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Associations of autozygosity with a broad range of human phenotypes

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In many species, the offspring of related parents suffer reduced reproductive success, a phenomenon known as inbreeding depression. In humans, the importance of this effect has remained unclear, partly because reproduction between close relatives is both rare and frequently associated with confounding social factors. Here, using genomic inbreeding coefficients (F_{ROH}) for >1.4 million individuals, we show that F_{ROH} is significantly associated ($p < 0.0005$) with apparently deleterious changes in 32 out of 100 traits analysed. These changes are associated with runs of homozygosity (ROH), but not with common variant homozygosity, suggesting that genetic variants associated with inbreeding depression are predominantly rare. The effect on fertility is striking: F_{ROH} equivalent to the offspring of first cousins is associated with a 55% decrease [95% CI 44–66%] in the odds of having children. Finally, the effects of F_{ROH} are confirmed within full-sibling pairs, where the variation in F_{ROH} is independent of all environmental confounding.

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Given the pervasive impact of purifying selection on all populations, it is expected that genetic variants with large deleterious effects on evolutionary fitness will be both rare and recessive[1]. However, precisely because they are rare, most of these variants have yet to be identified and their recessive impact on the global burden of disease is poorly understood. This is of particular importance for the nearly one billion people living in populations where consanguineous marriages are common[2], and the burden of genetic disease is thought to be disproportionately due to increased homozygosity of rare, recessive variants[3–5]. Although individual recessive variants are difficult to identify, the net directional effect of all recessive variants on phenotypes can be quantified by studying the effect of inbreeding[6], which gives rise to autozygosity (homozygosity due to inheritance of an allele identical-by-descent).

Levels of autozygosity are low in most of the cohorts with genome-wide data[7,8] and consequently very large samples are required to study the phenotypic impact of inbreeding[9]. Here, we meta-analyse results from 119 independent cohorts to quantify the effect of inbreeding on 45 commonly measured complex traits of biomedical or evolutionary importance, and supplement these with analysis of 55 more rarely measured traits included in UK Biobank[10].

Continuous segments of homozygous alleles, or runs of homozygosity (ROH), arise when identical-by-descent haplotypes are inherited down both sides of a family. The fraction of each autosomal genome in ROH > 1.5 Mb (F_{ROH}) correlates well with pedigree-based estimates of inbreeding[11].We estimate F_{ROH} using standard methods and software[6,12] for a total of 1,401,776 individuals in 234 uniform sub-cohorts. The traits measured in each cohort vary according to original study purpose, but together cover a comprehensive range of human phenotypes (Fig. 1, Supplementary Data 7). The five most frequently contributed traits (height, weight, body mass index, systolic and diastolic blood pressure) are measured in >1,000,000 individuals; a further 16 traits are measured >500,000 times.

We find that F_{ROH} is significantly associated with apparently deleterious changes in 32 out of 100 traits analysed. Increased F_{ROH} is associated with reduced reproductive success (decreased number and likelihood of having children, older age at first sex and first birth, decreased number of sexual partners), as well as reduced risk-taking behaviour (alcohol intake, ever-smoked, self-reported risk taking) and increased disease risk (self-reported overall health and risk factors including grip strength and heart rate). We show that the observed effects are predominantly associated with rare (not common) variants and, for a subset of traits, differ between men and women. Finally, we introduce a within-siblings method, which confirms that social confounding of F_{ROH} is modest for most traits. We therefore conclude that inbreeding depression influences a broad range of human phenotypes through the action of rare, recessive variants.

