.46E-02	1.44E-01	6.87E-01	3.69E-01	9.36E-01
BMI	1	rs545608	177899121	SEC16B	8.59E-03	1.24E-04	6.11E-03	1.27E-02	7.51E-01
	1	rs6689335	219628682	LYPLAL1	6.65E-01	1.90E-01	3.15E-02	1.13E-01	7.38E-01
	2	rs62104180	466003	FAM150B	2.75E-01	5.36E-02	2.52E-04	2.07E-01	1.48E-01
	2	rs675199	635864	TMEM18	7.08E-	1.01E-	1.49E-	9.67E-	2.06E-

	3			01	07	02	01	01
2	rs10203386	25136866	ADCY3	2.52E-01	4.94E-02	8.81E-03	8.92E-01	4.51E-01
2	rs1641155	58965211	FANCL	8.94E-01	4.64E-01	9.82E-01	3.09E-01	3.73E-01
3	rs1225053	131642852	CPNE4	1.78E-01	7.44E-01	9.53E-01	8.74E-01	4.52E-01
4	rs10016841	20213781	SLIT2	4.41E-01	8.52E-01	8.64E-03	5.42E-03	3.88E-03
4	rs12507026	45181334	GNPDA2	1.59E-01	6.19E-02	6.40E-02	1.46E-01	5.21E-01
6	rs34817112	27176628	PRSS16	9.93E-01	1.91E-02	1.52E-01	9.24E-03	9.21E-01
6	rs3132947	32176782	GPSM3	2.18E-01	1.92E-03	6.16E-01	1.41E-01	3.66E-01
6	rs987237	50803050	TFAP2B	1.24E-01	1.41E-02	4.31E-01	1.68E-01	2.49E-02
8	rs17150703	9745798	MSRA	2.62E-01	7.88E-01	3.15E-01	6.25E-02	9.09E-01
10	rs4132670	114767771	TCF7L2	3.03E-01	5.72E-01	1.73E-03	6.84E-04	2.36E-01
11	rs2049045	27694241	BDNF	1.67E-01	2.66E-01	1.59E-02	9.22E-01	2.62E-01
12	rs7132908	50263148	BCDIN3D	2.73E-01	2.94E-01	1.36E-03	2.15E-07	5.88E-04
12	rs11057413	124489162	ZNF664-FAM101A	1.02E-01	2.03E-01	6.54E-02	5.81E-03	9.57E-01
16	rs4072402	28937259	RABEP2	9.25E-01	1.30E-01	1.82E-02	2.72E-03	3.58E-01
16	rs12716979	31011821	STX1B	6.74E-03	9.39E-01	7.48E-03	2.07E-01	5.89E-01
16	rs11642015	53802494	FTO	5.01E-03	2.35E-04	1.28E-10	1.64E-09	9.24E-05
18	rs10871777	57851763	MC4R	4.63E-01	3.72E-03	3.52E-04	1.41E-02	3.22E-02
19	rs223869	461790	GIPR	4.83E-	7.04E-	5.95E-	1.74E-	6.53E-

