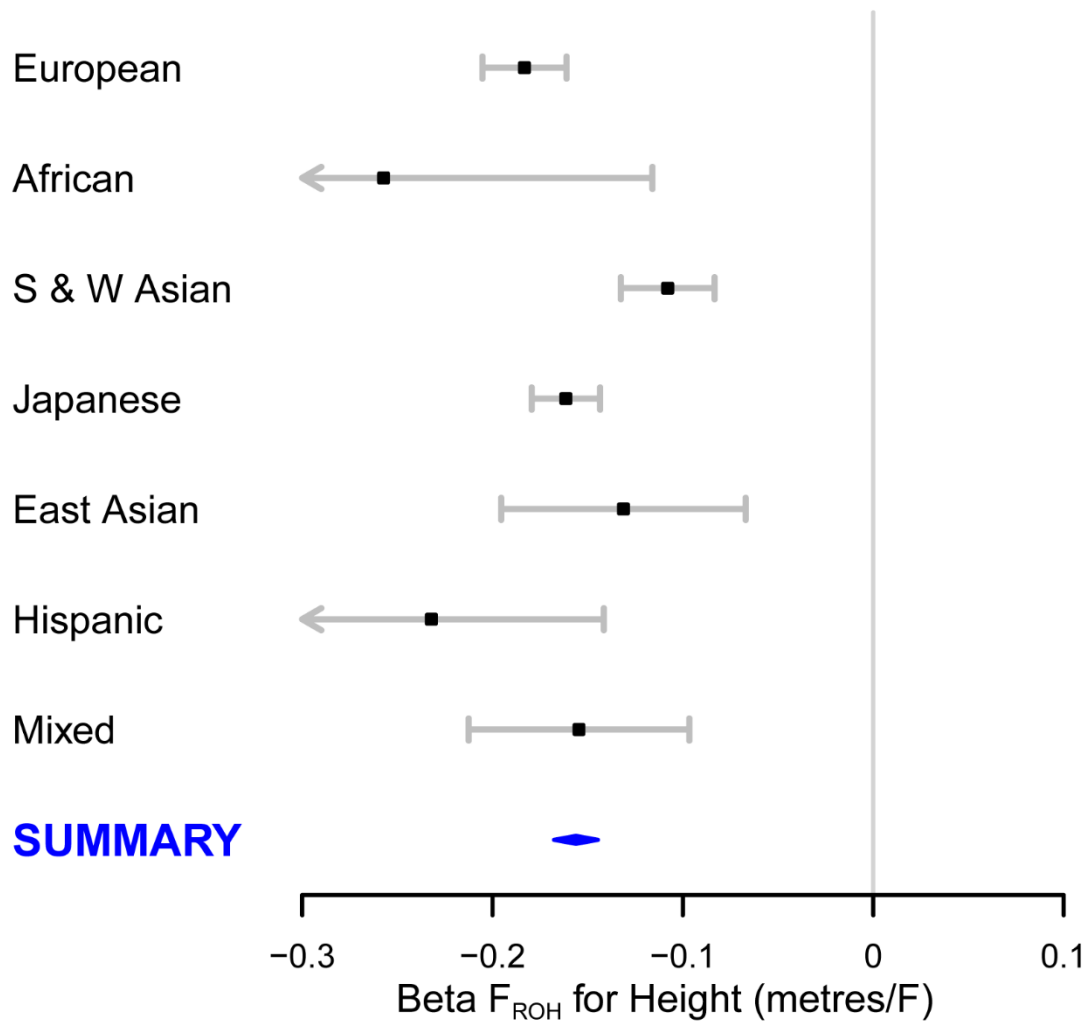
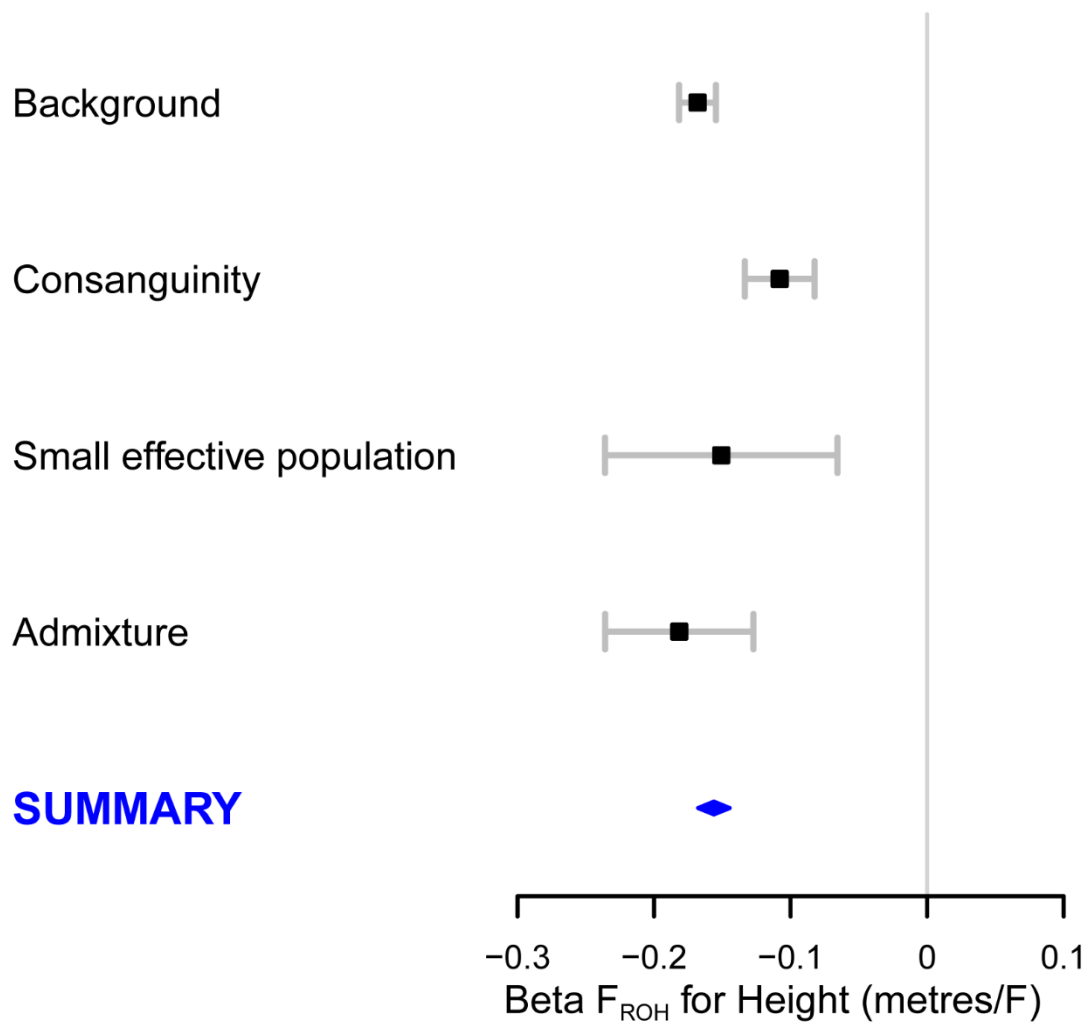


## SUPPLEMENTARY FIGURES

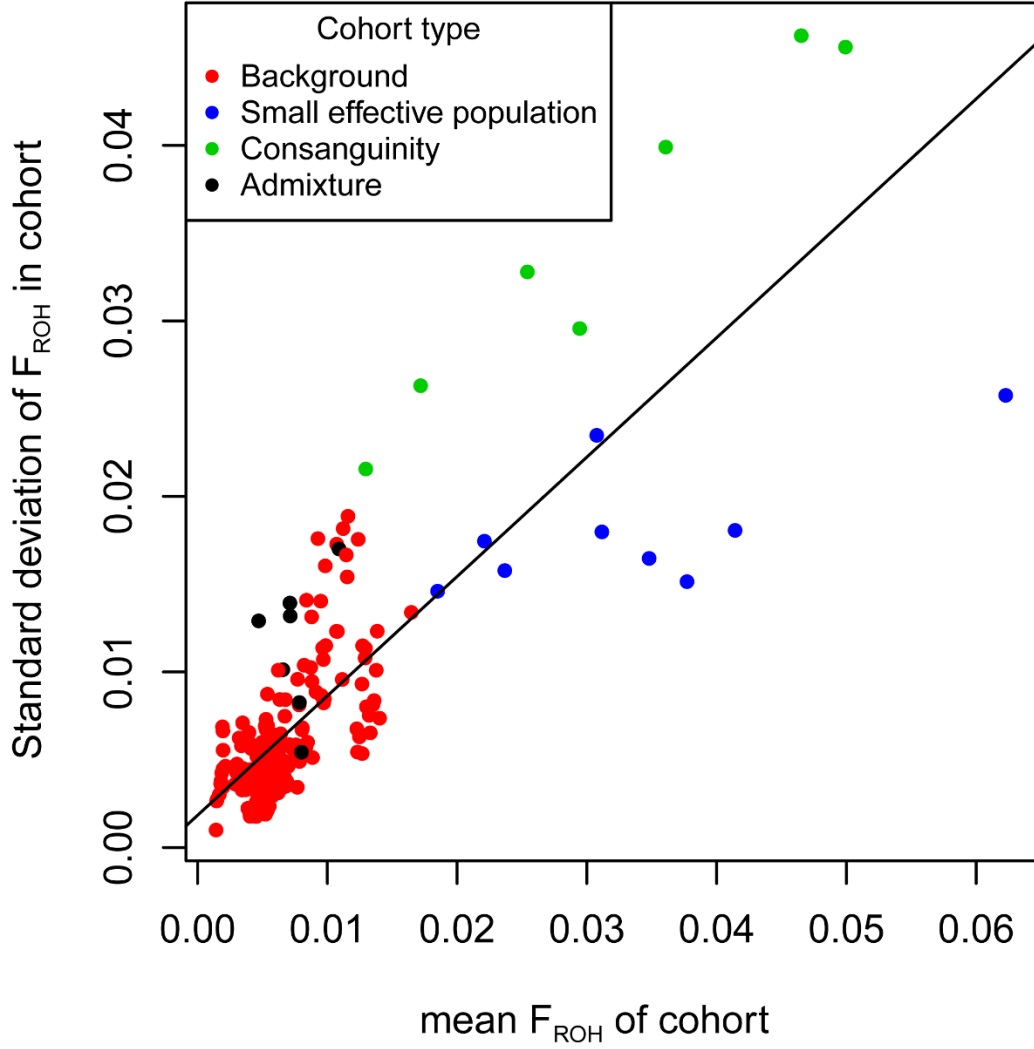


### Supplementary Figure 1: Effect of $F_{ROH}$ on height is robust to stratification by ancestral group.

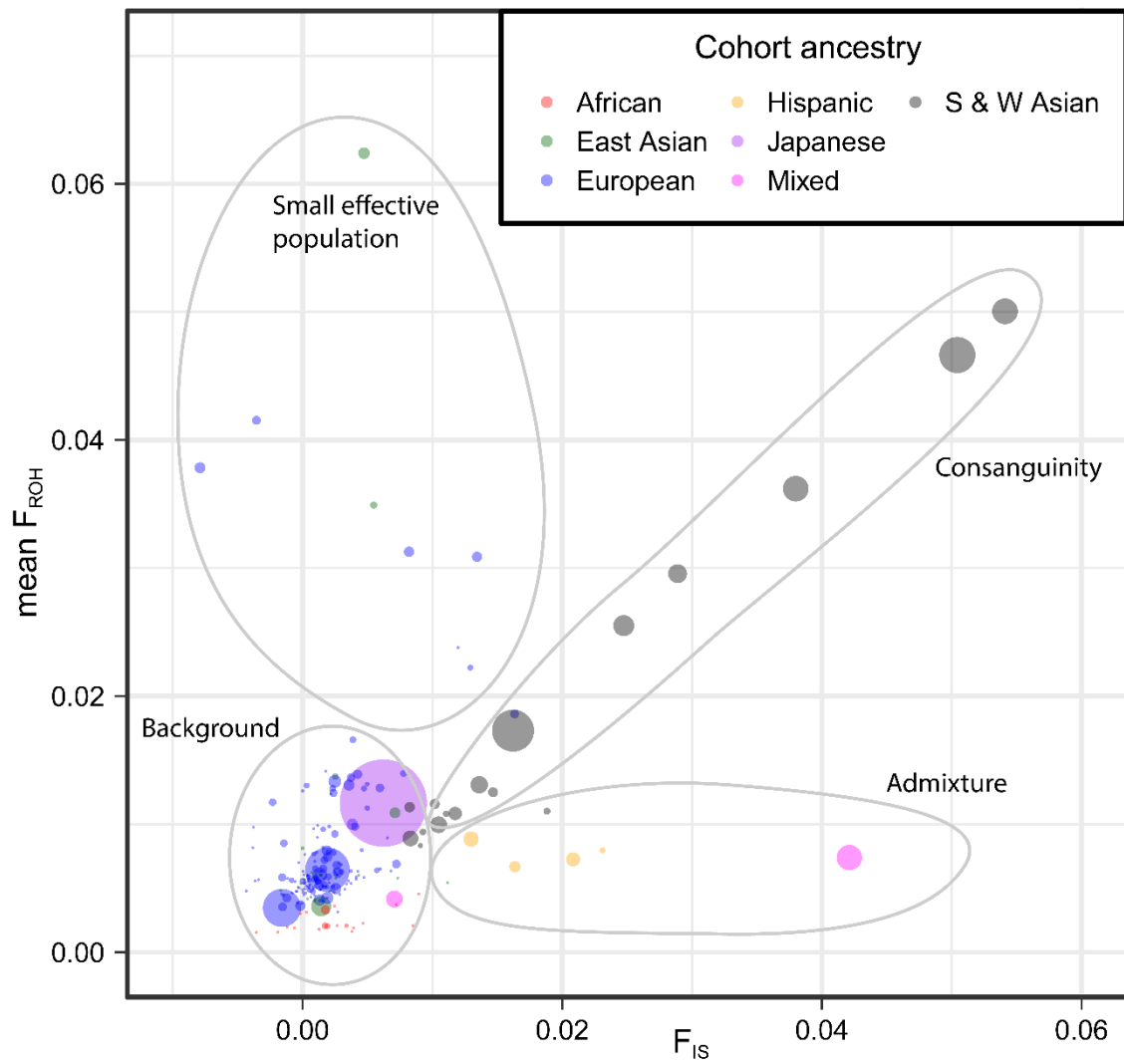
Cohorts were divided into eight broad ancestral groups (Supplementary Data Table 1) and meta-analysed separately. Although some heterogeneity is observed (heterogeneity  $p$ -value =  $3 \times 10^{-4}$ ),  $\beta_{F_{ROH}}$  is directionally consistent and differs significantly from 0 in all ancestral groups. All errors bars represent 95% confidence intervals.



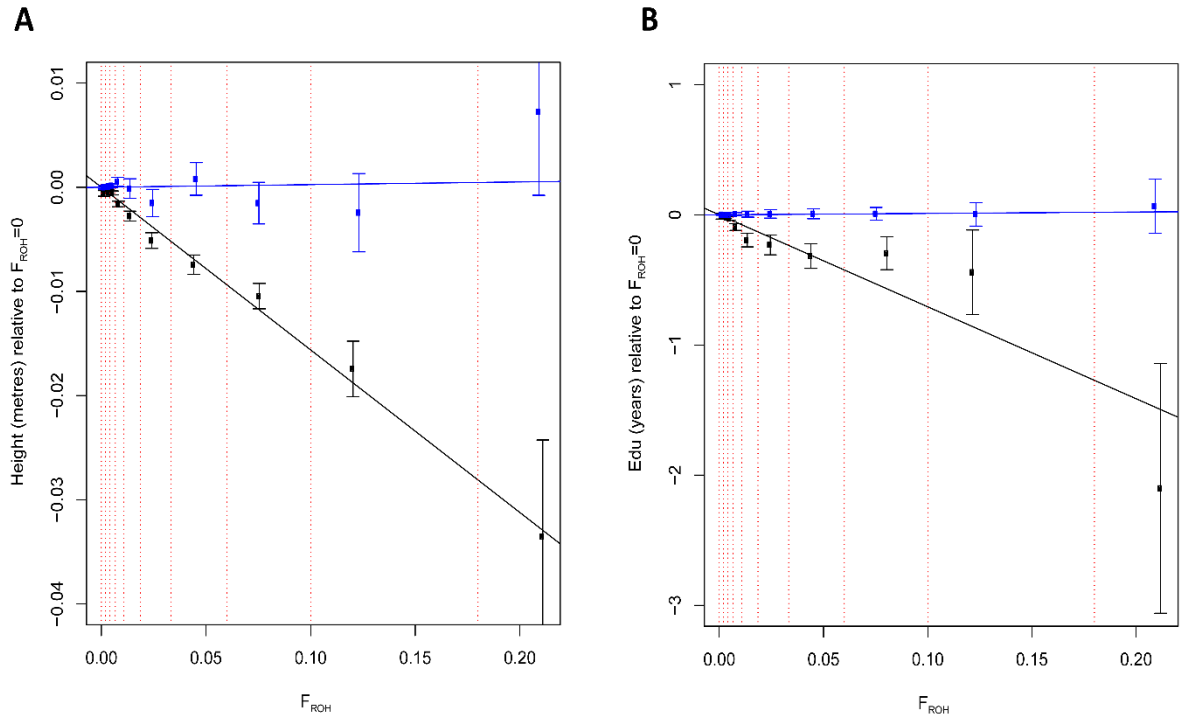
**Supplementary Figure 2: Effect of  $F_{ROH}$  on height is robust to stratification by inferred demographic history.** Cohorts were divided by inferred demographic history (Supplementary Fig. 4, Supplementary Data Table 1) and meta-analysed separately. A small amount of heterogeneity is observed (heterogeneity  $p$ -value = 0.008), but  $\beta_{F_{ROH}}$  is directionally consistent and differs significantly from 0 in all groups. In particular, in the small effective population size cohorts, where the variation of  $F_{ROH}$  is believed to be caused variations in cryptic relatedness between parents,  $\beta_{F_{ROH}}$  [-0.15, 95% CI -0.07 -0.23,  $p$ -value  $3 \times 10^{-4}$ ] is consistent with the global estimate. All errors bars represent 95% confidence intervals.