Results

Cohort characteristics. As expected, cohorts with different demographic histories varied widely in mean F_{ROH}. The within-cohort standard deviation of F_{ROH} is strongly correlated with the mean (Pearson's $r = 0.82$; Supplementary Fig. 3), and the most homozygous cohorts provide up to 100 times greater per-sample statistical power than cosmopolitan European-ancestry cohorts (Supplementary Data 5). To categorise cohorts, we plotted mean F_{ROH} against F_{IS} (Fig. 2). F_{IS} measures inbreeding as reflected by non-random mating in the most recent generation, and is calculated as the mean individual departure from Hardy–Weinberg equilibrium (F_{SNP}; see Methods). Cohorts with high rates of consanguinity lie near the $F_{ROH} = F_{IS}$ line, since most excess SNP homozygosity is caused by ROH. In contrast, cohorts with small effective population sizes, such as the Amish and Hutterite isolates of North America, have high average F_{ROH}, often despite avoidance of mating with known relatives, since identical-by-descent haplotypes are carried by many couples, due to a restricted number of possible ancestors.

Traits affected by F_{ROH}. To estimate the effect of inbreeding on each of the 100 phenotypes studied, trait values were regressed on F_{ROH} within each cohort, taking account of covariates including

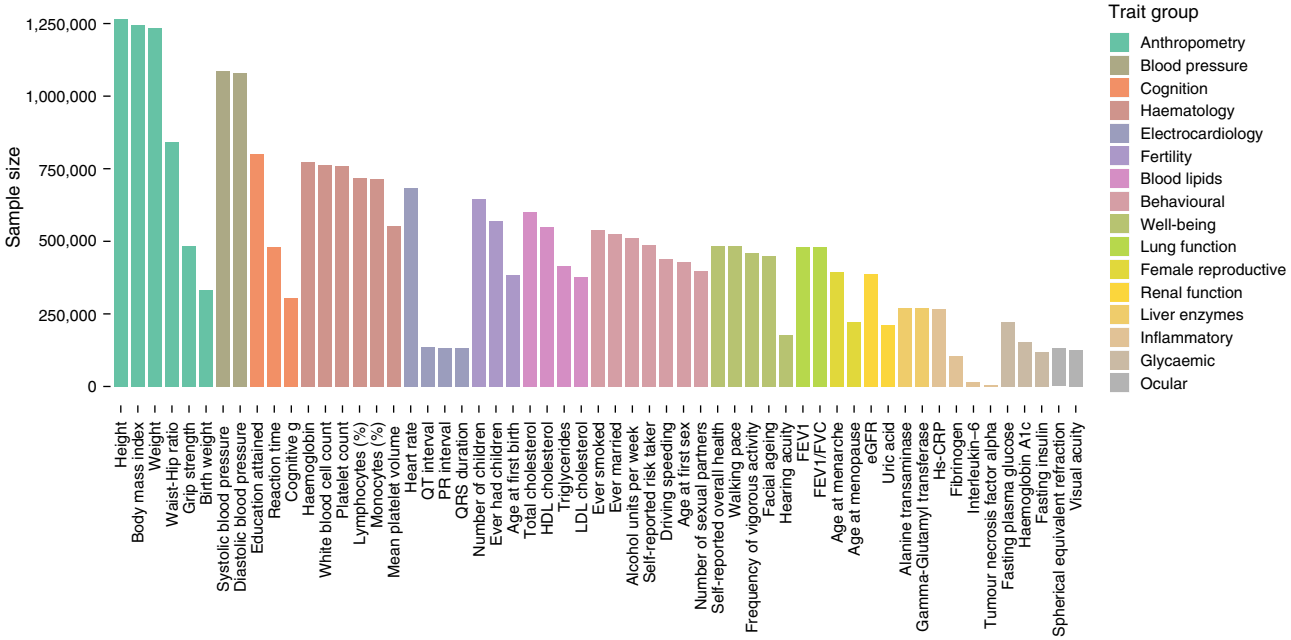

Fig. 1 Census of complex traits. Sample sizes are given for analyses of 57 representative phenotypes, arranged into 16 groups covering major organ systems and disease risk factors. HDL high-density lipoprotein, LDL low-density lipoprotein, hs-CRP high-sensitivity C-reactive protein, TNF-alpha tumour necrosis factor alpha, FEV1 forced expiratory volume in one second, FVC forced vital capacity, eGFR estimated glomerular filtration rate