		1	43		01	01	02	04	01
WC	1	rs10913469	177913519	SEC16B	1.63E-01	4.96E-03	2.74E-02	1.31E-01	2.15E-01
	2	rs62104180	466003	FAM150B	6.08E-02	1.46E-01	1.04E-04	4.77E-01	5.19E-01
	2	rs13412194	653245	TMEM18	4.87E-01	1.88E-07	3.70E-02	7.16E-01	3.15E-01
	3	rs7649970	12392272	PPARG	6.35E-01	1.49E-01	8.87E-02	7.91E-01	9.55E-01
	4	rs12507026	45181334	GNPDA2	2.12E-01	2.10E-02	4.08E-01	6.70E-02	8.13E-01
	6	rs13198716	26582035	ABT1	1.52E-01	1.50E-04	3.11E-02	2.45E-03	5.51E-01
	6	rs1062070	32148031	RNF5	2.30E-01	3.46E-05	2.32E-01	3.13E-01	1.96E-01
	6	rs4472337	34769765	UHRF1BP1	2.03E-01	6.15E-01	3.14E-02	5.56E-03	4.73E-01
	6	rs987237	50803050	TFAP2B	2.52E-02	9.32E-03	5.61E-01	2.19E-01	3.32E-02
	7	rs12667251	130449458	KLF14	2.61E-01	6.30E-01	6.99E-01	3.50E-01	8.05E-01
	12	rs7133378	124409502	CCDC92	3.59E-03	1.45E-01	7.05E-01	3.62E-03	6.79E-01
	16	rs8056890	28897452	ATP2A1	8.75E-01	1.52E-01	3.93E-02	4.24E-03	2.10E-01
	16	rs34898535	31025641	STX1B	5.92E-03	7.08E-01	1.69E-02	2.92E-01	9.87E-01
	16	rs1421085	53800954	FTO	3.04E-02	2.17E-04	1.44E-07	2.84E-08	1.10E-02
	18	rs11152213	57852948	MC4R	2.80E-02	1.36E-02	2.21E-03	3.39E-02	2.14E-01
	19	rs1800437	46181392	GIPR	1.84E-01	4.59E-01	1.62E-01	9.50E-04	1.81E-01
HC	1	rs6685593	203516075	OPTC	6.22E-01	8.84E-01	3.48E-01	7.42E-02	3.80E-01
	1	rs260509	219643	LYPLAL1	8.00E-	8.14E-	5.37E-	4.52E-	9.48E-

		8	649		03	01	02	01	01
	2	rs62104180	466003	FAM150B	3.95E-01	2.89E-01	2.27E-05	4.70E-02	1.62E-01
	2	rs6751993	635864	TMEM18	6.50E-01	2.35E-04	1.87E-02	5.09E-01	3.11E-01
	2	rs10200566	25130462	ADCY3	2.35E-01	1.73E-01	3.57E-02	7.90E-01	7.74E-01
	6	rs34158769	26336572	BTN3A2	4.31E-01	1.05E-02	1.14E-02	1.60E-02	9.93E-01
	6	rs3132947	32176782	GPSM3	9.79E-01	4.23E-03	2.53E-01	3.71E-01	7.46E-02
	6	rs72891717	50858235	TFAP2B	2.32E-01	2.19E-02	5.21E-01	8.67E-01	1.67E-01
	6	rs141783576	127439897	RSPO3	5.75E-01	5.59E-01	5.95E-02	8.08E-02	6.84E-01
	7	rs17789506	130445574	KLF14	6.09E-05	4.28E-01	5.89E-02	1.36E-01	2.73E-01
	12	rs10846580	124415453	CCDC92	6.97E-02	1.10E-01	4.89E-01	1.93E-02	6.48E-01
	16	rs8056890	28897452	ATP2A1	7.53E-01	2.66E-01	1.68E-02	2.05E-02	5.89E-01
	16	rs34898535	31025641	STX1B	1.60E-02	4.20E-01	1.62E-02	1.94E-01	2.77E-01
	16	rs1421085	53800954	FTO	1.18E-01	2.05E-03	5.32E-07	2.17E-06	1.94E-04
	18	rs11152213	57852948	MC4R	2.38E-01	2.19E-02	9.80E-04	1.41E-02	6.68E-03
	19	rs2238691	46179043	GIPR	8.71E-02	9.12E-01	2.66E-01	2.64E-04	2.85E-01
WHR	5	rs459193	55806751	C5orf67	9.25E-02	4.82E-01	1.92E-01	3.48E-04	6.67E-01
BFP	1	rs2820468	219673705	LYPLAL1	8.76E-01	1.19E-01	1.60E-02	8.66E-02	2.40E-01
	2	rs1128249	165528624	GRB14	3.18E-01	2.91E-02	3.55E-01	3.41E-04	5.58E-01
	3	rs900399	156798	CCNL1	1.04E-	2.63E-	2.15E-	1.13E-	1.64E-