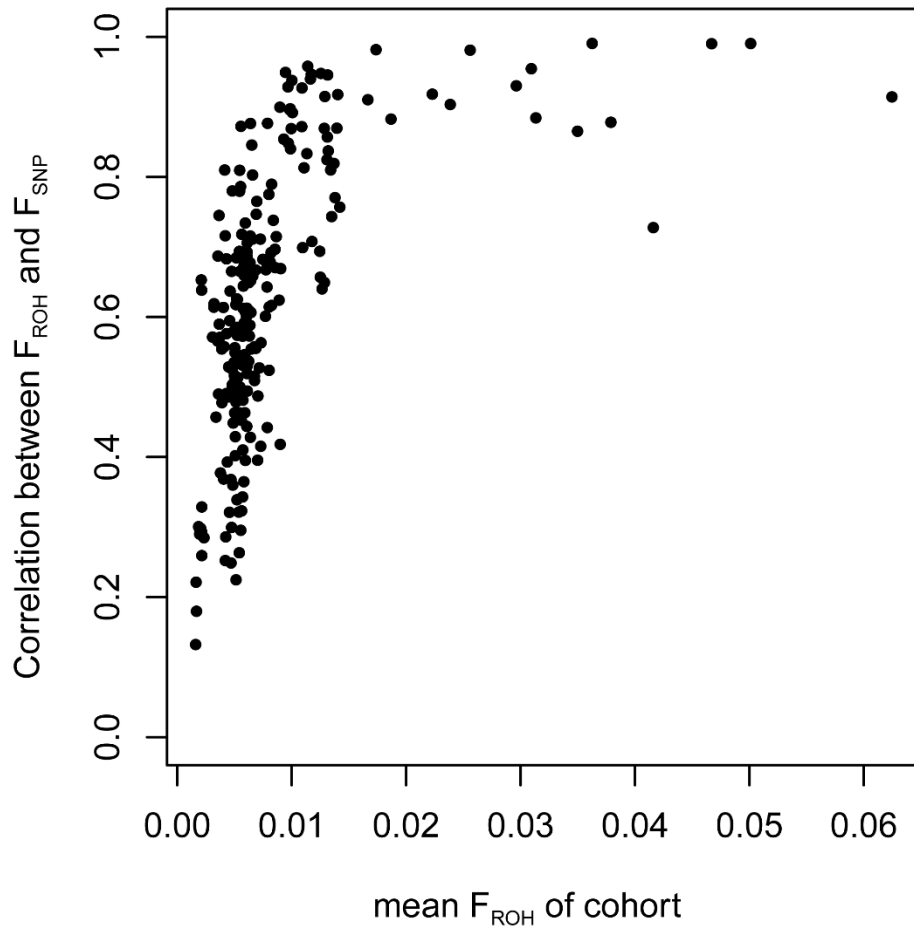
**Supplementary Figure 3: A strong correlation ( $r=0.82$ ,  $p\text{-value} = 9 \times 10^{-103}$ ) is observed between  $\sigma_{F_{\text{ROH}}}$  and mean  $F_{\text{ROH}}$ .** The standard deviation of  $F_{\text{ROH}}$  ( $\sigma_{F_{\text{ROH}}}$ ) is plotted against mean  $F_{\text{ROH}}$  for all cohorts. In regressions on  $F_{\text{ROH}}$  the statistical power is approximately proportional to  $\sigma_{F_{\text{ROH}}}^2$  and cohorts with high mean  $F_{\text{ROH}}$  generally provide greater per-sample statistical power. Also, for a given mean  $F_{\text{ROH}}$ , cohorts where ROH are primarily attributable to consanguinity rather than small effective population size provide greater statistical power.



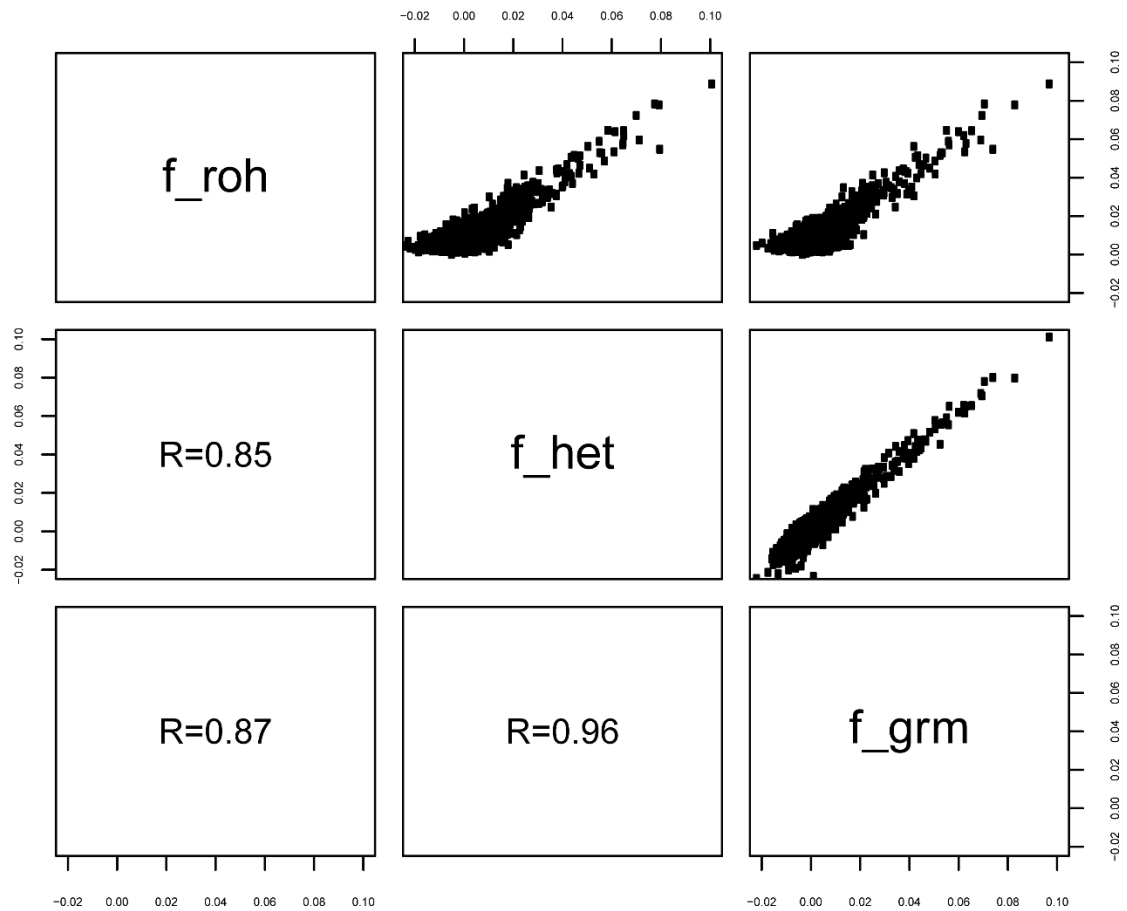
**Supplementary Figure 4: Assignment of cohorts to one of four inferred demographic histories.** Fig. 2 is replicated (see also Fig. 2 legend) and used to empirically assign cohorts to one of four inferred demographic histories. In cohorts where  $F_{IS} > 0.1$ , but the Cartesian distance to the 1:1 line was  $< 0.005$ , consanguinity was inferred to be the main origin of ROH. Cohorts which had not been defined as consanguineous but had mean  $F_{ROH} > 0.02$  were considered to have a small effective population. Cohorts with  $F_{IS} > 0.1$ , but not consanguineous nor small effective population, were defined as admixed and the remaining cohorts were described as *background*.



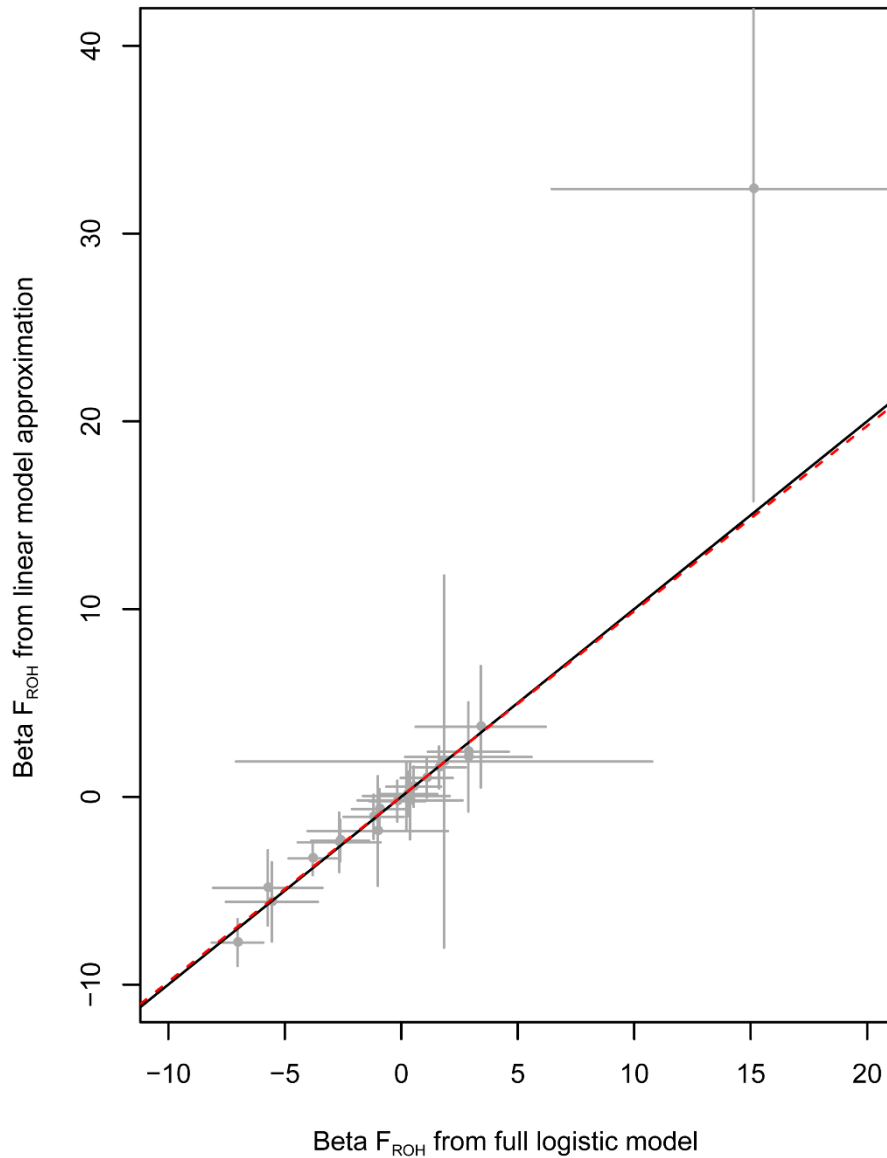
**Supplementary Figure 5: Effect of assortative mating on height and educational attainment (a): Linear decrease in height with increasing  $F_{ROH}$  but no decrease in a polygenic score for height.** In black, average height (in metres) is plotted in bins of increasing  $F_{ROH}$ . In blue, averages of a polygenic risk score for height are plotted in the same bins. Increased  $F_{ROH}$  is not associated with decreased polygenic score for height, providing evidence against a hypothesis of assortative mating generating the relationship with height. **(a): Decrease in education attained (EA) with increasing  $F_{ROH}$  but no decrease in a polygenic score for EA.** In black, average EA (in years) is plotted in bins of increasing  $F_{ROH}$ . In blue, average polygenic risk score for EA are plotted in the same bins. Increased  $F_{ROH}$  is not associated with decreased polygenic score for EA, providing evidence against a hypothesis of assortative mating generating the relationship with EA. All errors bars represent 95% confidence intervals.



**Supplementary Figure 6: Strong correlations between  $F_{\text{ROH}}$  and  $F_{\text{SNP}}$  are observed in cohorts with high average  $F_{\text{ROH}}$ .** The correlation between  $F_{\text{ROH}}$  and  $F_{\text{SNP}}$  is plotted against mean  $F_{\text{ROH}}$  for all cohorts. In low autozygosity cohorts the correlation between  $F_{\text{ROH}}$  and  $F_{\text{SNP}}$  is weak to moderate, as only a small fraction of homozygous SNPs is found in ROH. In contrast, in higher autozygosity cohorts, ROH represent a larger fraction of homozygous SNPs and the correlation between  $F_{\text{ROH}}$  and  $F_{\text{SNP}}$  is stronger.



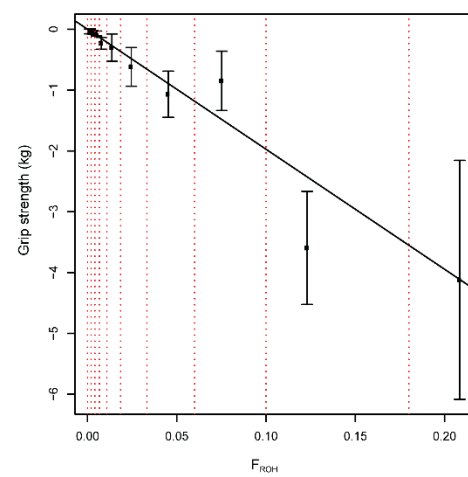
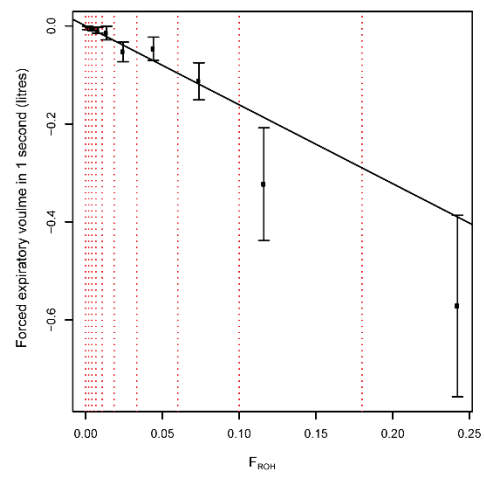
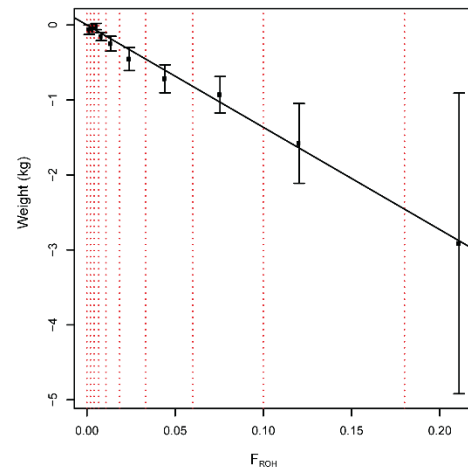
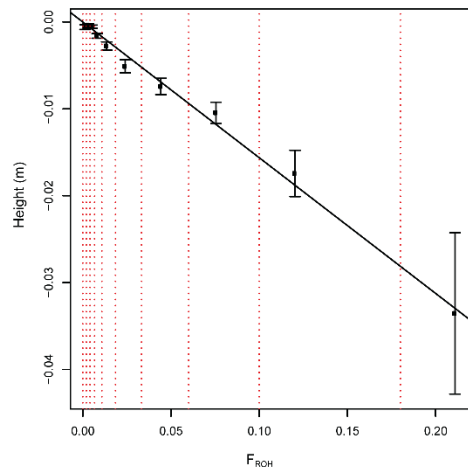
**Supplementary Figure 7: Scatter plots of  $F_{ROH}$  plotted against  $F_{SNP}$  and  $F_{GRM}$  in a single cohort (VIKING).** Scatter plots of three estimates of inbreeding coefficient ( $F_{ROH}$ ,  $F_{SNP}$  and  $F_{GRM}$ ) are shown in the upper right panels. The correlation between these estimates is shown in the lower left panels.



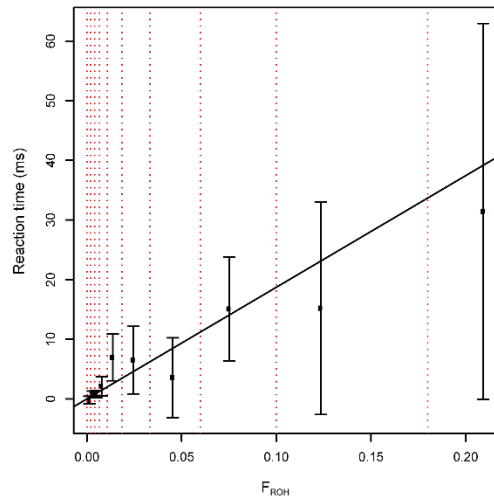
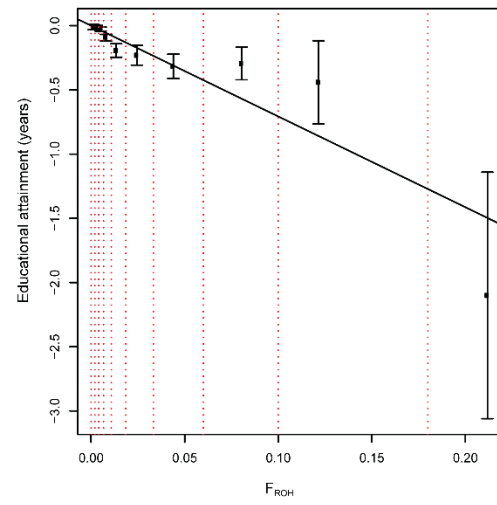
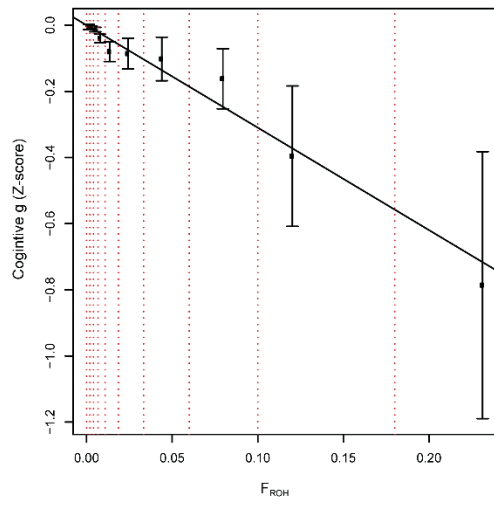
**Supplementary Figure 8: A linear model approximation of the full logistic model gives relatively unbiased estimates of  $\beta_{F_{ROH}}$ .** For all 22 binary traits analysed, estimates obtained from a two-step linear model approximation are plotted against estimates obtained from the full logistic model (See Methods). Estimates of  $\beta_{F_{ROH}}$  are shown in grey. The 1:1 unity line is shown in red, and a linear least-squares fit is shown in black. The gradient of the best fit line (1.02 95% CI 0.99-1.02) does not differ significantly from the unbiased expectation of 1 ( $p$ -value 0.87). For all but one trait, the linear model approximation is consistent with the full logistic model estimate of  $\beta_{F_{ROH}}$ . Self-declared infertility has the most extreme case:control ratio (632:472544) of any of the binary traits analysed and for this trait only the linear model significantly overestimates  $\beta_{F_{ROH}}$ . The linear model estimates are therefore marked with an asterisk where they appear in Supplementary Data Tables 12-14, 16-21. All errors bars represent 95% confidence intervals.