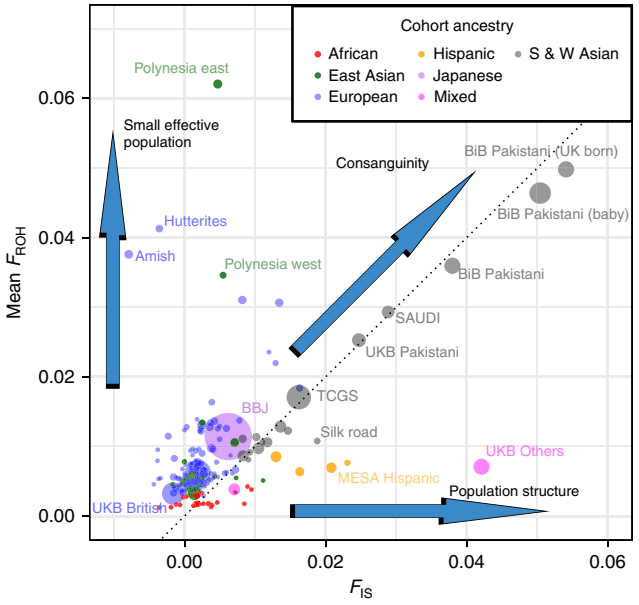

Fig. 2 Mean F_{ROH} and F_{IS} for 234 ROHgen sub-cohorts. Each cohort is represented by a circle whose area is proportional to the approximate statistical power ($N\sigma^2_{F_{ROH}}$) contributed to estimates of $\beta_{F_{ROH}}$. Mean F_{ROH} can be considered as an estimate of total inbreeding relative to an unknown base generation, approximately tens of generations past. F_{IS} measures inbreeding in the current generation, with $F_{IS} = 0$ indicating random mating, $F_{IS} > 0$ indicating consanguinity, and $F_{IS} < 0$ inbreeding avoidance[46]. In cohorts along the *y*-axis, such as the Polynesians and the Anabaptist isolates, autozygosity is primarily caused by small effective population size rather than preferential consanguineous unions. In contrast, in cohorts along the dotted unity line, all excess SNP homozygosity is accounted for by ROH, as expected of consanguinity within a large effective population. A small number of cohorts along the *x*-axis, such as Hispanic and mixed-race groups, show excess SNP homozygosity without elevated mean F_{ROH}, indicating population genetic structuring, caused for instance by admixture and known as the Wahlund effect. A few notable cohorts are labelled. BBJ Biobank Japan, BiB Born in Bradford, UKB UK Biobank, MESA Multiethnic Study of Atherosclerosis, TCGS Tehran Cardiometabolic Genetic Study

age, sex, principal components of ancestry and, in family studies, a genomic relationship matrix (GRM) (Supplementary Data 3). Cross-cohort effect size estimates were then obtained by fixed-effect, inverse variance-weighted meta-analysis of the within-cohort estimates (Supplementary Data 10). Twenty-seven out of 79 quantitative traits and 5 out of 21 binary traits reach experiment-wise significance (0.05/100 or $p < 0.0005$; Fig. 3a, b). Among these are replications of the previously reported effects on reduction in height[13], forced expiratory lung volume in one second, cognition and education attained[6]. We find that the 32 phenotypes affected by inbreeding can be grouped into five broader categories: reproductive success, risky behaviours, cognitive ability, body size, and health.