			732		05	01	01	02	02
	6	rs2523625	31315648	HLA-B	2.66E-01	2.87E-01	1.35E-01	6.76E-01	6.38E-01
	16	rs62033406	53824226	FTO	1.14E-02	2.47E-04	4.43E-03	3.52E-02	1.02E-01
BMR	6	rs10456362	28221816	ZKSCAN4	8.90E-01	8.38E-03	6.68E-01	1.60E-01	9.13E-01
	11	rs80083564	27733143	BDNF	4.20E-01	1.69E-02	1.00E-01	5.22E-01	9.89E-01
	12	rs78719460	133395038	GOLGA3	3.41E-01	8.69E-01	3.04E-01	9.40E-01	6.67E-01
	16	rs1421085	53800954	FTO	2.07E-01	2.60E-07	1.52E-06	1.45E-07	1.54E-03
	18	rs476828	57852587	MC4R	1.20E-01	1.22E-03	9.98E-03	6.47E-02	1.62E-02

Note: p values smaller than 1.33×10^{-4} are highlighted in pink.

Table S3. GEI examples.

(a) GEI effect between the *CHRNA5-A3-B4* locus and smoking on FFR

Phenotype	Top vQTL SNP	Effect size (Standard error)		P values		
		never smokers (n= 188,860)	ever smokers (n= 160,488)	vQTL analysis	QTL analysis	GEI test
FFR	rs56077333	0.0105 (0.0035)	-0.0453 (0.0042)	1.09E-14	2.11E-06	4.55E-25

(b) GEI effect between the WNT16-CPED1 locus and age on BMD

Phenotype	Top vQTL SNP	Effect size (Standard error)				*P* values		
		Age group 1: 40-49 years (*n* = 59,734)	Age group 2: 50-59 years (*n* = 108,736)	Age group 3: 60-69 years (*n* = 156,173)	Age group 4: 70-74 years (*n* = 23,250)	vQTL analysis	QTL analysis	GEI test
BMD	rs10254825	0.1448 (0.0081)	0.1650 (0.0059)	0.1907 (0.0050)	0.1765 (0.0119)	2.01E-45	0	1.16E-07

(c) Associations of *FTO* locus with obesity-related traits stratified by physical activity (PA) levels

Phenotype	Top vQTL SNP	Effect size (Standard error)			*P* values		
		Low PA group (*n* = 103,374)	Intermediate PA group (*n* = 145,889)	High PA group (*n* = 97,506)	vQTL analysis	QTL analysis	GEI test
BMI	rs11642015	0.1018 (0.0049)	0.0715 (0.0037)	0.0609 (0.0041)	1.73E-73	7.43E-217	1.28E-10
WC	rs1421085	0.0858 (0.0048)	0.0652 (0.0037)	0.0524 (0.0042)	3.27E-52	3.21E-166	1.44E-07
HC	rs1421085	0.0825 (0.0049)	0.0623 (0.0037)	0.0505 (0.0042)	1.65E-48	2.05E-152	5.32E-07
BMR	rs1421085	0.0842 (0.0049)	0.0608 (0.0037)	0.0531 (0.0043)	8.95E-47	9.23E-154	1.52E-06

(d) Associations of *FTO* locus with obesity-related traits stratified by sedentary behaviour (SB) levels

Phenotype	Top vQTL	Effect size (Standard error)	*P* values

	SNP	SB group 1: 0-5 hours (*n* = 244,215)	SB group 2: 6-11 hours (*n* = 89,712)	SB group 3: 12-17 hours (*n* = 5,445)	vQTL analysis	QTL analysis	GEI test
BMI	rs11642015	0.0694 (0.0027)	0.1001 (0.0052)	0.1085 (0.0234)	1.73E-73	7.43E-217	1.64E-09
WC	rs1421085	0.0593 (0.0028)	0.0879 (0.0050)	0.1089 (0.0223)	3.27E-52	3.21E-166	2.84E-08
HC	rs1421085	0.0577 (0.0028)	0.0815 (0.0052)	0.1199 (0.0230)	1.65E-48	2.05E-152	2.17E-06
BMR	rs1421085	0.0576 (0.0028)	0.0849 (0.0052)	0.1024 (0.0233)	8.95E-47	9.23E-154	1.45E-07