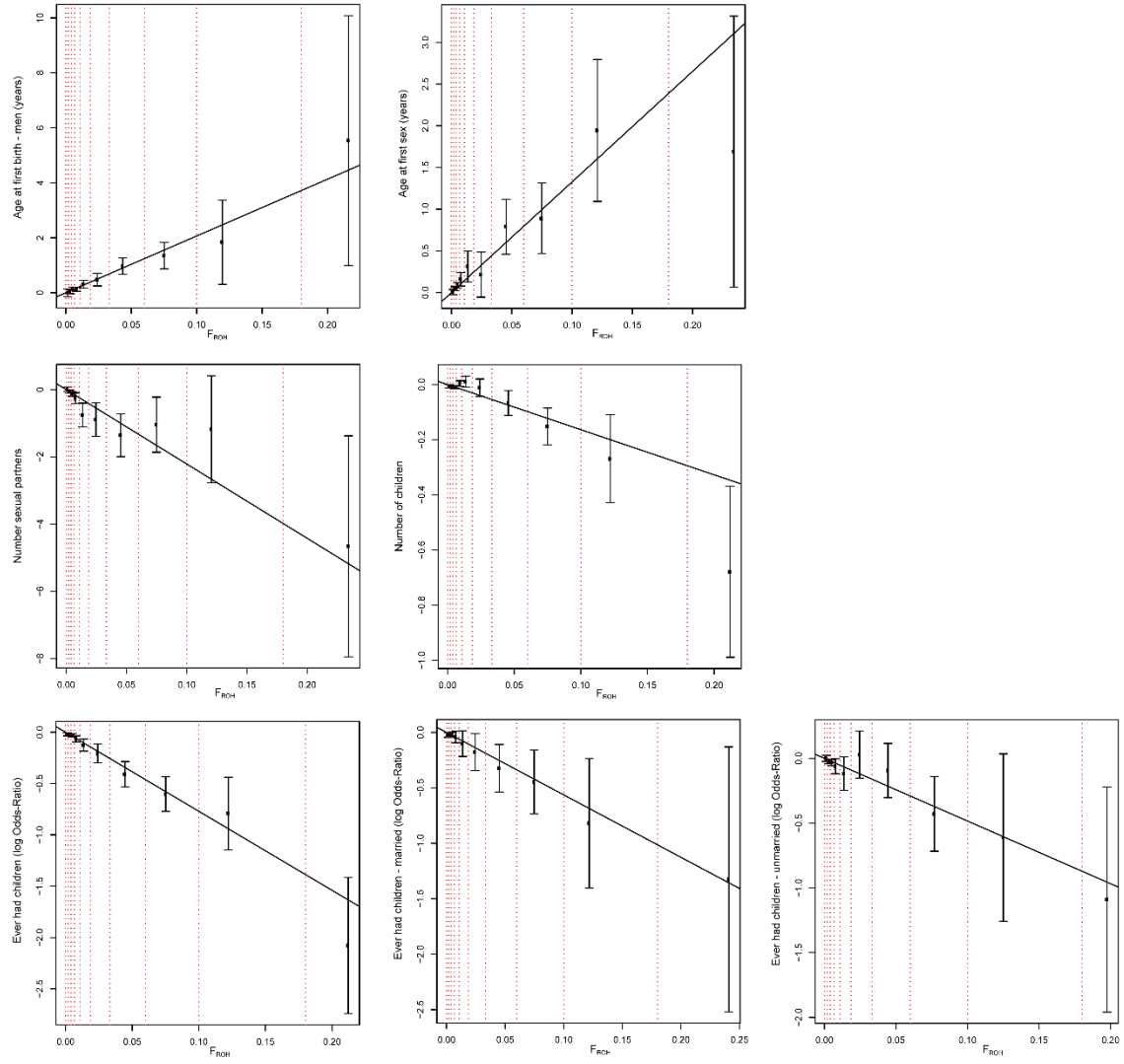
9a



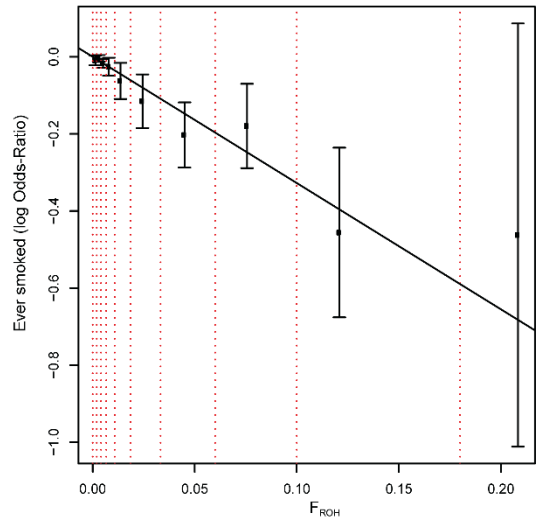
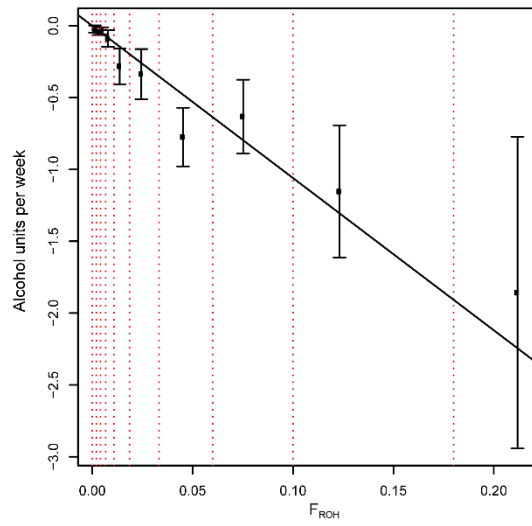
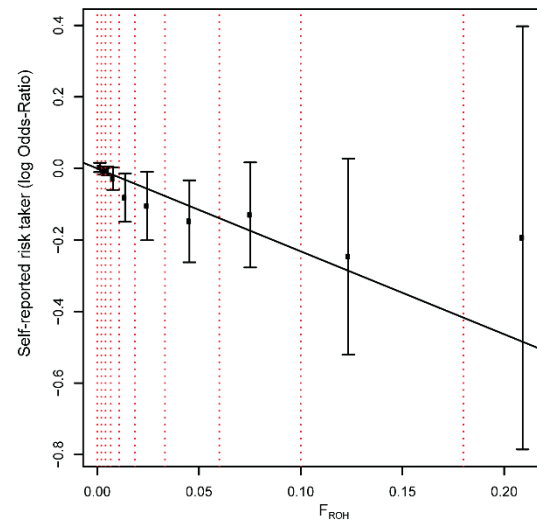
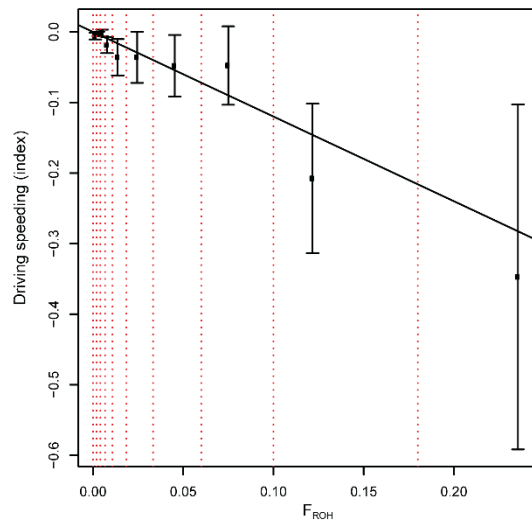
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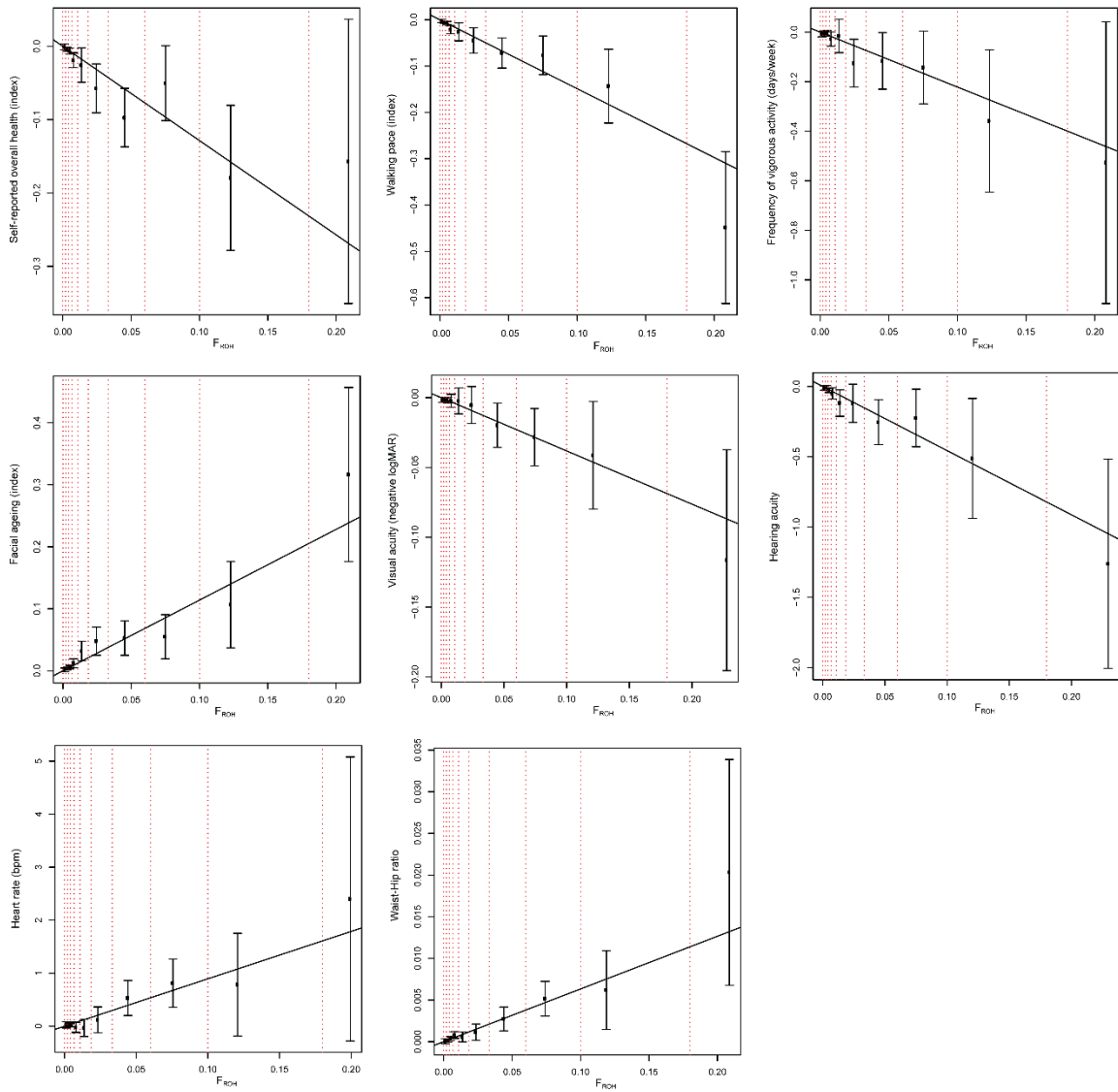
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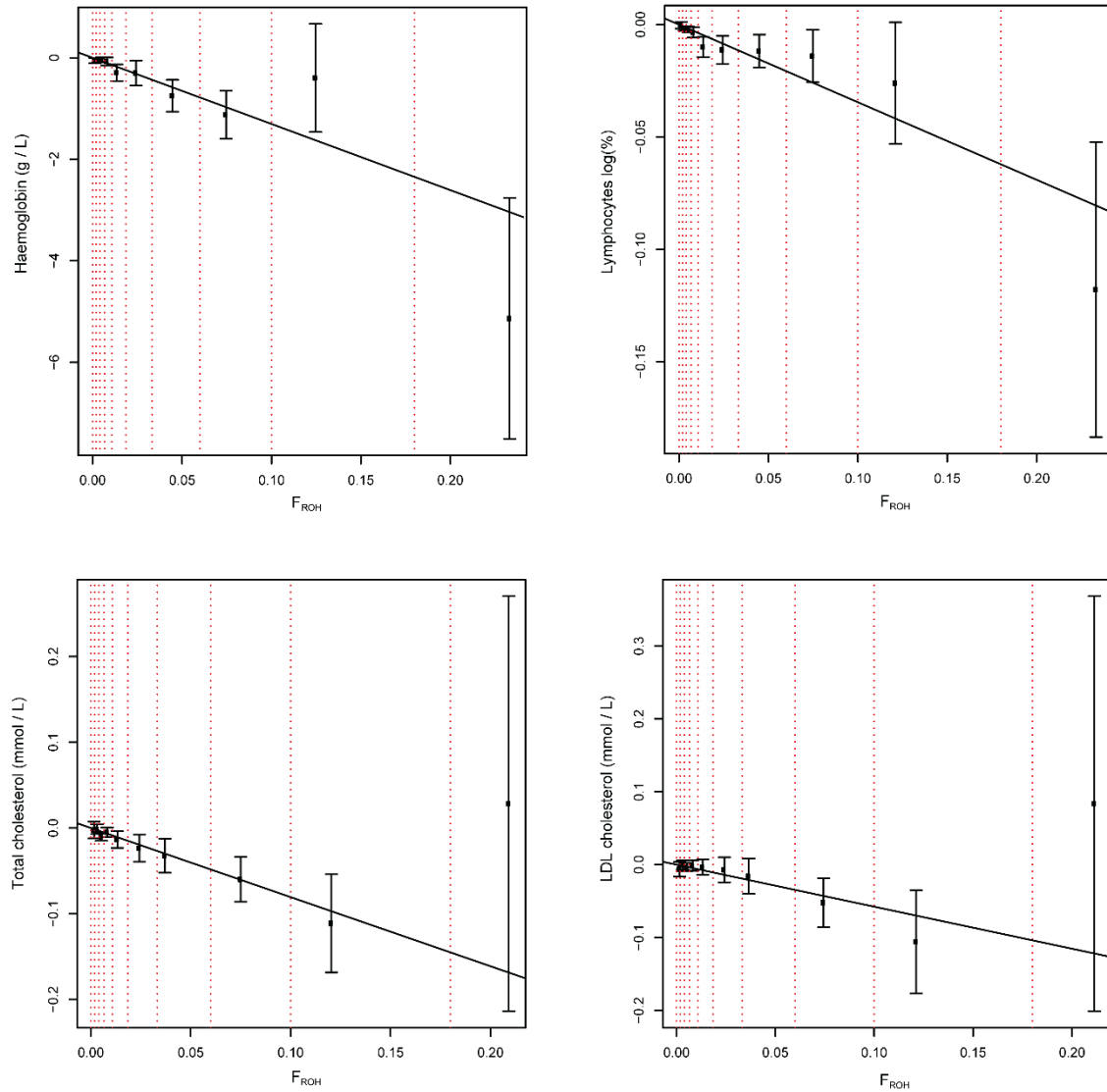


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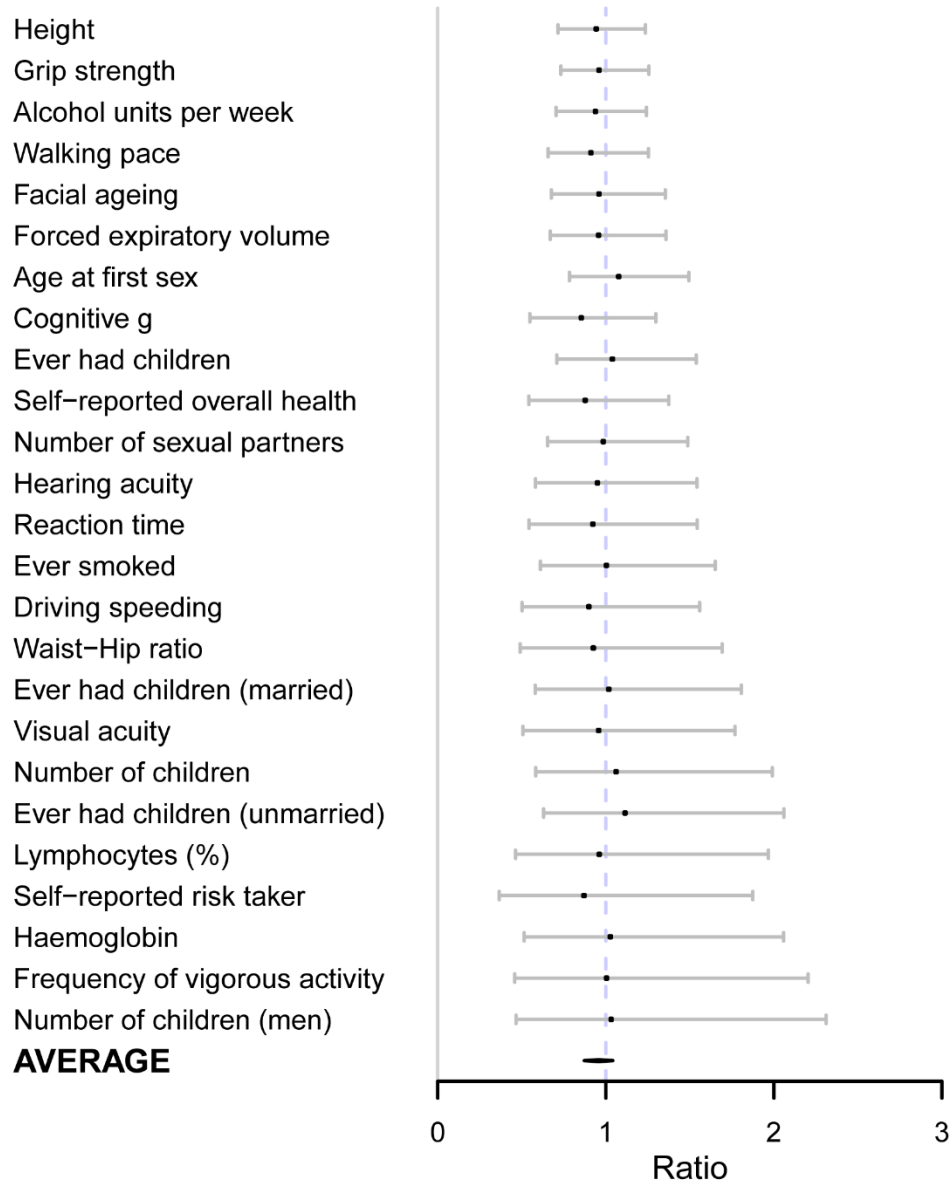
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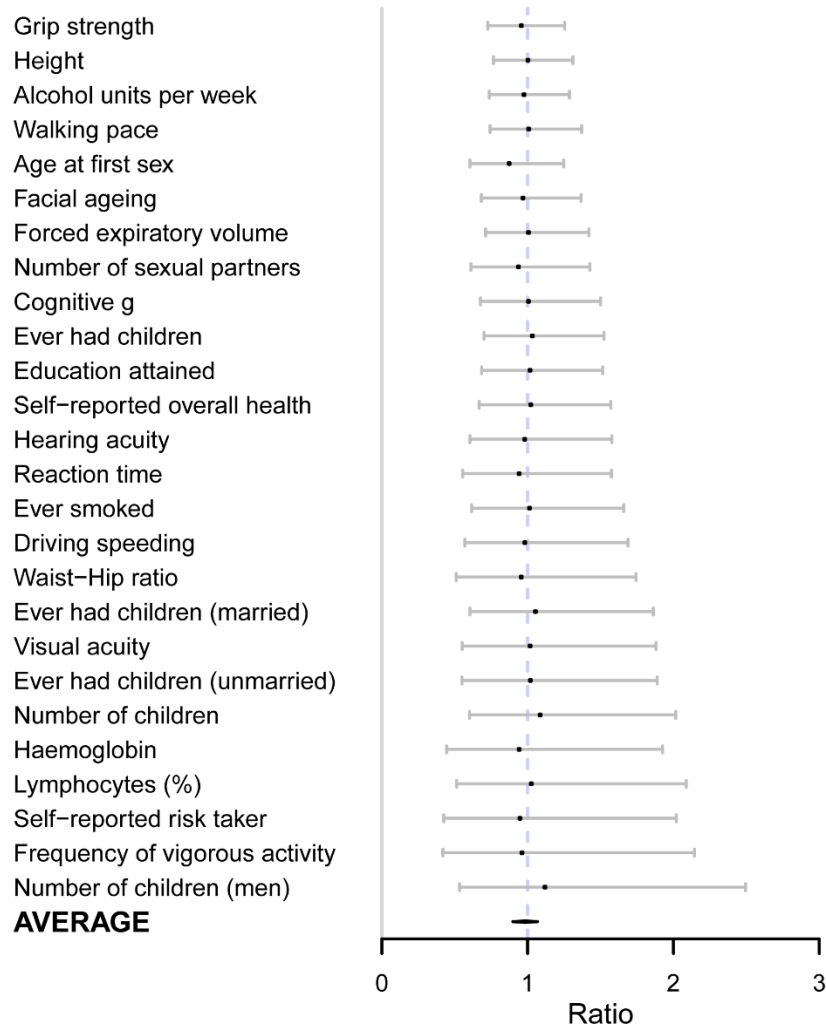


**Supplementary Figure 9: Significant traits show a dosed response to increasing  $F_{ROH}$ .** For all traits that reach experiment-wise significance in the meta-analysis, mean trait residuals are plotted in bins of increasing  $F_{ROH}$  (Methods) as also shown for height and Ever had children in Fig. 5a, b. Traits have been grouped into six categories (a) **Anthropometry**, (b) **Cognition**, (c) **Reproduction**, (d) **Risk-taking behaviour**, (e) **Well-being/Frailty**, (f) **Blood**. Although significant heterogeneity is observed for three traits (Height heterogeneity  $p$ -value =  $7 \times 10^{-8}$ , Educational Attainment heterogeneity  $p$ -value =  $2 \times 10^{-8}$ , Number ever born heterogeneity  $p$ -value =  $7 \times 10^{-5}$ ) there is otherwise a dosed repose to increasing  $F_{ROH}$  for all traits. A dosed response across a wide range of  $F_{ROH}$  would be expected of a causal genetic effect, but not necessarily of environmental confounding. Although the effect of a confounder on a trait may be proportional, there is no a priori reason to expect a linear association between any confounder and  $F_{ROH}$ , especially extending to the large effects seen in very high  $F_{ROH}$  samples ( $F_{ROH} > 0.18$ ). All errors bars represent 95% confidence intervals.