Despite the greater individual control over reproduction in the modern era, due to contraception and fertility treatments, we find that increased F_{ROH} has significant negative effects on five traits closely related to fertility. For example, an increase of 0.0625 in F_{ROH} (equivalent to the difference between the offspring of first cousins and those of unrelated parents) is associated with having 0.10 fewer children [$\beta_{0.0625} = -0.10 \pm 0.03$ 95% confidence interval (CI), $p = 1.8 \times 10^{-10}$]. This effect is due to increased F_{ROH} being associated with reduced odds of having any children ($OR_{0.0625} = 0.65 \pm 0.04$, $p = 1.7 \times 10^{-32}$) as opposed to fewer children among parents ($\beta_{0.0625} = 0.007 \pm 0.03$, $p = 0.66$). Since autozygosity also decreases the likelihood of having children in the subset of individuals who are, or have been, married, ($OR_{0.0625} = 0.71 \pm 0.09$, $p = 3.8 \times 10^{-8}$) it appears that the cause is a reduced ability or desire to have children, rather than reduced opportunity. Consistent with this interpretation, we observe no significant effect on the likelihood of marriage ($OR_{0.0625} = 0.94 \pm 0.07$, $p = 0.12$) (Fig. 3b). All effect size, odds ratios and 95% CI are stated as the difference between $F_{ROH} = 0$ and $F_{ROH} = 0.0625$.

The effects on fertility may be partly explained by the effect of F_{ROH} on a second group of traits, which capture risky or addictive behaviour. Increased F_{ROH} is associated with later age at first sex ($\beta_{0.0625} = 0.83 \pm 0.19$ years, $p = 5.8 \times 10^{-17}$) and fewer sexual partners ($\beta_{0.0625} = -1.38 \pm 0.38$, $p = 2.0 \times 10^{-12}$) but also reduced alcohol consumption ($\beta_{0.0625} = -0.66 \pm 0.12$ units per week, $p = 1.3 \times 10^{-22}$), decreased likelihood of smoking ($OR_{0.0625} = 0.79 \pm 0.05$, $p = 5.9 \times 10^{-13}$), and a lower probability of being a self-declared risk-taker ($OR_{0.0625} = 0.84 \pm 0.06$, $p = 3.4 \times 10^{-5}$) or exceeding the speed limit on a motorway ($p = 4.0 \times 10^{-8}$). Conservative beliefs are likely to affect these traits, and are known to be confounded with F_{ROH} in some populations[14], however, fitting religious participation as a covariate in UKB reduces, but does not eliminate the reported effects (Supplementary Fig. 10b, Supplementary Data 20). Similarly, fitting educational attainment as an additional covariate reduces 16 of 25 significant effect estimates, but actually increases 9, including age at first sex and number of children (Supplementary Fig. 10a, Supplementary Data 20). This is because reduced educational attainment is associated with earlier age at first sex and increased number of children, which makes it an unlikely confounder for the effects of F_{ROH}, which are in the opposite directions.

A third group of traits relates to cognitive ability. As previously reported, increased autozygosity is associated with decreased general cognitive ability, *g*[6,15] and reduced educational attainment[6]. Here, we also observe an increase in reaction time ($\beta_{0.0625} = 11.6 \pm 3.9$ ms, $p = 6.5 \times 10^{-9}$), a correlate of general cognitive ability (Fig. 3a, Supplementary Data 10).

A fourth group relates to body size. We replicate previously reported decreases in height and forced expiratory volume[6] (Supplementary Data 21) and we find that increased F_{ROH} is correlated with a reduction in weight ($\beta_{0.0625} = 0.86 \pm 0.12$ kg, $p = 3.4 \times 10^{-28}$) and an increase in the waist to hip ratio ($\beta_{0.0625} = 0.004 \pm 0.001$, $p = 1.4 \times 10^{-11}$).

The remaining effects are loosely related to health and frailty; higher F_{ROH} individuals report significantly lower overall health and slower walking pace, have reduced grip strength ($\beta_{0.0625} = -1.24 \pm 0.19$ kg, $p = 6.9 \times 10^{-24}$), accelerated self-reported facial ageing, and poorer eyesight and hearing. Increased F_{ROH} is also associated with faster heart rate ($\beta_{0.0625} = 0.56 \pm 0.24$ bpm, $p = 5.9 \times 10^{-6}$), lower haemoglobin ($\beta_{0.0625} = 0.81 \pm 0.24$ gL^{-1}, $p = 1.6 \times 10^{-11}$), lymphocyte percentage, and total cholesterol ($\beta_{0.0625} = -0.05 \pm 0.015$ mmol L^{-1}, $p = 5.2 \times 10^{-10}$).