10a



10b

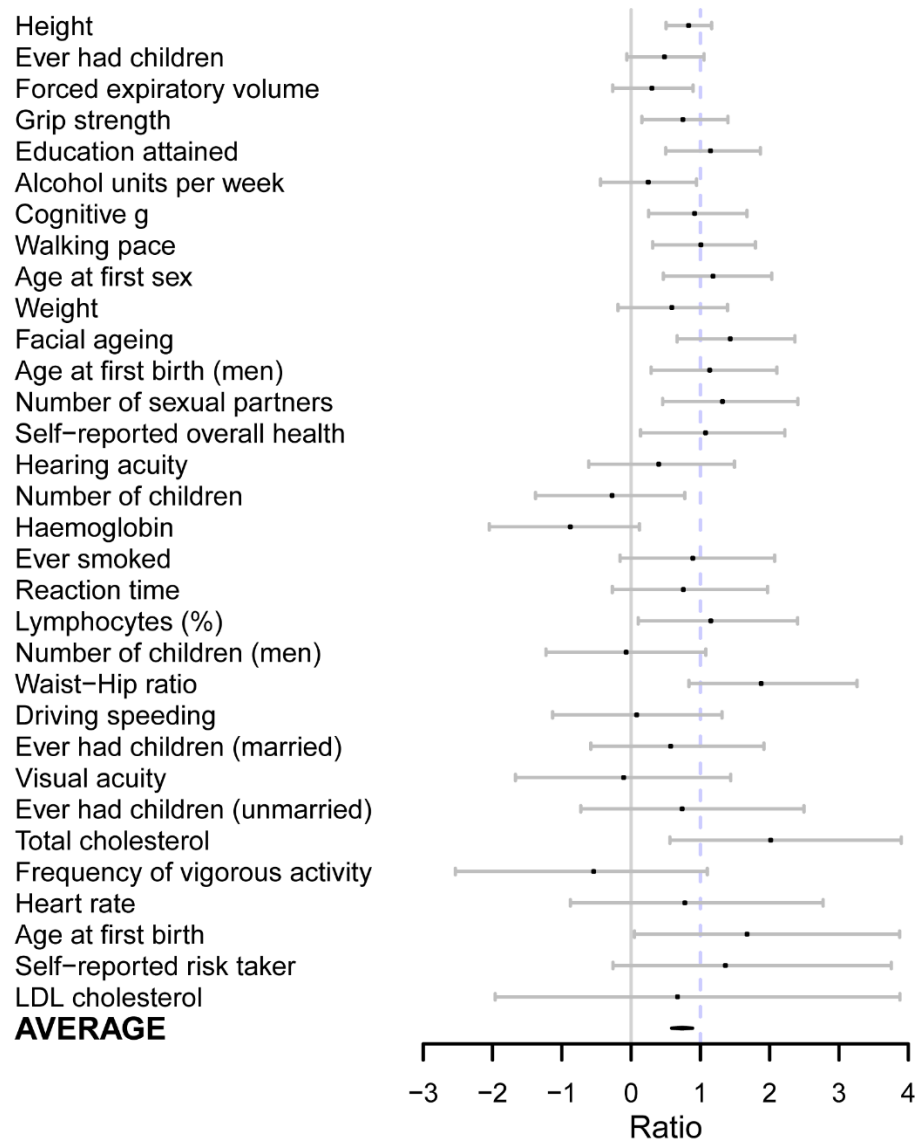


**Supplementary Figure 10: Effect of fitting potential confounders as covariates. (a) Educational Attainment.** For all traits that reach significance in UK Biobank, the ratio of effect size estimates with Educational Attainment (EA) fitted as an additional covariate ( $\beta_{F_{ROH}}^{+EA}$ ) to the corresponding effect size estimates without EA ( $\beta_{F_{ROH}}$ ) are shown. The largest change is seen in Cognition (g) where fitting EA reduces  $\beta_{F_{ROH}}$  by 14.6%. However, since  $F_{ROH}$  is known to directly influence both g and EA, this change is not necessarily evidence of non-genetic effects. Overall fitting EA reduces the magnitude of  $\beta_{F_{ROH}}$  for 16 traits, but increases it for 9 traits, including number and likelihood of having children.

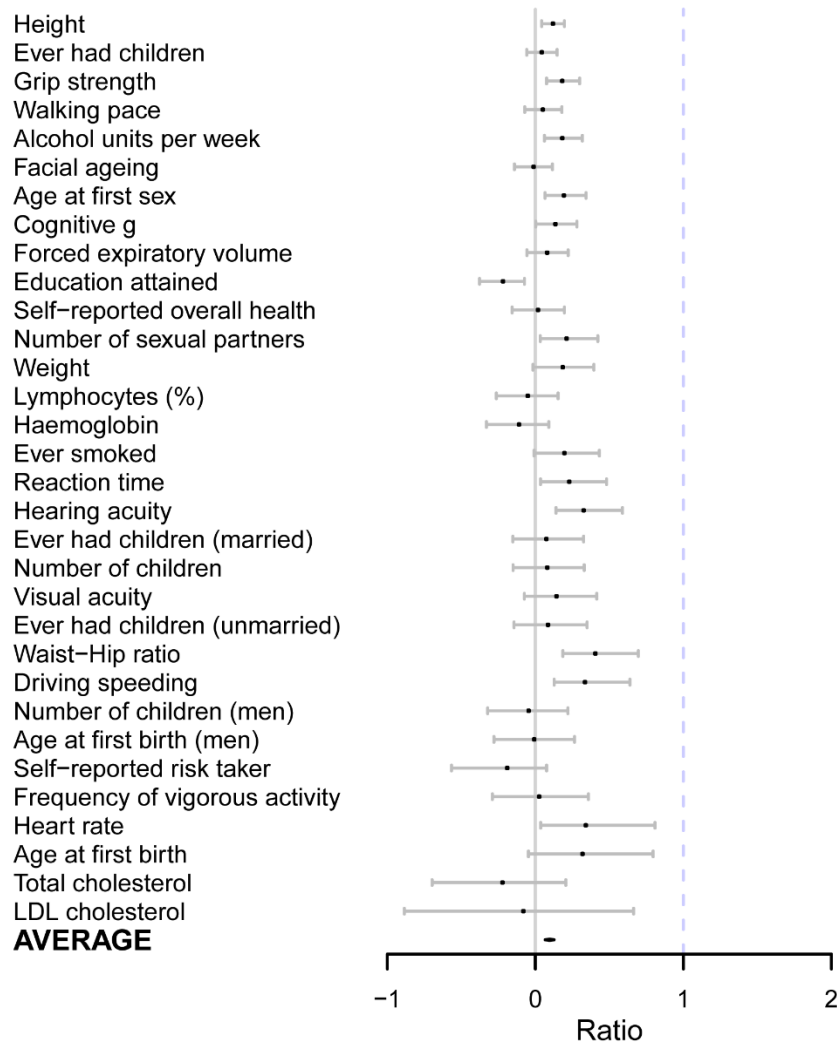
**(b) Religious participation.** For the same traits (plus EA), the ratio of effect size estimates with a measure of religious participation (see Methods) fitted as an additional covariate ( $\beta_{F_{ROH}}^{+R}$ ) to the corresponding effect size estimates without religious participation ( $\beta_{F_{ROH}}$ ) are shown. The largest reductions in  $\beta_{F_{ROH}}$  are seen for age at first sex (-12.7%) and number of sexual partners (-6.2%), suggesting that these traits may be partially confounded by social associations between  $F_{ROH}$  and religious beliefs. However, overall, fitting religious participation as a covariate increases  $\beta_{F_{ROH}}$  for 14 of 26 traits, again including number and likelihood of having children. All errors bars represent 95% confidence intervals.



11a

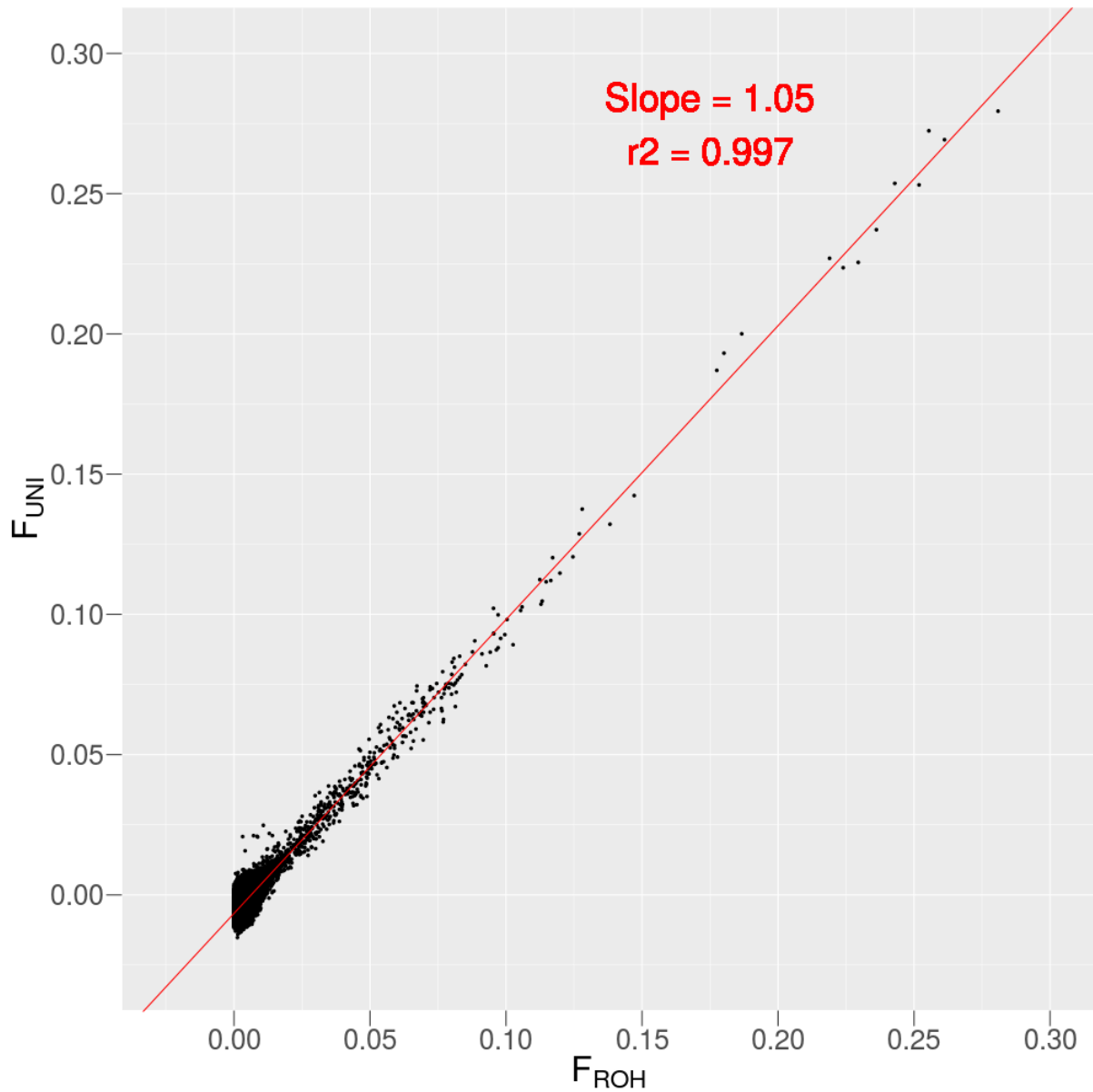


11b

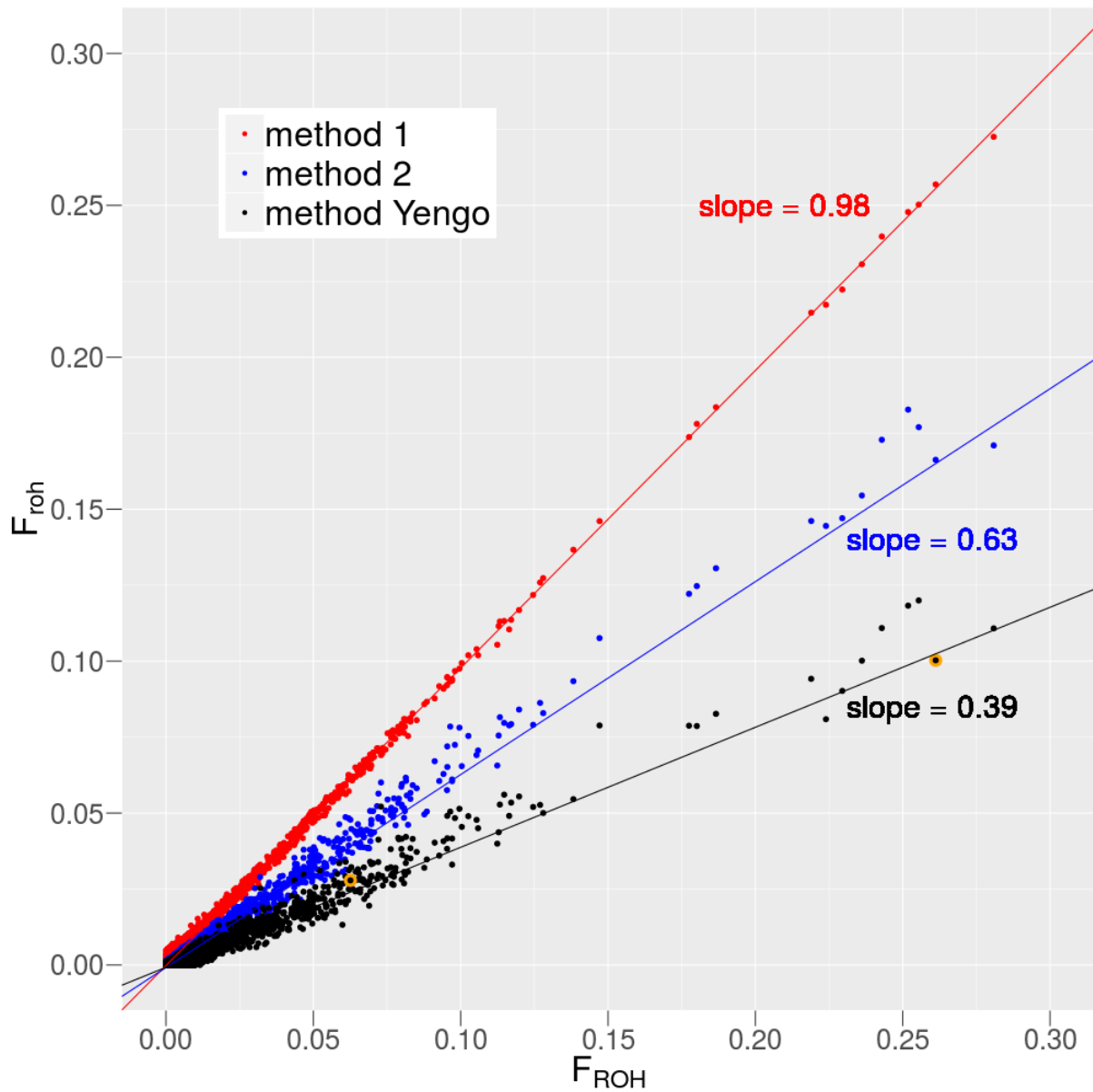


**Supplementary Figure 11: Conditional effects of ROH < 5Mb and SNP homozygosity outside ROH.**

Multivariate models were run for all traits including 3 different measures for homozygosity:  $F_{\text{SNP\_OutsideROH}}$ ,  $F_{\text{ROH}<5\text{Mb}}$  and  $F_{\text{ROH}>5\text{Mb}}$  (See Methods). **(a) Relative effect of ROH < 5Mb.** The conditional effect of  $F_{\text{ROH}<5\text{Mb}}$  divided by  $\beta_{F_{\text{ROH}}}$  is shown for all significant traits. Across all traits, the meta-analysed average of this ratio is 0.74 [95% CI 0.59-0.89,  $p$ -value  $5 \times 10^{-22}$ , heterogeneity  $p$ -value 0.132]. ROH of length less than 5 Mb are believed to be largely unconfounded by recent consanguinity, supporting the hypothesis that environmental confounding is responsible for only a small fraction (approximately 25%) of the reported effects. **(b) Relative effect of SNP homozygosity outside ROH.** The conditional effect of  $F_{\text{SNP\_OutsideROH}}$  divided by  $\beta_{F_{\text{ROH}}}$  is shown for all significant traits. Although there is some heterogeneity, as might be expected from different trait architectures, for all traits the effect of  $F_{\text{SNP\_OutsideROH}}$  is significantly less than the effect of  $F_{\text{ROH}}$ . Averaging across all traits, the meta-analysed average of  $\beta_{F_{\text{SNP\_OutsideROH}}} : \beta_{F_{\text{ROH}}}$  is 0.12 [95% CI 0.04-0.20,  $p$ -value  $2 \times 10^{-10}$ , heterogeneity  $p$ -value 0.001], showing that ROH have a larger effect on inbreeding depression on complex traits than does common SNP homozygosity outside ROH. All errors bars represent 95% confidence intervals.

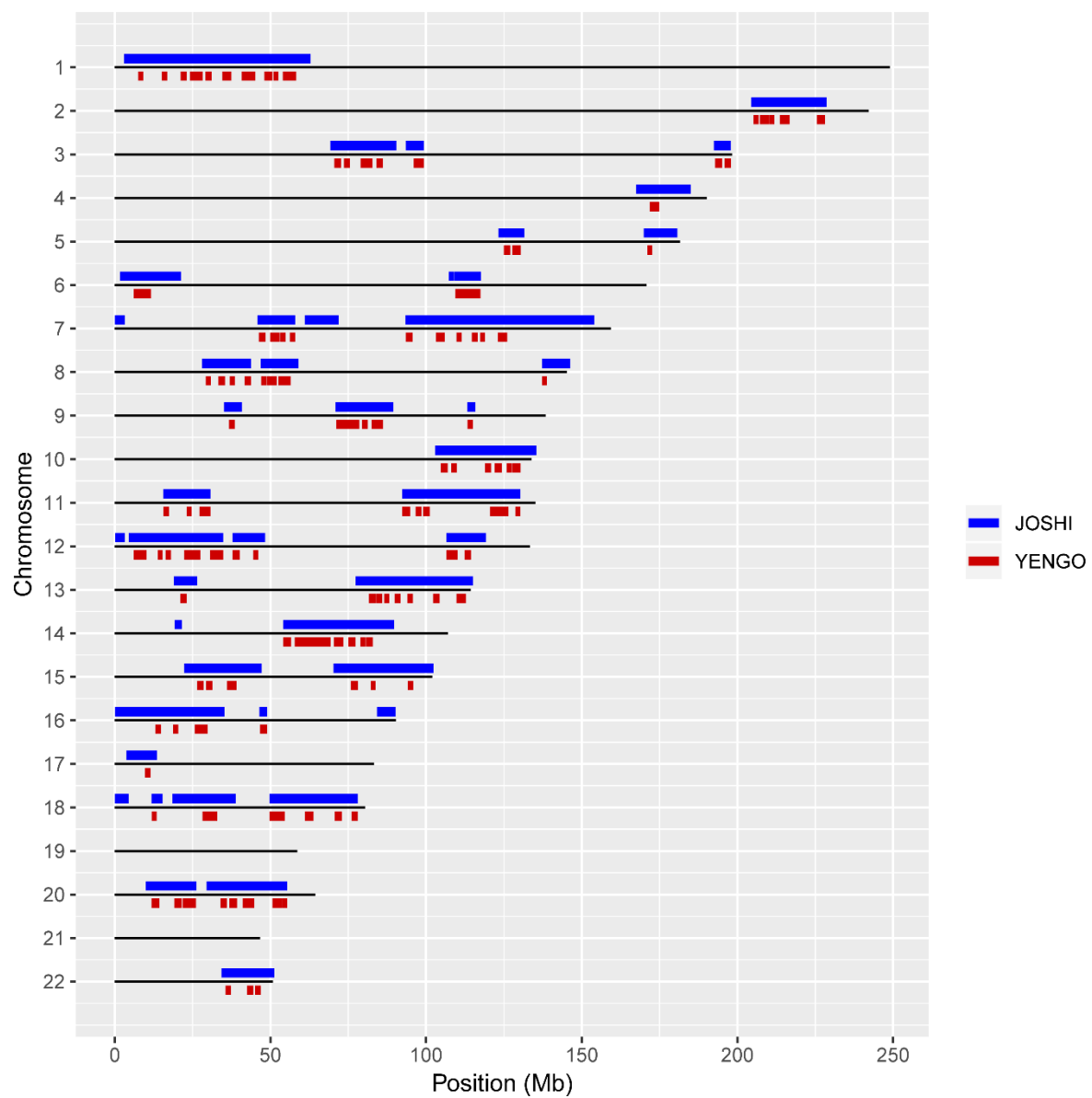


**Supplementary Figure 12: Good correspondence between  $F_{\text{UNI}}$  and  $F_{\text{ROH}}$ .** For 141,774 British samples in UK Biobank  $F_{\text{UNI}}$ , calculated from excess homozygosity of imputed genotypes, is plotted against  $F_{\text{ROH}}$ , calculated from SNP array genotypes. A weighted linear regression line is shown in red. Because average inbreeding coefficients are low ( $\bar{F}_{\text{ROH}} = 0.003$  in this population), it is high  $F$  individuals who contribute most of the statistical power to estimates of  $\beta_F$ . Weighting the regression by an estimate of power contribution  $(F_i^{\text{ROH}} - \bar{F}_{\text{ROH}})^2$ , we estimate  $\beta_{F_{\text{UNI}}, F_{\text{ROH}}} = 1.05$  and  $r^2 = 0.997$ . The good correspondence between  $F_{\text{UNI}}$  and  $F_{\text{ROH}}$  suggests both have minimal bias in estimating  $F$ .

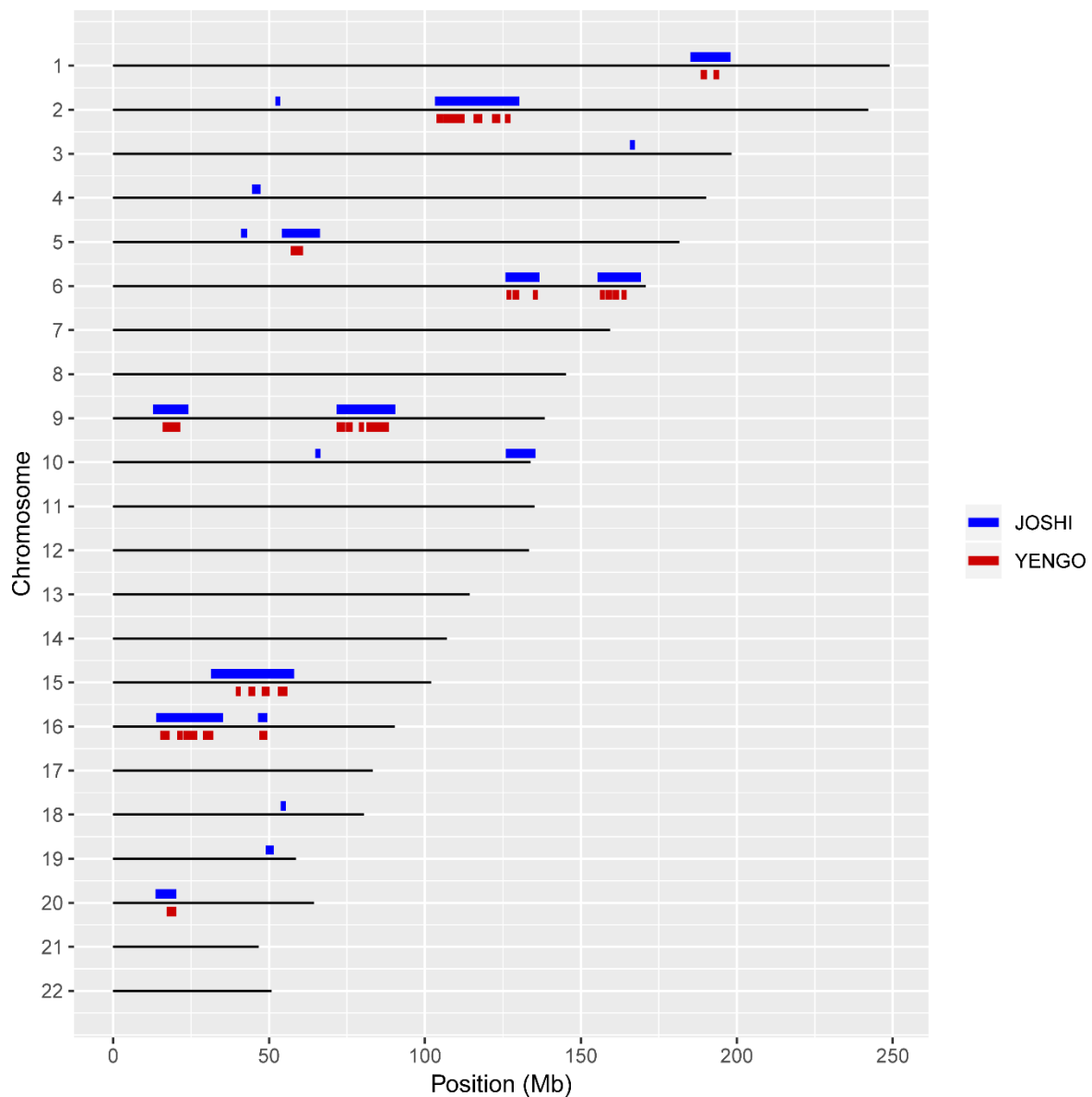


**Supplementary Figure 13: Comparison of  $F_{roh}$  from imputed data and  $F_{ROH}$  from SNP array genotypes.** For 141,774 British samples in UK Biobank,  $F_{roh}$  calculated from imputed genotypes is plotted against  $F_{ROH}$  calculated from SNP array genotypes for three methods of imputed genotype preparation. In method 1, in red, uncertain genotypes are removed. In method 2, in blue, uncertain genotypes are set to missing and in method Yengo, in black, no genotype filtering is performed. Increasingly permissive treatments of uncertain genotypes introduce increasing downward bias in  $F_{roh}$ . Two high  $F_{ROH}$  are highlighted in orange and further explored in Supplementary Figures 14a,b.

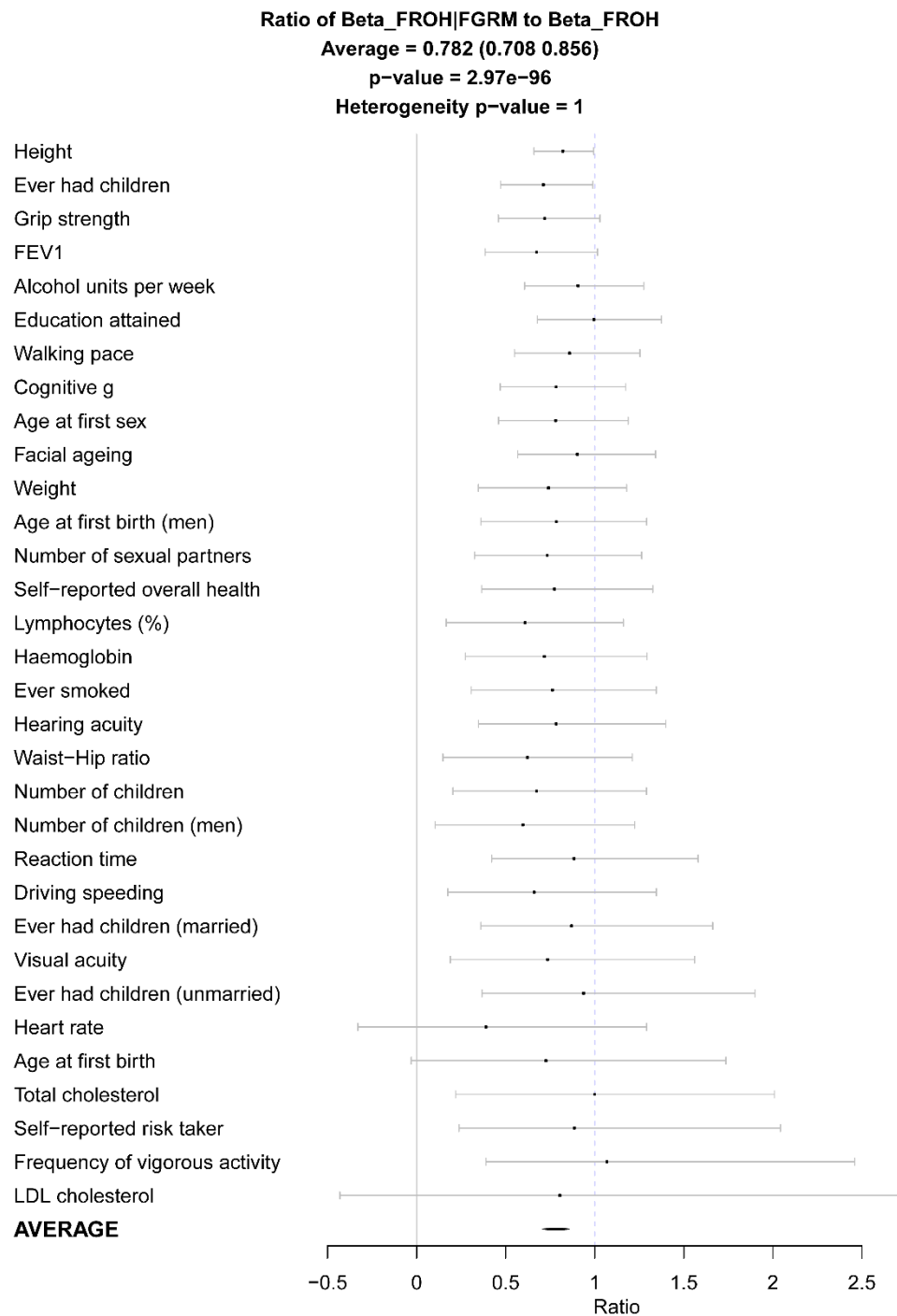
14a

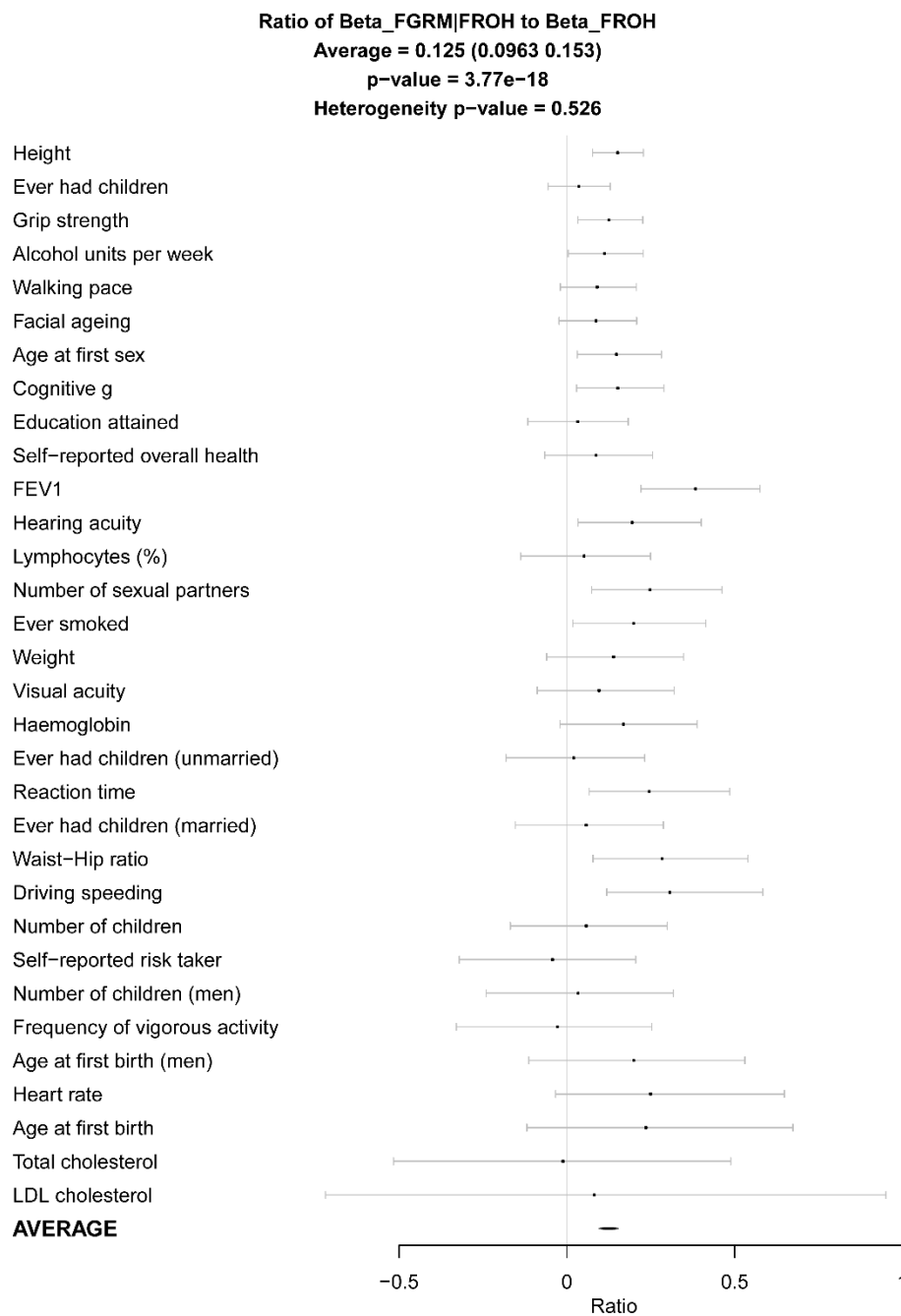


14b



**Supplementary Figure 14: Comparing ROH calling from SNP array genotypes and imputed dosages.** For two high  $F_{\text{ROH}}$  individuals, the locations of called ROH are compared for two methods. The method shown in blue calls ROH from SNP array genotypes using the parameters used in Joshi et al. (2015). The method shown in red calls ROH from hard called imputed dosages following the method described in Yengo et al (2017). In both individuals the long ROH detected in SNP array genotypes, and which are thought to be autozygous segments, are broken up in the imputed data method by the presence of miscalled heterozygotes. **(a) Individual with  $F_{\text{ROH}} = 0.261$  thought to be offspring of first-degree relatives. (b) Individual with  $F_{\text{ROH}} = 0.0626$  thought to be offspring of third-degree relatives.**