Sex-specific effects of F_{ROH}. Intriguingly, for a minority of traits (13/100), the effect of F_{ROH} differs between men and women (Fig. 3c, Supplementary Data 12). For example, men who are the offspring of first cousins have 0.10 mmol L^{-1} [95% CI 0.08–0.12] lower total cholesterol on average, while there is no significant effect in women; LDL shows a similar pattern. More generally, for these traits, the effect in men is often of greater magnitude than the effect in women, perhaps reflecting differing relationships between phenotype and fitness.

Associations most likely caused by rare, recessive variants. The use of ROH to estimate inbreeding coefficients is relatively new in inbreeding research[11,16–19]. Earlier frequency-based estimators

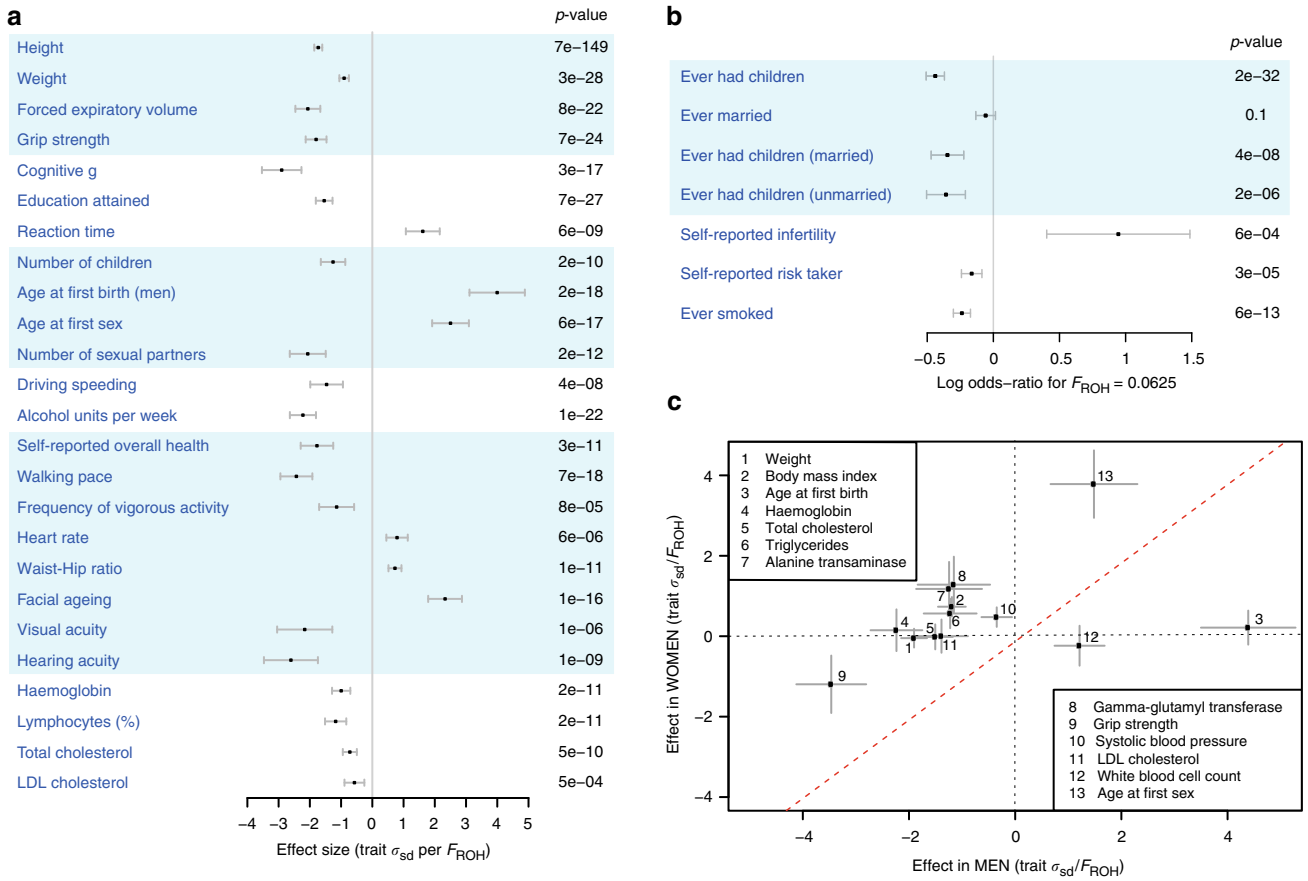

Fig. 3 Scope of inbreeding depression. **a** Effect of F_{ROH} on 25 quantitative traits. To facilitate comparison between traits, effect estimates are presented in units of within-sex standard deviations. Traits shown here reached Bonferroni-corrected significance of $p = 0.0005$ (=0.05/100 traits). Sample sizes, within-sex standard deviations, and effect estimates in measurement units are shown in Supplementary Data 9. FEV1 forced expiratory volume in one second. Traits are grouped by type. **b** Effect of F_{ROH} on eight binary traits with associated p values. Effect estimates are reported as ln(Odds-Ratio) for the offspring of first cousins, for which $E(F_{ROH}) = 0.0625$. Self-declared infertility is shown for information, although this trait does not reach Bonferroni corrected significant ($OR_{0.0625} = 2.6 \pm 1.1$, $p = 0.0006$). Numbers of cases and controls and effect estimates for all binary traits are shown in Supplementary Data 10. **c** Sex-specificity of ROH effects. The effect of F_{ROH} in men versus that in women is shown for 13 traits for which there was evidence of significant differences in the effects between sexes. For 11 of these 