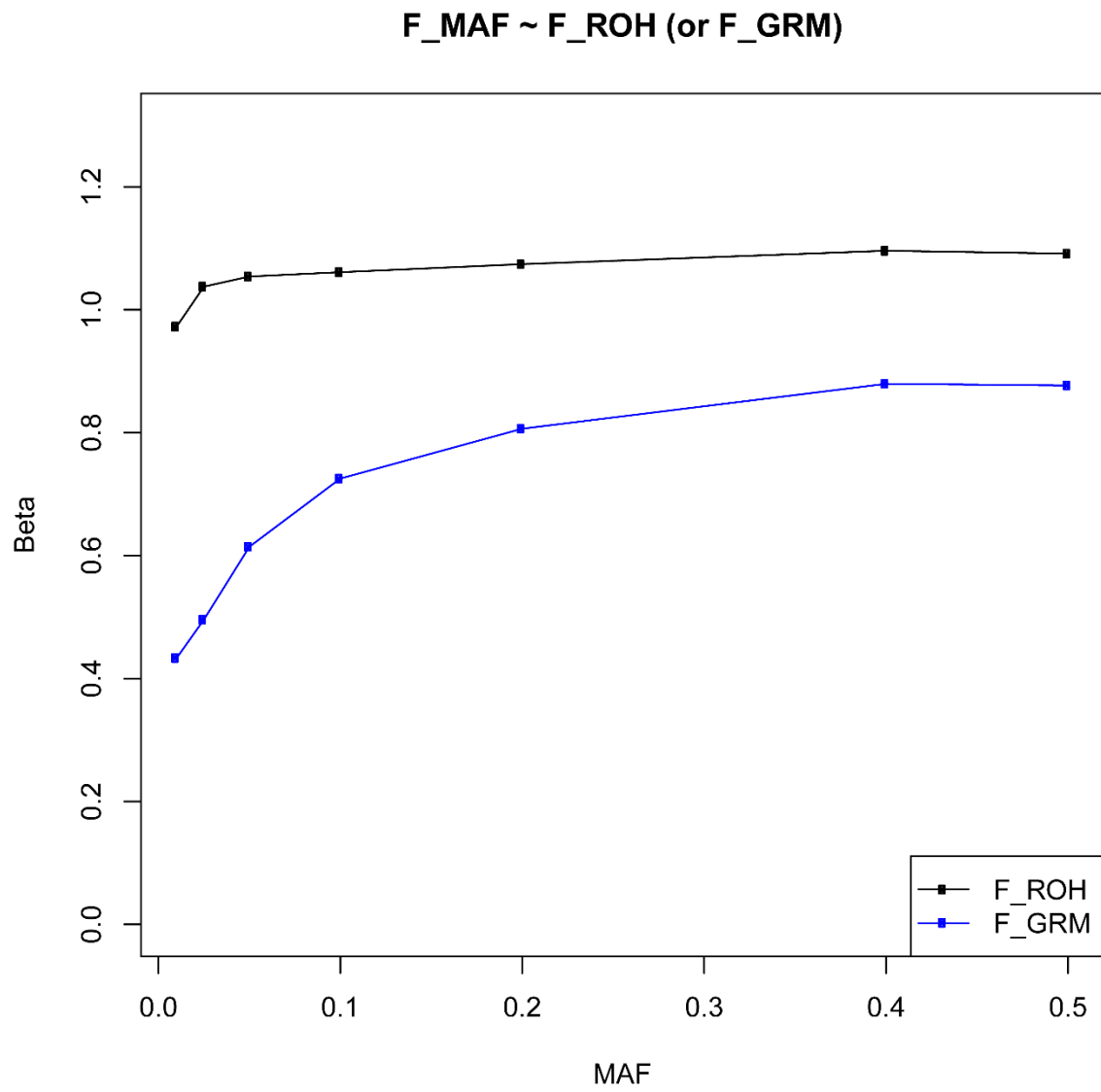


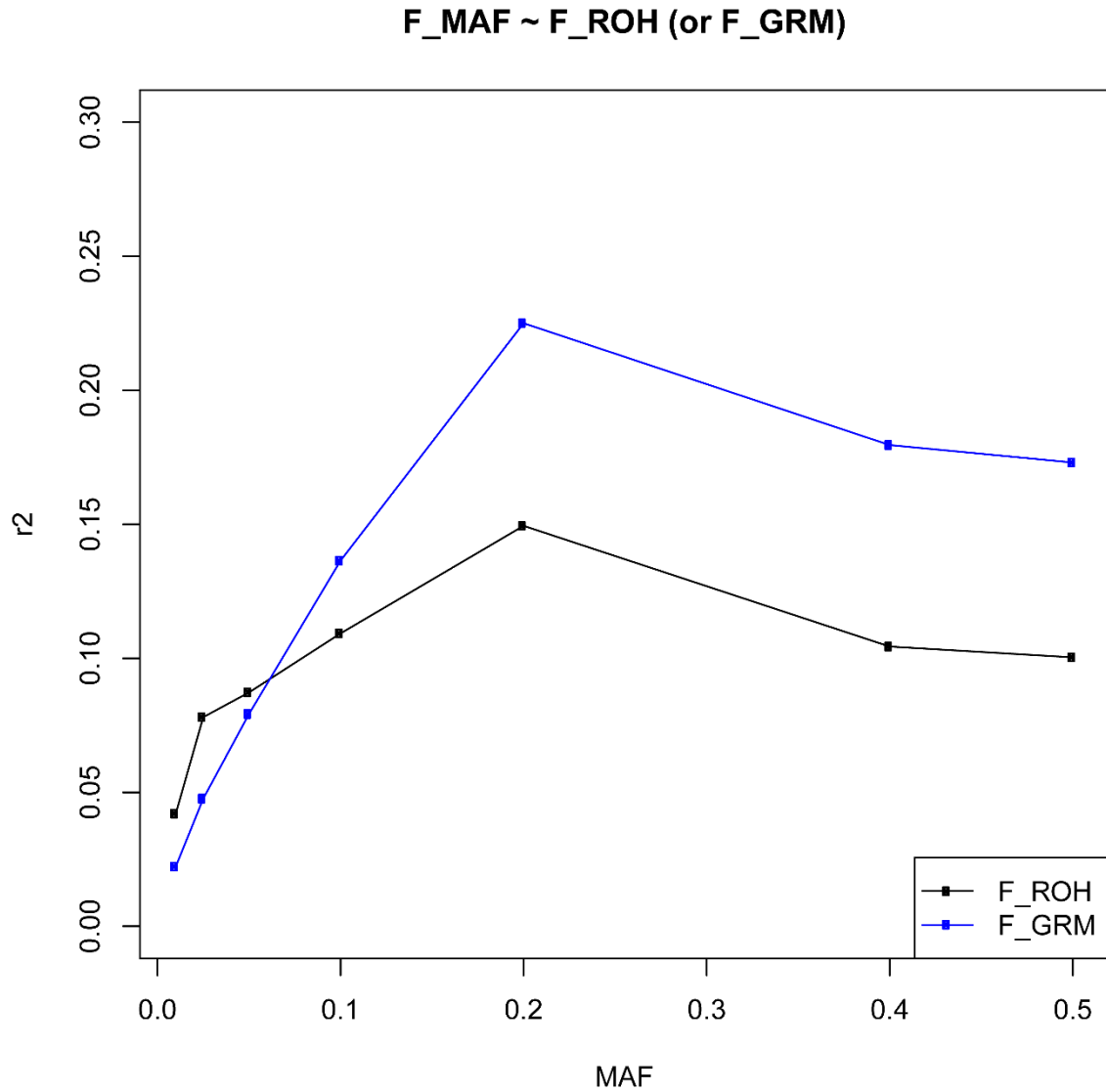


**Supplementary Figure 15: Comparing effect estimates from bivariate models to the equivalent univariate estimates.** For all significant traits, effect estimates were obtained from bivariate models of  $Trait \sim F_{ROH} + F_{GRM}$  and compared to univariate estimates from the model  $Trait \sim F_{ROH}$ . **(a) Ratio of  $\beta_{F_{ROH}|F_{GRM}}$  to  $\beta_{F_{ROH}}$ .** For all significant traits the ratio  $\frac{\beta_{F_{ROH}|F_{GRM}}}{\beta_{F_{ROH}}}$  is plotted. A meta-analysis across all traits gives an average ratio of 0.78 [95% CI 0.71-0.86]. **(b) Ratio of  $\beta_{F_{GRM}|F_{ROH}}$  to  $\beta_{F_{ROH}}$ .** For all significant traits the ratio  $\frac{\beta_{F_{GRM}|F_{ROH}}}{\beta_{F_{ROH}}}$  is plotted. A meta-analysis across all traits gives an average ratio of 0.12 [95% CI 0.10-0.15]. All errors bars represent 95% confidence intervals.



16a





**Supplementary Figure 16: Univariate relationships between estimates of inbreeding coefficient ( $F_{ROH}$ ,  $F_{GRM}$ ) and the excess homozygosity at specific allele frequencies.** The excess homozygosity of SNPs at seven allele frequencies ( $F_{MAF}$ ) was calculated for 402,559 genetically British samples in the phase 2 UKB imputation. **(a) Effect estimates of  $F_{ROH}$  and  $F_{GRM}$  on  $F_{MAF}$ .** Univariate models of  $F_{MAF} \sim F_{ROH}$  and  $F_{MAF} \sim F_{GRM}$  were fitted at each allele frequency. A one unit increase in  $F_{ROH}$  is associated with a one unit increase in  $F_{MAF}$  across all allele frequencies. In contrast, the slope of  $\beta_{F_{MAF}, F_{GRM}}$  is downwardly biased at all allele frequencies. **(b) Correlations between of  $F_{ROH}$ ,  $F_{GRM}$  and  $F_{MAF}$ .** Univariate models of  $F_{MAF} \sim F_{ROH}$  and  $F_{MAF} \sim F_{GRM}$  were fitted at each allele frequency. Despite the downward bias of its effect estimate,  $F_{GRM}$  is more strongly correlated with  $F_{MAF}$  at most allele frequencies.

## SUPPLEMENTARY TABLES

**Supplementary Table 1: Genetic correlations between risk and reproductive traits.** Genetic correlations estimated in UKB by LD score regression and their corresponding  $p$ -values. 5 reproductive traits and 4 risk traits are shown. The sign of age at first sex has been reversed so that larger trait values are associated with higher reproductive output. Positive correlations are shown in blue, with darker shades signifying Bonferroni-corrected significance. Unsurprisingly, positive genetic correlations are found within the groups of risk and reproductive success but, perhaps more unexpectedly, the genetic correlations between risk and reproductive traits are also most often positive. This is particularly true for smoking and self-declared risk taking.

		Ever had children	Number of children	<i>Earlier</i> age at first sex	Number of sexual partners	Alcohol units	Ever smoked	Driving speed
Number of children	Rg	0.93						
	$p$	0						
<i>Earlier</i> age at first sex	Rg	0.57	0.53					
	$p$	3E-175	2E-200					
Number of sexual partners	Rg	0.08	0.10	0.52				
	$p$	1E-02	1E-03	2E-168				
Alcohol units	Rg	0.15	0.11	0.14	0.37			
	$p$	5E-02	1E-01	1E-02	7E-07			
Ever smoked	Rg	0.27	0.28	0.60	0.49	0.37		
	$p$	4E-26	2E-30	0	1E-119	3E-08		
Driving speed	Rg	0.00	0.03	0.01	0.29	0.2192	0.14	
	$p$	1	0.40	0.80	8E-24	2E-03	3E-07	
Self-declared risk taking	Rg	0.23	0.27	0.42	0.57	0.28	0.33	0.39
	$p$	5E-11	2E-16	9E-77	2E-137	3E-04	5E-46	3E-41

**Supplementary Table 2: Number of SNPs extracted from UKB imputation by allele frequency.** The excess homozygosity of SNPs at seven allele frequencies ( $F_{\text{MAF}}$ ) was calculated for 402,559 genetically British samples in the phase 2 UKB imputation. The number of SNPs used at each frequency is shown.

MAF	Number of SNPs used in calculation of $F_{\text{MAF}}$
0.01	84835
0.025	122498
0.05	198310
0.1	261504
0.2	369777
0.4	253826
0.5	301191

### SUPPLEMENTARY NOTE 1: Trait descriptions

45 quantitative traits were initially chosen for analysis in a potentially wide range of cohorts from the ROHgen consortium. During the initial meta-analysis of these traits, the full release of >500,000 samples from UK Biobank (UKB) became available and, it was decided to include a further 55 less-commonly measured traits available in UKB. Of these new traits, 21 were binary, requiring an extension to the existing analysis plan. 7 of the UKB traits were also measured in some ROHgen cohorts and were thus analysed in a subset of ROHgen cohorts willing to rerun the new analysis plan. In summary, a total of 100 complex traits were analysed; 45 in a potentially wide range of ROHgen cohorts, 7 in a subset of ROHgen cohorts and 48 in UKB only. All are defined below, under headings in the format **short name – full name – units**.

**afb - Age at first birth – years.** Age of subject (either male or female) when their first child was born. Nulliparous samples and reported ages less than 12 or greater than 80 were excluded.

**afb\_men - Age at first birth (men) – years.** Men only. Unlike most other traits, age at first birth was treated as a separate trait for men and women, and the full set of analyses was therefore performed on both sexes separately. Age at first birth (men) is the age of a male subject when their first child was born. Nulliparous samples and reported ages less than 12 or greater than 80 were excluded.

**afb\_women - Age at first birth (women) – years.** Women only. Unlike most other traits, age at first birth was treated as a separate trait for men and women, and the full set of analyses was therefore performed on both sexes separately. Age at first birth (women) is the age of a female subject when their first child was born. Nulliparous samples and reported ages less than 12 or greater than 60 were excluded.

**age\_menarche - Age at menarche – years.** Women only. Reported age at menarche. Women with age at menarche less than 5 or greater than 25 were excluded.

**age\_menopause - age at menopause (years).** Women only. Age at natural menopause. Women whose menopause was due to surgical operations (hysterectomy/ovariectomy), cancer treatment

(radiation, chemotherapy) or on HRT before menopause were excluded. Responses below 35 or greater than 70 were also excluded.

**birth\_weight – Birth weight – kg.** Individual's own weight at birth. Participants who were known to be part of a multiple birth (twins, triplets, etc.) were set to NA. Values less than 0.5 kg or greater than 7 kg were excluded.

**bmi – Body mass index –  $\text{kgm}^{-2}$ .** Weight in kilograms divided by height in metres squared. Values less than 10 or greater than 150 were excluded.

**dp\_dia – Diastolic blood pressure – mmHg.** Averaged readings taken during a single session. Guidance was to take the unweighted mean of second and third readings although cohorts were given discretion to use best judgement where appropriate. Participants known to be on hypertension medication had 10mmHg added to their readings. Values less than 20 or greater than 200 were excluded.

**bp\_sys – Systolic blood pressure – mmHg.** Averaged readings taken during a single session. Guidance was to take the unweighted mean of second and third readings although cohorts were given discretion to use best judgement where appropriate. Participants known to be on hypertension medication had 15mmHg added to their readings. Values less than 50 or greater than 300 were excluded.

**edu – Education Attained – years.** Based on SSGAC, Education Attained was defined in accordance with the ISCED 1997 classification(UNESCO), relating to seven categories of educational attainment that are internationally comparable. Subjects age <30 were excluded as were values  $\notin \{1,7,10,13,15,19,22\}$ .

Definition	US years of schooling
Pre-primary education	1
Primary education or first stage of basic education	7
Lower secondary or second stage of basic education	10
(Upper) secondary education	13
Post-secondary non-tertiary education	15
First stage of tertiary education (not leading directly to an advanced research qualification)	19
Second stage of tertiary education (leading directly to an advanced research qualification e.g. PhD)	22

**fev1 – Forced expiratory volume in 1 second – Litres.** Where multiple blows were available the maximum valid reading was used. Values less than 0 or greater than 10 were excluded.

**fev1perfv – Forced expiratory volume in 1 second / forced vital capacity – no units.** Values less than 0 or greater than 15 were excluded.

**fpg – Fasting plasma glucose –  $\text{mmolL}^{-1}$ .** Known diabetic subjects were excluded, as were subjects with  $\text{fpg} > 7$  or  $\text{hba1c} > 6.5$ . Measurements made in whole blood (not plasma) were multiplied by 1.13 to estimate fpg.

**g – Cognitive g – z-score.** The first unrotated principal component of three or more tests of different domains of cognition. Care was taken to ensure this was in the direction of larger values being associated with greater cognition. Specifically, the sign of the correlation between Cognitive g and

Education attained was ensured to be positive in all cohorts. This trait was rank-normalised and values less than -10 or greater than 8 were excluded.

**hb – Haemoglobin –  $\text{gL}^{-1}$ .** Concentration of haemoglobin. Values less than 0 or greater than 500 were set to NA.

**hba1c – Glycosylated haemoglobin – % of hb (DCCT)<sup>2</sup>.** Set to NA for known diabetics and all subjects for whom  $\text{HbA1c} > 6.5$  or  $\text{fpg} > 7$ . Also, set to NA for subjects with known major blood abnormalities (thalassaemia, sickle cell anaemia, etc.), subjects who have had a blood transfusion in the previous 3 months.

**hdl – High-density lipoprotein cholesterol –  $\text{mmolL}^{-1}$ .** Taken only from fasted or semi-fasted subjects. If semi-fasted a covariate specifying fasting time was required. Values greater than 5.17 were set to NA.

**height – Height – meters.** Standing height in meters. Values less than 1.2 or greater than 2.5 were set to NA.

**hr – Heart rate – beats per minute.** Participants on cardiac medications (Beta blockers, antiarrhythmics) were excluded as were those with previous myocardial infarction or heart failure. Values less than 20 or greater than 150 were set to NA.

**ldl – Low-density lipoprotein cholesterol –  $\text{mmolL}^{-1}$ .** Taken only from fasted or semi-fasted subjects. If semi-fasted a covariate specifying fasting time was required. If HDL cholesterol, total cholesterol and Triglycerides were all provided, LDL cholesterol was calculated using Friedewald's equation. Alternatively, LDL cholesterol could be supplied if directly measured. Samples known to be on lipid lowering medication were adjusted by dividing by a factor of 0.7. Values less than 0 or greater than 10.34 were set to NA.

**log.egfr – Estimated glomerular filtration rate –  $\text{mLmin}^{-1}1.73\text{m}^{-2}$ .** Glomerular filtration rate was estimated from measured creatinine (in  $\text{mgdL}^{-1}$ ) using the formula  $186 * \text{creatinine}^{-1.154} * \text{age}^{-0.203}$ . In cohorts with African or African-American ancestry these values were multiplied by a correction factor of 1.21. Values of creatinine greater than 20 or eGFR greater than 200 were set to NA.

**log.fast\_ins – Fasting insulin –  $\text{pmolL}^{-1}$ .** Known diabetic samples, as well as samples with  $\text{fpg} > 7$  or  $\text{HbA1c} < 6.5$  were excluded. Values of fasting insulin greater than 1000 were set to NA.

**log.fibrinogen – Fibrinogen –  $\text{gL}^{-1}$ .** Plasma fibrinogen levels. Values greater than 20 were set to NA.

**log.hscrp – high sensitivity C-reactive protein –  $\text{nmolL}^{-1}$ .** Serum levels of C-reactive protein (CRP) detected with high sensitivity systems (lower detection limit around  $1 \text{ nmolL}^{-1}$ ). Samples known to be on anti-inflammatory drugs (ATC codes L01, L03, L04, L02A, L02B) were set to NA, as were values greater than  $952 \text{ nmolL}^{-1}$ .

**log.il6 – Interleukin-6 –  $\text{pgmL}^{-1}$ .** Serum levels of Interleukin-6. Samples known to be on anti-inflammatory drugs (ATC codes L01, L03, L04, L02A, L02B) were set to NA, as were values greater than  $100 \text{ pgmL}^{-1}$ .

**log.lymphoc – Lymphocytes – %.** Percentage of lymphocytes per white blood cell count. Values greater than 100 were set to NA.

**log.mpv – Mean platelet volume – fL.** Mean platelet volume in femtolitres. Values greater than 30 were set to NA.

**log.tnfa – Tumour necrosis factor alpha – pgmL<sup>-1</sup>.** Samples known to be on anti-inflammatory drugs (ATC codes L01, L03, L04, L02A, L02B) were set to NA, as were values greater than 100 pgmL<sup>-1</sup>.

**log.triglyc – Triglycerides – mmolL<sup>-1</sup>.** Taken only from fasted or semi-fasted subjects. If semi-fasted a covariate specifying fasting time was required. Values of Triglycerides greater than 33.9 mmolL<sup>-1</sup> were set to NA.

**log.wbc – White blood cell count – 10<sup>9</sup> per Litre.** Values greater than 30 x 10<sup>9</sup> per Litre were excluded.

**log10.alt – Alanine transaminase – IU per Litre.** Plasma concentrations of Alanine transaminase (also called Glutamic-pyruvate transaminase). Values greater than 500 IU per Litre were set to NA.

**log10.ggt – Gamma-Glutamyl Transferase – IU per Litre.** Plasma concentrations of Gamma-Glutamyl Transferase. Values greater than 1000 IU per Litre were set to NA.

**monoc – Monocytes - %.** Percentage of monocytes in white blood cell count. Values greater than 40 were set to NA.

**neb – Number ever born – count.** Number of children the subject has brought into being. Subjects aged less than 45 were excluded from this analysis.

**neb\_men – Number ever born (men) – count.** Men only. Unlike most other traits, number ever born was treated as a separate trait for men and women, and the full set of analyses was therefore performed on both sexes separately. Number ever born (men) is the number of children fathered by a male subject. Subjects aged less than 45 were excluded from this analysis.

**neb\_women – Number ever born (women) – count.** Women only. Unlike most other traits, number ever born was treated as a separate trait for men and women, and the full set of analyses was therefore performed on both sexes separately. Number ever born (women) is the number of children given birth to by a female subject. Subjects aged less than 45 were excluded from this analysis.

**plt – Platelet count - 10<sup>9</sup> per Litre.** Platelet count in whole blood. Values less than 20 or greater than 1000 were set to NA.

**pr – PR interval – ms.** Electrocardiographic PR interval. Participants on cardiac medications (Beta blockers, antiarrhythmics) were exclude as were those with previous myocardial infarction or heart failure. Values less than 80 or greater than 320 were set to NA.

**qrs – QRS duration – ms.** Electrocardiographic QRS duration. Participants on cardiac medications (Beta blockers, antiarrhythmics) were exclude as were those with previous myocardial infarction or heart failure. Values less than 30 or greater than 120 were set to NA.

**qt – QT interval – ms.** Electrocardiographic QT interval. Participants on cardiac medications (Beta blockers, antiarrhythmics) were exclude as were those with previous myocardial infarction or heart failure. Values less than 200 or greater than 700 were set to NA.

**ser – Spherical equivalent refraction – no units.** The mean of left and right eyes calculated from spherical and cylindrical power of each eye by the standard formula  $ser = sphere + 0.5 * cylinder$ . Samples known to have had eye surgery were set to NA, as were values less than -15 or greater than +15.

**tot\_chol – Total cholesterol – mmolL<sup>-1</sup>.** Taken only from fasted or semi-fasted subjects. If semi-fasted a covariate specifying fasting time was required. Samples known to be on lipid lowering medication were adjusted by dividing by a factor of 0.8. Values greater than 16.8 molL<sup>-1</sup> were set to NA.

**uric – Uric acid – umolL<sup>-1</sup>.** Serum urate concentration. Values greater than 1190 umolL<sup>-1</sup> were set to NA.

**weight – Weight – kg.** Weight in kilograms. Values less than 20 kg or greater than 250 kg were set to NA.

**whr – Waist : Hip ratio – no units.** Calculated when both waist and hip circumference were available in centimetres. Values of waist or hip circumference less than 20 or greater than 300 were set to NA, as were values of waist : hip ratio less than 0.3 or greater than 2.

**alcohol\_units - Alcohol units per week – UK units per week.** Self-declared alcohol consumption in UK units (10 ml of ethanol) per week. Where necessary this was estimated from alcohol intake frequency and average drink sizes. Values were capped to 100 units per week.

**ever\_married\_glm – Ever married – TRUE/FALSE.** Subjects who were known to be (or have been) married or in a long-term cohabiting relationship were encoded as 1 while all others were encoded as 0.