13 traits the magnitude of effect is greater in men than in women. Traits such as liver enzymes levels (alanine transaminase, gamma-glutamyl transferase) show sex-specific effects of opposite sign (positive in women, negative in men), which cancel out in the overall analysis. BMI body mass index, LDL low-density lipoprotein. All errors bars represent 95% confidence intervals

such as F_{SNP} and F_{GRM}[20], made use of excess marker homozygosity[21–23] and did not require physical maps. We performed both univariate and multivariate regressions to evaluate the effectiveness of F_{ROH} against these measures. The correlations between them range from 0.13 to 0.99 and are strongest in cohorts with high average inbreeding (Supplementary Data 6, Supplementary Fig. 6). Significantly, univariate regressions of traits on both F_{SNP} and F_{GRM} show attenuated effect estimates relative to F_{ROH} (Supplementary Data 13). This attenuation is greatest in low autozygosity cohorts, suggesting that F_{ROH} is a better estimator of excess homozygosity at the causal loci (Fig. 4c).

To explore this further, we fit bivariate models with F_{ROH} and F_{GRM} as explanatory variables. For all 32 traits that were significant in the univariate analysis, we find that $\widehat{\beta}_{F_{ROH}|F_{GRM}}$ is of greater magnitude than $\widehat{\beta}_{FGRM|FROH}$in the conditional analysis (Fig. 4b, Supplementary Data 22). This suggests that inbreeding depression is predominantly caused by rare, recessive variants made homozygous in ROH, and not by the chance homozygosity of variants in strong LD with common SNPs (Fig. 4d, Supplementary Note 5). We also find that ROH of different lengths have similar effects per unit length (Fig. 4a, Supplementary Fig. 11a), consistent with their having a causal effect on traits and not with confounding by socioeconomic or other factors, as shorter ROH arise from deep in the pedigree are thus less correlated with recent consanguinity.

Quantifying the scope of social confounding. Previous studies have highlighted the potential for F_{ROH} to be confounded by non-genetic factors[6,24]. We therefore estimated the effect of F_{ROH} within various groups, between which confounding might be expected either to differ, or not be present at all.

For example, the effect of F_{ROH} on height is consistent across seven major continental ancestry groups (Supplementary Fig. 1, Supplementary Data 18), despite differing attitudes towards consanguinity, and consequently different burdens and origins of ROH. Similarly, grouping cohorts into consanguineous, more cosmopolitan, admixed and those with homozygosity due to ancient founder effects also shows consistent effects (Supplementary Fig. 2, Supplementary Data 19). Equally, categorising samples into bins of increasing F_{ROH} shows a dose-dependent response of the study traits with increased F_{ROH} (Supplementary Data 17 and

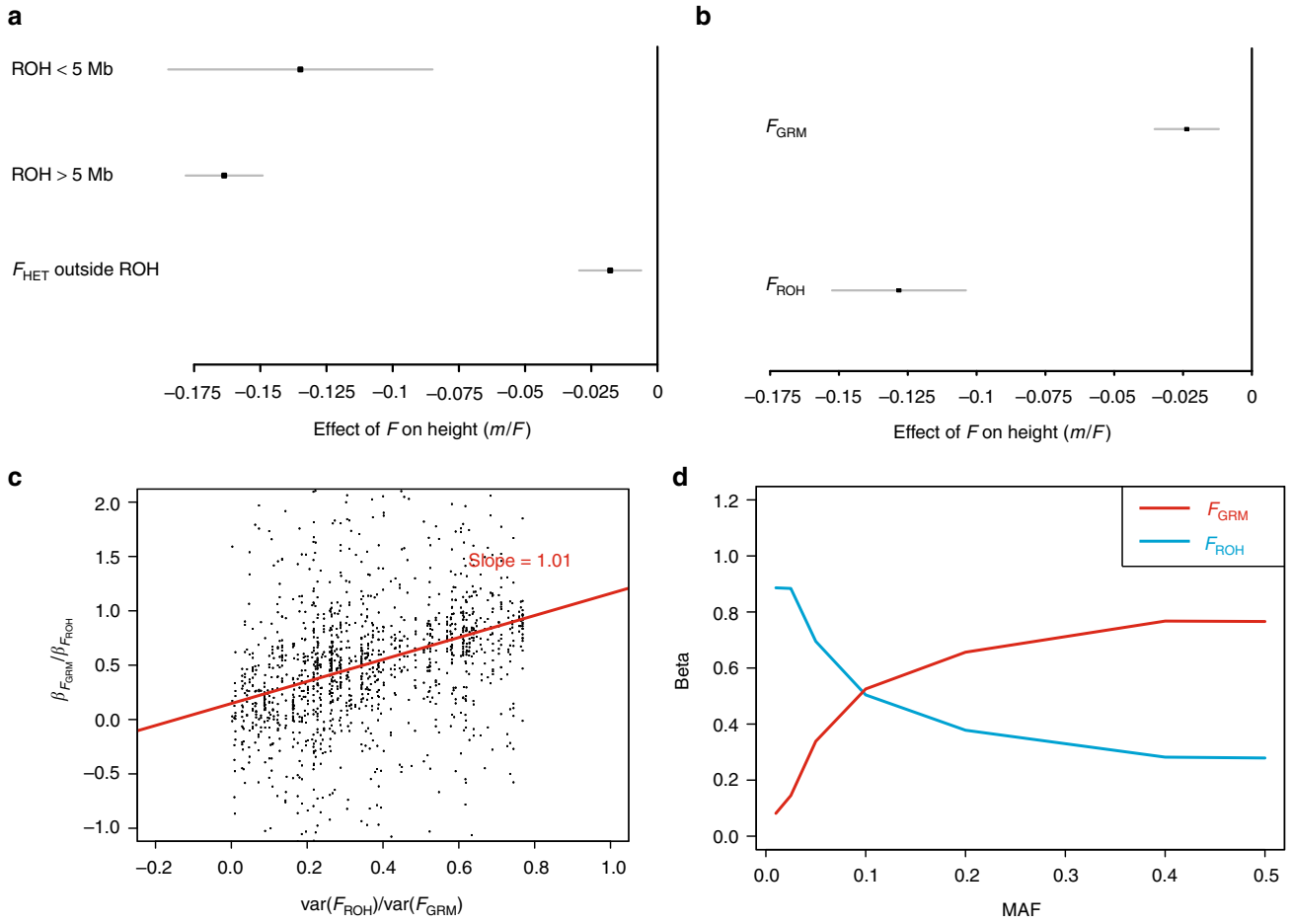

Fig. 4 Inbreeding depression caused by ROH. **a** Effect of different ROH lengths on height, compared with the effect of SNP homozygosity outside of ROH. The effects of shorter (<5 Mb) and longer (>5 Mb) ROH per unit length are similar and strongly negative, whereas the effect of homozygosity outside ROH is much weaker. The pattern is similar for other traits (Supplementary Fig. 11a; Supplementary Data 14). **b** $\boldsymbol{F_{ROH}}$ is more strongly associated than $\boldsymbol{F_{GRM}}$ in a bivariate model of height. Meta-analysed effect estimates, and 95% confidence intervals, are shown for a bivariate model of height (Height $\sim F_{ROH} + F_{GRM}$). The reduction in height is more strongly associated with F_{ROH} than F_{GRM}, as predicted if the causal variants are in weak LD with the common SNPs used to calculate F_{GRM} (Supplementary Note 5). The pattern is similar for other traits (Supplementary Fig. 15a, b; Supplementary Data 22). **c** F_{ROH} is a lower variance estimator of the inbreeding coefficient