**ever\_smoked\_glm – Ever smoked – TRUE/FALSE.** Subjects who reported either being current smokers or having previously smoked on all or most days were encoded as 1, while those who had never or only occasionally smoked were encoded as 0.

**neb\_parious – Number ever born (parous) – count.** In samples with one or more children, number ever born (parous) is equal to number of children ever born (neb). All other samples are set to NA.

**parous\_glm – Ever had children – TRUE/FALSE.** For all samples with a non-missing value of number ever born (neb) a trait was defined with value 1 for samples with neb>0 and value 0 for samples with neb=0.

**parous\_married\_glm – Ever had children (married) – TRUE/FALSE.** Ever had children defined only for samples for whom ever married = 1. Set to NA for all samples where ever married is 0 or NA.

**parous\_unmarried\_glm – Ever had children (unmarried) – TRUE/FALSE.** Ever had children defined only for samples for whom ever married = 0. Set to NA for all samples where ever married is 1 or NA.

**age\_at\_first\_sex – Age at first sex – years.** Response to the question *What was your age when you first had sexual intercourse?* Participants who declined to answer, or who gave an answer less than 3 were excluded. Participants who answered *Never had sex* were set to their current age. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=2139>.

**age\_facial\_hair – Relative age of facial hair – index.** Men only. Response to the question *When did you start to grow facial hair?* Participants were given five options: *Younger than average*, *About average age*, *Older than average*, *Do not know* and *Prefer not to answer* which were encoded -1, 0, 1, NA and NA respectively. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=2375>.

**age\_voice\_broke – Relative age voice broke – index.** Men only. Response to the question *When did your voice break?* Participants were given five options: *Younger than average*, *About average age*,



*Older than average, Do not know* and *Prefer not to answer* which were encoded -1, 0, 1, NA and NA respectively. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=2385>.

**alb – Age at last birth – years.** Women only. Response to the question *How old were you when you had your LAST child?* Responses less than 8 or greater than 65 were excluded. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=2764>.

**ankle\_width – Mean ankle width – mm.** Average of left and right ankle width as measured by the spacing between measurement transducer pads on each heel. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=4100>.

**any\_pain\_glm – Any reported pain – TRUE/FALSE.** Participants were asked the question *In the last month have you experienced any of the following that interfered with your usual activities? (You can select more than one answer)* and given ten options: *Headache, Facial pain, Neck or shoulder pain, Back pain, Stomach or abdominal pain, Hip pain, Knee pain, Pain all over the body, None of the above* and *Prefer not to answer*. Participants who selected any of the first eight options were coded as 1, those who selected only *None of the above* were coded as 0 and the remainder were treated as NA. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=6159>.

**any\_same\_sex\_glm – Any same-sex partners – TRUE/FALSE.** Participants were asked the question *Have you ever had sexual intercourse with someone of the same sex?* and given the options *Yes, No* and *Prefer not to answer* which were encoded 1, 0 and NA respectively. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/coding.cgi?id=100352>.

**back\_pain\_glm – Backpain – TRUE/FALSE.** Participants were asked the question *In the last month have you experienced any of the following that interfered with your usual activities? (You can select more than one answer)* and given ten options: *Headache, Facial pain, Neck or shoulder pain, Back pain, Stomach or abdominal pain, Hip pain, Knee pain, Pain all over the body, None of the above* and *Prefer not to answer*. Participants who selected *Back pain* were coded as 1, those who selected only *Prefer not to answer* were coded as NA and the remainder set to 0. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=6159>.

**baldness – Baldness pattern – index.** Men only. Male participants were asked the question *Which of the following best describes your hair/balding pattern?* and shown four images of increasing hair loss (patterns 1 to 4). Responses were coded 1 to 4, where 4 represents most hair loss. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=2395>.

**body\_pain\_glm – Whole body pain – TRUE/FALSE.** Participants were asked the question *In the last month have you experienced any of the following that interfered with your usual activities? (You can select more than one answer)* and given ten options: *Headache, Facial pain, Neck or shoulder pain, Back pain, Stomach or abdominal pain, Hip pain, Knee pain, Pain all over the body, None of the above* and *Prefer not to answer*. Participants who selected *Pain all over the body* were coded as 1, those who selected only *Prefer not to answer* were coded as NA and the remainder set to 0. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=6159>.

**broken\_bones\_glm – Broken bones – TRUE/FALSE.** Participants were asked the question *Have you fractured/broken any bones in the last 5 years?* and given the options *Yes, No, Do not know* and *Prefer not to answer* which were encoded 1, 0, NA and NA respectively. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=2463>.

**cancer\_diagnosis\_glm – Cancer diagnosis – TRUE/FALSE.** Participants were asked the question *Has a doctor ever told you that you have had cancer?* and given the options *Yes, No, Do not know* and

*Prefer not to answer* which were encoded 1, 0, NA and NA respectively. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=2453>.

**dead\_glm – Dead – TRUE/FALSE.** Death records in UKB are periodically updated by linkage to national death registries. At data download on 13/12/2017, 13739 participants had record dates of death and were thus encoded at 1. Those without a death register entry were encoded as 0. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=40000>.

**depression\_glm – Self-reported mood disorder – TRUE/FALSE.** Participants were asked the question *Have you ever seen a general practitioner (GP) for nerves, anxiety, tension or depression?* and given the options *Yes, No, Do not know* and *Prefer not to answer* which were encoded 1, 0, NA and NA respectively. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=2090>.

**diabetes\_diagnosis\_glm – Diabetes diagnosis – TRUE/FALSE.** Participants were asked the question *Has a doctor ever told you that you have diabetes?* and given the options *Yes, No, Do not know* and *Prefer not to answer* which were encoded 1, 0, NA and NA respectively. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=2443>.

**facial\_ageing – Facial ageing – index.** Participants were asked the question *Do people say that you look:* and given the options *Younger than you are, Older than you are, About your age, Do not know* and *Prefer not to answer* which were encoded -1, 1, 0, NA and NA respectively. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=1757>.

**family\_satisfaction – Family satisfaction – index.** Participants were asked the question *In general how satisfied are you with your family relationships?* and given the options *Extremely happy, Very happy, Moderately happy, Moderately unhappy, Very unhappy, Extremely unhappy, Do not know* and *Prefer not to answer* which were encoded 6, 5, 4, 3, 2, 1, NA and NA respectively. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=4559>.

**fat\_pc – Body fat percentage – %.** Body composition estimated by impedance measurement. Values less than 1% or greater than 75% were excluded. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=23099>.

**financial\_satisfaction – Financial satisfaction – index.** Participants were asked the question *In general how satisfied are you with your financial situation?* and given the options *Extremely happy, Very happy, Moderately happy, Moderately unhappy, Very unhappy, Extremely unhappy, Do not know* and *Prefer not to answer* which were encoded 6, 5, 4, 3, 2, 1, NA and NA respectively. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=4581>.

**grip\_strength – Grip strength – kg.** Average of left and right hand grip strength as measured by a hydraulic hand dynamometer. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=46>.

**handedness – Left-handed – index.** Participants were asked the question *Are you right or left handed?* and given the options *Right-handed, Left-handed, Use both right and left hands equally* and *Prefer not to answer* which were encoded -1, 1, 0 and NA respectively. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=1707>.

**happiness – Self-reported happiness – index.** Participants were asked the question *In general how happy are you?* and given the options *Extremely happy, Very happy, Moderately happy, Moderately unhappy, Very unhappy, Extremely unhappy, Do not know* and *Prefer not to answer* which were

encoded 6, 5, 4, 3, 2, 1, NA and NA respectively. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20458>.

**headache – Headaches – TRUE/FALSE.** Participants were asked the question *In the last month have you experienced any of the following that interfered with your usual activities? (You can select more than one answer)* and given ten options: *Headache, Facial pain, Neck or shoulder pain, Back pain, Stomach or abdominal pain, Hip pain, Knee pain, Pain all over the body, None of the above and Prefer not to answer*. Participants who selected *Headache* were coded as 1, those who selected only *Prefer not to answer* were coded as NA and the remainder set to 0. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=6159>.

**health\_satisfaction – Health satisfaction – index.** Participants were asked the question *In general how satisfied are you with your health?* and given the options *Extremely happy, Very happy, Moderately happy, Moderately unhappy, Very unhappy, Extremely unhappy, Do not know and Prefer not to answer* which were encoded 6, 5, 4, 3, 2, 1, NA and NA respectively. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=4548>.

**hearing\_acuity – Hearing acuity – no units.** Mean of left and right ear Speech Reception Threshold (SRT), defined here as the signal-to-noise ratio at which half of the presented speech can be understood correctly. This value was multiplied by -1 so that larger values correspond to better hearing. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20019>.

**heelbone\_density – Heelbone density – Z-score.** Mean of left and right heelbone density T-score calculated from an ultrasound heel Bone Mineral Density measurement and normalised within each sex. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=4106>.

**infertility\_self\_declared\_glm – Self-reported infertility – TRUE/FALSE.** UKB participants were asked in a verbal interview with a trained nurse to describe any serious illness or disabilities. Responses were classified in a tree-structured list used by clinic nurses to code non-cancer illnesses. The values 1403 and 1404 correspond to female and male infertility respectively and participants with these either of these responses were encoded 1. All other participants who completed the verbal interview were encoded 0. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20002>.

**irritability\_glm – Self-reported irritability – TRUE/FALSE.** Participants were asked the question *Are you an irritable person?* and given the options *Yes, No, Do not know and Prefer not to answer* which were encoded 1, 0, NA and NA respectively. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=1940>.

**job\_satisfaction – Job satisfaction – index.** Participants were asked the question *In general how satisfied are you with the work that you do?* and given the options *Extremely happy, Very happy, Moderately happy, Moderately unhappy, Very unhappy, Extremely unhappy, Do not know and Prefer not to answer* which were encoded 6, 5, 4, 3, 2, 1, NA and NA respectively. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=4537>.

**match\_time – Reaction time – ms.** Participants were shown two cards at a time on a touchscreen and instructed to press a button as quickly as possible when the symbols on the cards match. This field is the mean duration to first press of snap-button summed over rounds in which both cards matched. It gives a crude measure of the raw processing + reaction speed of a participant. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20023>.

**memory – Memory – count.** The participant was shown a 2-digit number to remember. The number then disappeared and after a short while they were asked to enter the number onto the screen. The number became one digit longer each time they remembered correctly (up to a maximum of 12 digits). This trait is the longest number correctly recalled during the numeric memory test. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=4282>.

**miscarriage – Miscarriage – TRUE/FALSE.** Women only. Female participants were asked the question *Have you ever had any stillbirths, spontaneous miscarriages or terminations?* and given the options *Yes, No, Do not know* and *Prefer not to answer* which were encoded 1, 0, NA and NA respectively. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=2774>.

**moderate\_activity – Frequency of moderate activity – count.** Participants were asked the question *In a typical week, on how many days did you do 10 minutes or more of moderate physical activities like carrying light loads, cycling at normal pace? (Do not include walking).* Values less than 0 or greater than 7 were rejected. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=884>.

**moody\_glm – Moody – TRUE/FALSE.** Participants were asked the question *Does your mood often go up and down?* and given the options *Yes, No, Do not know* and *Prefer not to answer* which were encoded 1, 0, NA and NA respectively. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=1920>.

**motorway\_speeding – Driving speed – index.** Participants were asked the question *How often do you drive faster than the speed limit on the motorway?* and given the options *Never/rarely, Sometimes, Often, Most of the time, Do not drive on the motorway, Do not know* and *Prefer not to answer* which were encoded 0, 1, 2, 3, NA, NA and NA respectively. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=1100>.

**neuroticism – Neuroticism – index.** An externally derived summary score of neuroticism, based on 12 neurotic behaviour domains reported in UKB. Values range from 0 to 12 with higher scores corresponding to increased neurotic behaviour. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20127>.

**number\_sexual\_partners – Number sexual partners – count.** Participants were asked the question *About how many sexual partners have you had in your lifetime?* Subjects who answered *Do not know* or *Prefer not to answer* were set to NA, otherwise values were capped at 100. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=2149>.

**overall\_health – Self-reported overall health – index.** Participants were asked the question *In general how would you rate your overall health?* and given the options *Excellent, Good, Fair, Poor, Do not know* and *Prefer not to answer* which were encoded 3, 2, 1, 0, NA and NA respectively. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=2178>.

**pacemaker\_glm – Pacemaker – TRUE/FALSE.** Participants were asked by an interviewer if they have a pace-maker before the body impedance measures. Those that answered *Yes* were encoded 1, otherwise 0. <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=3079>.

**pgrs\_edu – Polygenic score for Education Attained – years.** A polygenic score for Education Attained (EA) calculated from 159 genome-wide significant SNPs reported in a GWAS of Education Attained [Okbay et al. 2016] and imputed in UKB using the UK10K + 1000 Genomes panel. This polygenic score explains 0.9% of the residual variance of EA in the UKB British cohort after conditioning on sex and age.

**pgrs\_height – Polygenic score for Height – metres.** A polygenic score for height calculated from 697 genome-wide significant SNPs reported in a GWAS of height [Wood et al. 2014] and imputed in UKB using the UK10K + 1000 Genomes panel. This polygenic score explains 18.7% of the residual variance of height in the UKB British cohort after conditioning on sex and age.

**potassium – Urinary Potassium – mM<sup>L</sup><sup>-1</sup>.** Potassium in urine measured by ISE (ion selective electrode) analysis on a Beckman Coulter AU5400. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=30520>.

**risk\_glm – Self-reported risk taker – TRUE/FALSE.** Participants were asked the question *Would you describe yourself as someone who takes risks?* and given the options *Yes, No, Do not know* and *Prefer not to answer* which were encoded 1, 0, NA and NA respectively. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=2040>.

**sleep\_duration – Sleep duration – hours.** Participants were asked the question *About how many hours sleep do you get in every 24 hours? (please include naps).* Subjects who answered *Do not know* or *Prefer not to answer* were set to NA, as were values less than 1 or greater than 23. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=1160>.

**sodium – Urinary Sodium – mM<sup>L</sup><sup>-1</sup>.** Sodium in urine measured by ISE (ion selective electrode) analysis on a Beckman Coulter AU5400. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=30530>.

**vigorous\_activity – Frequency of vigorous activity – count.** Participants were asked the question *In a typical week, how many days did you do 10 minutes or more of vigorous physical activity? (These are activities that make you sweat or breathe hard such as fast cycling, aerobics, heavy lifting).* Values less than 0 or greater than 7 were rejected. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=904>.

**visual\_acuity – Visual acuity – negative log(MAR).** Mean of left and right visual acuity as defined by the smallest size letters that can be reliably identified at a 4 metres. The UK Biobank system is based on a traditional LogMar chart. This log(MAR) value was multiplied by -1 so that larger values correspond to better vision. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=5201>.

**walking\_pace – Walking pace – index.** Participants were asked the question *How would you describe your usual walking pace?* and given the options *Slow pace, Steady average pace, Brisk pace, None of the above* and *Prefer not to answer* which were encoded 0, 1, 2, NA and NA respectively. For more details see <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=924>.

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#### SUPPLEMENTARY NOTE 4: Comparison of inbreeding coefficient estimates

**Introduction.** Accurate estimation of the Inbreeding Depression ( $\beta_F$ ) requires precise and unbiased estimates of individual inbreeding coefficients ( $F$ ). Numerous methods have been proposed for estimating inbreeding coefficients from dense SNP marker data. Broadly, these can be grouped into two categories: methods that consider the excess homozygosity at a large number of, preferably independent, markers (e.g.  $F_{\text{HOM}}$ ,  $F_{\text{UNI}}$ ) and methods that identify autozygous genomic segments from unbroken tracts of homozygous genotypes, which are unlikely to occur by chance (e.g.  $F_{\text{ROH}}$ ).

To maximize statistical power and minimize bias in  $\hat{\beta}_F$ , an estimator of  $F$  should be both unbiased, ( $E[\hat{F}] = F$ ) and precise,  $MSE(\hat{F} - F) \ll \text{var}(F)$ . Extensive comparisons of different estimators have been made by previous studies. Many of these conclude that  $F_{\text{ROH}}$  calculated from appropriately parameterized ROH calling gives estimates of  $F$  with minimal bias and lower variance than independent SNP methods<sup>1-4</sup>. In contrast, Yengo et al. (PNAS 2017) claim that  $\hat{\beta}_{F_{\text{ROH}}}$  may be upwardly biased by as much as 162%, and provide apparent evidence of this in both simulated and real data<sup>5</sup>. Furthermore, Yengo et al. show, in both theory and simulation, that two independent SNP methods ( $F_{\text{UNI}}$  and  $F_{\text{HOM}}$ ) give unbiased estimates of  $\beta_F$  when causal SNPs are a random subset of all genotyped SNPs. This would cast doubt on the validity of using  $F_{\text{ROH}}$  to estimate  $\beta_F$ , and suggests  $F_{\text{UNI}}$  might be a more appropriate measure. To understand the apparent contradictions between different studies, we have repeated and extended the investigations described in Yengo et al.

Yengo et al. base their study on genotype data derived from the first phase of the UK Biobank (UKB) imputation. 9,493,148 SNPs with a minor allele frequency (MAF) of >1%, INFO score of > 0.3 and

HWE p-value > 1e-06 were selected from the imputation of 140,720 British individuals. SNP dosages were rounded to the nearest whole genotype and LD pruning  $r^2 > 0.9$  was performed to reduce the number of SNPs to 3,857,369.  $F_{\text{UNI}}$  was calculated by the formula presented by Yang et al. (2011)<sup>6</sup> as  $\hat{F}^{\text{III}}$  (implemented in PLINK<sup>7</sup> by parameters --ibc Fhat3) and ROH were called by two PLINK parameterizations, including the values proposed in Joshi et al. (2015)<sup>8</sup>. Joshi et al. validated the PLINK parameters for moderately dense SNP chips, but not for the different characteristics (SNP density, error rate) of genotypes called from imputed dosages. In particular, the PLINK method allows only one heterozygote or 5 missing genotypes within each ROH.

**$F_{\text{ROH}}$  calculated from SNP chip genotypes agrees well with  $F_{\text{UNI}}$  indicating minimal bias.**

We followed the method described in Yengo et al. to calculate both  $F_{\text{UNI}}$  and  $F_{\text{ROH}}$  from the UKB imputation, but initially compared Yengo's  $F_{\text{UNI}}$  to our  $F_{\text{ROH}}$  calculated from SNP chip data available for the same phase one individuals. From now on, we use lowercase roh to refer to measures based on imputed data and uppercase ROH to refer to those from SNP-chip genotypes. We find good correspondence between  $F_{\text{UNI}}$  and  $F_{\text{ROH}}$  (Supplementary Fig. 12). Since  $F_{\text{UNI}}$  is believed to be an unbiased estimator of  $F$ , the correspondence between  $F_{\text{UNI}}$  and  $F_{\text{ROH}}$  places limits on the possible bias of  $F_{\text{ROH}}$ . Specifically, if we model  $F_{\text{ROH}}$  as  $F_i^{\text{ROH}} = \theta F_i + \epsilon_i$ , then

$$\frac{r^2}{\beta_{F_{\text{UNI}}, F_{\text{ROH}}}} \leq \theta \leq \frac{1}{\beta_{F_{\text{UNI}}, F_{\text{ROH}}}} \quad (19)$$

(see Supplementary note 6). Substituting the regression values from Supplementary Fig. 12 gives  $0.94 \leq \theta \leq 0.95$ . I.e. the good correspondence between  $F_{\text{UNI}}$  and  $F_{\text{ROH}}$  limits the potential error in  $F_{\text{ROH}}$  to a small downward bias. This very small underestimate of  $F$  may be caused by autozygosity not captured in  $F_{\text{ROH}}$ , namely ROH of less than 1.5 Mb length or ROH in sparsely genotyped regions.

**Calculating  $F_{\text{roh}}$  from imputed genotypes can introduce large downward bias.** To call ROH from the UKB imputation we followed the method described by Yengo et al., but identified only 9,067,605 SNPs (out of a total of 72,355,667) matching their inclusion criteria (MAF > 1%, INFO > 0.3, HWE exact p-value > 1e-6). We then used PLINK 2.0 to convert the imputed genotype probabilities to the hard-called genotypes required for LD pruning and ROH calling. PLINK first converts genotype probabilities to an estimated dosage which is then rounded to the nearest genotype  $\in [0 \ 1 \ 2]$ . By default, a genotype is recorded if the estimated dosage is within 0.15 of any of  $[0 \ 1 \ 2]$ , otherwise the genotype is recorded as missing. Using these default parameters introduces 3.9% missingness into our dataset. We nevertheless proceeded to LD-prune this dataset, both with these missing data (method 2), and having removed all SNPs with a missing fraction > 0.03 (method 1). However, Yengo et al. state that *Imputed SNPs were called to the genotypes having the largest posterior probability* which is achieved by changing the PLINK hardcall parameter from 0.15 to 0.499999 (method Yengo). After LD pruning 3,061,484 SNPs remain for 141,774 British individuals.

For all three methods of data preparation, we called ROH and calculated  $F_{\text{roh}}$  using the Joshi et al. PLINK parameters also used by Yengo et al. We find that calling ROH from hard-called imputed dosages (method Yengo) gives  $F_{\text{roh}}$  with an expected value of just 0.39 of the  $F_{\text{ROH}}$  obtained from SNP chip genotypes (Supplementary Figure 13). More stringent treatments of uncertain genotype probabilities (methods 2 and 1) give progressively less downwards bias. To understand the cause of this downward bias in  $F_{\text{roh}}$  we plotted the genome wide distribution of ROH for two high  $F$  individuals, highlighted in orange in Supplementary Figure 13.

For these two individuals all ROH called from SNP chip genotypes (in blue) and the Yengo et al. imputed data method (in red) are shown in Supplementary Figs 14a,b. Individual 1 has an  $F_{\text{ROH}} =$

0.261, amongst the highest observed in UKB, and is most likely the progeny of 1<sup>st</sup> degree relatives where  $E[F] = 0.25$ . Individual 2 has  $F_{\text{ROH}} = 0.0626$  and is most likely the offspring of first cousins (3<sup>rd</sup> degree relatives) where  $E[F] = 0.0625$ . Calling ROH from hard-called imputed dosages fragments, and consequently fails to identify, many of the ROH found in SNP chip data. The resultant downward bias in  $F_{\text{roh}}$  is sufficient to explain an upward bias of up to 156% ( $1/0.39$ ) in  $\hat{\beta}_{F_{\text{roh}}}$ .

In summary, calculating  $F_{\text{ROH}}$  from dense SNP chip genotypes, with the parameters used in this study, gives valid estimates of inbreeding coefficients. In contrast, calculating  $F_{\text{roh}}$  from unfiltered imputed genotypes, as done in Yengo et al., introduces a large bias which appears to be responsible for the poor performance of  $F_{\text{roh}}$  in that study.

**$\hat{\beta}_{F_{\text{GRM}}}$  is downwardly biased in real data.** Yengo et al. also show, in both theory and simulation, that  $\hat{\beta}_{F_{\text{UNI}}}$  is an unbiased estimate of  $\beta_F$  in certain conditions, for example, when causal SNPs are a random subset of all observed SNPs. In real UKB data they find that  $\hat{\beta}_{F_{\text{roh}}}$  is systematically of greater magnitude than  $\hat{\beta}_{F_{\text{UNI}}}$ , which they therefore interpret as empirical evidence that  $\hat{\beta}_{F_{\text{ROH}}}$  is upwardly biased. We have already shown that calling ROH from imputed data may cause an upward bias of  $\hat{\beta}_{F_{\text{roh}}}$ , however, interestingly, we also observe that estimates obtained from unbiased SNP-chip genotypes ( $\hat{\beta}_{F_{\text{ROH}}}$ ) are systematically larger than estimates obtained from frequency-based measures ( $\hat{\beta}_{F_{\text{SNP}}}$  and  $\hat{\beta}_{F_{\text{GRM}}}$ ) (Supplementary Data Table 13). Note, we use the nomenclature  $F_{\text{GRM}}$  to refer the  $\hat{F}^{\text{III}}$  calculation used in the ROHgen consortium. Although  $F_{\text{GRM}}$  and  $F_{\text{UNI}}$  are identical calculations (PLINK –ibc Fhat3),  $F_{\text{GRM}}$  is calculated from SNP-chip genotypes with a minimum MAF of 5%, while Yengo et al. calculated  $F_{\text{UNI}}$  from hard called imputed dosages with a minimum MAF of 1%. We explain the differences between  $\hat{\beta}_{F_{\text{ROH}}}$  and  $\hat{\beta}_{F_{\text{GRM}}}$  below.

**Causal variants for Inbreeding Depression are not in strong LD with common SNPs.** For all traits, we fit bivariate models with  $F_{\text{ROH}}$  and  $F_{\text{GRM}}$  as explanatory variables. For all 32 traits that were significant in the univariate analysis, we find that  $\hat{\beta}_{F_{\text{ROH}}|F_{\text{GRM}}}$  is of greater magnitude than  $\hat{\beta}_{F_{\text{GRM}}|F_{\text{ROH}}}$  in the conditional analysis (Supplementary Data Table 22). Furthermore, for 30 of these traits  $\hat{\beta}_{F_{\text{GRM}}|F_{\text{ROH}}}$  does not differ significantly from zero. I.e., for many traits, the variation of  $F_{\text{GRM}}$  which is independent of  $F_{\text{ROH}}$  is not associated with any change in trait values. In Supplementary Note 5 we show that these results are consistent with inbreeding depression caused by rare, but not common, variants. Furthermore, we observe that the downward bias of  $\hat{\beta}_{F_{\text{GRM}}}$  is proportional to the ratio  $\frac{\text{var}(F_{\text{ROH}})}{\text{var}(F_{\text{GRM}})}$  (Fig 4c), as expected when the difference between  $F_{\text{GRM}}$  and  $F_{\text{ROH}}$  can be considered as estimation error (See Supplementary Note 7).

In summary, Yengo et al showed that  $\hat{\beta}_{F_{\text{UNI}}}$  is unbiased when causal variants are a random subset of the observed SNPs. Although we agree with this statement, we find the evidence does not support the assumption of a random sample, but reveals the importance of rare variants, whose excess homozygosity is well predicted by  $F_{\text{ROH}}$  (Supplementary Fig 16a).

**Comparison of genomic measures of inbreeding with genealogy.** As a further assessment of the relative abilities of  $F_{\text{ROH}}$ ,  $F_{\text{SNP}}$  and  $F_{\text{GRM}}$  to capture inbreeding, we analysed Pearson's product-moment correlations between the genomic inbreeding measures and pedigree inbreeding ( $F_{\text{PED}}$ ) for 47,927 Icelanders with mostly-complete (info score > 0.6)<sup>9</sup> 10 generation pedigrees. To decrease the confounding effects of pedigree mis-specification, a small number of individuals (n=20) with extreme discrepancies between genetics and genealogy ( $F_{\text{ROH}} > 0.05$  &  $F_{\text{SNP}} < 0.001$ ) were removed. The

correlation was highest for  $F_{ROH}$  ( $r = 0.779$ ), lowest for  $F_{SNP}$  (0.632) and intermediate for  $F_{GRM}$  (0.682), further validating the utility of  $F_{ROH}$  as the most accurate genomic measure of inbreeding.

#### SUPPLEMENTARY NOTE 5: Interpretation of $Trait \sim F_{ROH} + F_{GRM}$ models.

**Are inbreeding effects caused by rare or common variants?**  $F_{ROH}$  is an estimate of autozygosity, which increases the homozygosity of all variants, both common and rare. In contrast,  $F_{GRM}$  is calculated from common SNPs (>5% MAF) and correlates well with the homozygosity of common SNPs, but less well with rare SNPs which may be in weak Linkage Disequilibrium (LD). We therefore performed bivariate models of all traits in real data ( $Trait \sim F_{ROH} + F_{GRM}$ ) to establish whether the observed inbreeding effects associate more strongly with  $F_{ROH}$  or  $F_{GRM}$ . For all significant traits, we find the observed associations more attributable to  $F_{ROH}$  (Supplementary Data Table 22; Supplementary Figs 15a,b) suggesting inbreeding effects are caused by rare genetic variants. A recent study<sup>10</sup> found evidence for a similar conclusion, but to further support this interpretation we investigate below how both  $F_{ROH}$  and  $F_{GRM}$  predict the excess homozygosity of SNPs at a range of allele frequencies.

**Relationships between  $F_{ROH}$ ,  $F_{GRM}$  and excess homozygosity at different allele frequencies.** For any trait exhibiting inbreeding depression, the degree of depression will be related to the excess homozygosity (above Hardy-Weinberg expectation) of the causal variants. In Supplementary note 8, we show that inbreeding depression, which is equal to the sum of the dominance deviations at the causal loci, is proportional to the inbreeding coefficient ( $F_{QTL}$ ) defined in equation (39) below.

$$ID_i = \sum_{i=1}^m \delta_i = \beta_F * F_{QTL} \quad (38)$$

Where

$$F_{QTL} = \frac{1}{m} \sum_{i=1}^m \frac{w_i(x_i^2 - (1 + 2p_i)x_i + 2p_i^2)}{2p_iq_i} \quad (39)$$

and

$$w_i = \frac{2p_iq_id_i}{\frac{1}{m} \sum_{i=1}^m 2p_iq_id_i} \quad (40)$$

We note that the unweighted form of equation (39) is identical to  $\hat{F}^{III}$  introduced by Yang et al (2011)<sup>6</sup>, and implemented in PLINK by the parameters -ibc Fhat3. This is the same formula used to calculate  $F_{GRM}$  and  $F_{UNI}$  from different sets of marker SNPs. In summary, if the causal loci and effect sizes are known, a weighted calculation of  $\hat{F}^{III}$  at the causal loci is directly proportional to the degree of inbreeding depression. We have used this, below, to simplify the simulation of inbreeding depression caused by variants at specific allele frequencies.

If we imagine inbreeding depression caused exclusively by variants at one allele frequency then, in the absence of strong selection or assortative mating on the causal loci in the current generation, the expectation of  $F_{QTL}$  will be equal to  $\hat{F}^{III}$  calculated at marker variants of the same allele frequency (henceforth called  $F_{MAF}$ ).

To calculate  $F_{MAF}$  across a range of allele frequencies we extracted SNPs at seven frequencies (MAF=0.01, 0.025, 0.05, 0.1, 0.2, 0.4 & 0.5) from 402,559 genetically British samples in the phase 2 UKB imputation. Selected SNPs were required to have a minor allele frequency (AF) within 10% of the specified MAF ( $0.9 \cdot \text{MAF} < \text{AF} < 1.1 \cdot \text{MAF}$ ) and HWE p-value  $> 1e-6$ . The numbers of SNPs retained at each MAF are reported in Supplementary Table 2.  $F_{ROH}$  and  $F_{GRM}$  had previously been calculated, from SNP-chip genotypes, as part of the ROHgen meta-analysis.

To investigate the relationships between  $F_{ROH}$ ,  $F_{GRM}$  and  $F_{MAF}$  we fit univariate ( $F_{MAF} \sim F_{ROH}$  and  $F_{MAF} \sim F_{GRM}$ ) and bivariate models ( $F_{MAF} \sim F_{ROH} + F_{GRM}$ ) at each allele frequency. In the univariate models we find  $F_{ROH}$  to be an unbiased predictor of  $F_{MAF}$  across the entire frequency spectrum, while  $F_{GRM}$  is downwardly biased, particularly at low MAF (Supplementary Fig. 16a). Despite this downward bias,  $F_{GRM}$  is more strongly correlated than  $F_{ROH}$  at all MAF  $> 5\%$  (Supplementary Figure 16b). In the bivariate model  $F_{GRM}$  is a stronger predictor of the homozygosity of common SNPs ( $>10\%$ ), but  $F_{ROH}$  is a stronger predictor for rare SNPs (Fig. 4d).

**Observed associations consistent with the homozygosity of rare, not common, SNPs.** In real data models of  $Trait \sim F_{ROH} + F_{GRM}$ , we consistently find the observed associations are preferentially attributed to  $F_{ROH}$  rather than  $F_{GRM}$  (Supplementary Data Table 22, Figure 4c, Supplementary Figs 15a,b). In light of Figure 4d, these results are compatible with the action of rare, not common, causal variants.

#### SUPPLEMENTARY NOTE 6: Limits of bias in $F_{ROH}$

If  $F_{UNI}$  is an unbiased estimate of  $F$  then it can be expressed as

$$F_{UNI} = F + \varepsilon \quad (20)$$

If  $F_{ROH}$  is a potentially biased estimate of  $F$  then it can be expressed as

$$F_{ROH} = \theta F + \theta \varepsilon' \quad (21)$$

The regression slope ( $\beta$ ) of  $F_{UNI}$  on  $F_{ROH}$  is known, and

$$\beta = \frac{\text{cov}(F_{UNI}, F_{ROH})}{\text{var}(F_{ROH})}$$

Substituting (20) and (21) and assuming independent errors gives

$$\beta = \frac{\theta \text{var}(F)}{\theta^2 \text{var}(F) + \theta^2 \text{var}(\varepsilon')} \quad (22)$$

Rearranging (22) gives

$$\theta = \left( \frac{1}{\beta} \right) \left( 1 + \frac{\text{var}(\varepsilon')}{\text{var}(F)} \right)^{-1} \quad (23)$$

The range of  $\frac{\text{var}(\varepsilon')}{\text{var}(F)}$  is limited by the correlation between  $F_{UNI}$  and  $F_{ROH}$ , and we can put

$\left( 1 + \frac{\text{var}(\varepsilon')}{\text{var}(F)} \right)^{-1}$  in terms  $\frac{\text{var}(\varepsilon)}{\text{var}(\varepsilon')}$  of by considering that



$$\frac{\text{var}(F_{\text{ROH}})}{\text{var}(F_{\text{GRM}})} = \frac{r^2}{\beta^2} \quad (24)$$

Again substituting (20) and (21) in equation (24) gives

$$\frac{\theta^2 \text{var}(F) + \theta^2 \text{var}(\varepsilon')}{\text{var}(F) + \text{var}(\varepsilon)} = \frac{r^2}{\beta^2} \quad (25)$$

Rearranging (25) gives

$$\frac{\text{var}(\varepsilon')}{\text{var}(F)} = \frac{\theta^2 \beta^2 - r^2}{r^2 \frac{\text{var}(\varepsilon)}{\text{var}(\varepsilon')} - \theta^2 \beta^2} \quad (26)$$

Substituting equation (26) into equation (23)

$$\theta^2 = \left(\frac{1}{\beta}\right) \left( \frac{r^2 \frac{\text{var}(\varepsilon)}{\text{var}(\varepsilon')} - \theta^2 \beta^2}{r^2 \left( \frac{\text{var}(\varepsilon)}{\text{var}(\varepsilon')} - 1 \right)} \right) \quad (27)$$

As  $\frac{\text{var}(\varepsilon)}{\text{var}(\varepsilon')} \rightarrow 0$ , i.e. if  $F_{\text{UNI}}$  is precise and estimation errors entirely on  $F_{\text{ROH}}$  then equation (27)  $\rightarrow$

$$\theta = \left(\frac{1}{\beta}\right) \left( \frac{\theta^2 \beta^2}{r^2} \right) \quad (28)$$

$$\theta = \frac{r^2}{\beta} \quad (29)$$

As  $\frac{\text{var}(\varepsilon)}{\text{var}(\varepsilon')} \rightarrow \infty$ , i.e. if  $F_{\text{ROH}}$  is precise and estimation errors entirely on  $F_{\text{UNI}}$  then equation (27)  $\rightarrow$

$$\theta = \frac{1}{\beta} \quad (30)$$

Therefore, from the bounds of  $\frac{\text{var}(\varepsilon)}{\text{var}(\varepsilon')}$  and equations (29) and (30)

$$\frac{r^2}{\beta_{F_{\text{UNI}}, F_{\text{ROH}}}} \leq \theta \leq \frac{1}{\beta_{F_{\text{UNI}}, F_{\text{ROH}}}} \quad (31)$$

#### SUPPLEMENTARY NOTE 7: Expected attenuation bias in $\hat{\beta}_{F_{\text{GRM}}}$

If  $F_{\text{GRM}}$  varies around  $F_{\text{ROH}}$  and the difference ( $\varepsilon$ ) has no effect on the trait ( $y$ ) then

$$F_{\text{GRM}} = F_{\text{ROH}} + \varepsilon \quad (32)$$

And

$$\beta_{F_{\text{GRM}}} = \frac{\text{cov}(F_{\text{GRM}}, y)}{\text{var}(F_{\text{GRM}})} \quad (33)$$

$$\beta_{F_{\text{GRM}}} = \frac{\text{cov}(F_{\text{ROH}} + \varepsilon, y)}{\text{var}(F_{\text{GRM}})} \quad (34)$$

Because  $\varepsilon$  has no effect on the trait ( $y$ )

$$\beta_{F_{GRM}} = \frac{cov(F_{ROH}, y)}{var(F_{GRM})} \quad (35)$$

$$\beta_{F_{GRM}} = \beta_{F_{ROH}} * \frac{var(F_{ROH})}{var(F_{GRM})} \quad (36)$$

$$\frac{\beta_{F_{GRM}}}{\beta_{F_{ROH}}} = \frac{var(F_{ROH})}{var(F_{GRM})} \quad (37)$$

#### SUPPLEMENTARY NOTE 8: Calculation of $F_{QTL}$ at known causal loci.

If  $x_i \in [0, 1, 2]$  is the number of copies of the reference allele at locus  $i$  of  $m$  causal loci, then the number of reference homozygotes at the locus is  $\frac{x_i(x_i-1)}{2}$ , the number of heterozygotes is  $-x_i(x_i - 2)$ , and the number of alternate homozygotes is  $\frac{(x_i-2)(x_i-1)}{2}$ .

If  $p_i$  is the frequency of the reference allele, and  $q_i$  is the frequency of the alternate allele, then the inbreeding depression with complete inbreeding ( $\beta$ ) is

$$\beta = - \sum_{i=1}^m 2p_i q_i d_i \quad (41)$$

Where  $d_i$  is the difference between the heterozygote and mean homozygote value. We wish to define an inbreeding coefficient ( $F_{QTL}$ ) which is directly proportional to realised inbreeding depression (the sum of the dominance deviations). I.e.

$$\beta F_{QTL} = \sum_{i=1}^m \delta_i \quad (42)$$

The dominance deviations ( $\delta_i$ ) for the three genotypes at a locus can be written in terms of  $d_i$ :  $\delta_i \in [-2q_i^2 d_i, 2p_i q_i d_i, -2p_i^2 d_i]$ . Substituting these dominance deviations and the genotype counts into equation (42) gives

$$\beta F_{QTL} = \sum_{i=1}^m -\frac{x_i(x_i-1)}{2} 2q_i^2 d_i - x_i(x_i-2) 2p_i q_i d_i - \frac{(x_i-2)(x_i-1)}{2} 2p_i^2 d_i \quad (43)$$

Rearranging equation (43) gives

$$\beta F_{QTL} = \sum_{i=1}^m -d_i (x_i^2 - (1+2)p_i x_i + 2p_i^2) \quad (44)$$

Substituting for  $\beta$  from equation (41) gives

$$F_{QTL} = \frac{1}{m} \sum_{i=1}^m w_i \frac{x_i^2 - (1+2p_i)x_i + 2p_i^2}{2p_i q_i} \quad (45)$$

Where

$$w_i = \frac{2p_i q_i d_i}{\frac{1}{m} \sum_{i=1}^m 2p_i q_i d_i} \quad (46)$$

## SUPPLEMENTARY REFERENCES

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