than F_{GRM}. The ratio of $\beta_{F_{GRM}} : \beta_{F_{ROH}}$ is plotted against $\frac{\mathrm{var}(F_{ROH})}{\mathrm{var}(F_{GRM})}$ for all traits in all cohorts. When the variation of F_{GRM} which is independent of F_{ROH} has no effect on traits, $\hat{\beta}_{F_{GRM}}$ is downwardly biased by a factor of $\frac{\mathrm{var}(F_{ROH})}{\mathrm{var}(F_{GRM})}$ (Supplementary Note 4). A linear maximum likelihood fit, shown in red, has a gradient consistent with unity [1.01; 95% CI 0.84–1.18], as expected when the difference between F_{GRM} and F_{ROH} is not informative about the excess homozygosity at causal variants (Supplementary Note 5). **d** F_{ROH} is a better predictor of rare variant homozygosity than F_{GRM}. The excess homozygosities of SNPs, extracted from UK Biobank imputed genotypes, were calculated at seven discrete minor allele frequencies (F_{MAF}), and regressed on two estimators of inbreeding in a bivariate statistical model (see Supplementary Note 5). The homozygosity of common SNPs is better predicted by F_{GRM}, but rare variant homozygosity is better predicted by F_{ROH}. The results from real data (Fig. 4b, Supplementary Figs 15a, b and Supplementary Data 22) are consistent with those simulated here, if the causal variants are predominantly rare. All errors bars represent 95% confidence intervals

Fig. 5a, b show the response for height and ever having children; Supplementary Figs 9a–f for all significant traits). The proportionality of these effects is consistent with a genetic cause, while it is difficult to envisage a confounder proportionally associated across the *entire* range of observed F_{ROH}. In particular, the highest F_{ROH} group ($F_{ROH} > 0.18$), equivalent to the offspring of first-degree relatives, are found to be, on average, 3.4 [95% CI 2.5–4.3] cm shorter and 3.1 [95% CI 2.5–3.7] times more likely to be childless than an $F_{ROH} = 0$ individual.

Next, we estimated $\beta_{F_{ROH}}$ for 7153 self-declared adopted individuals in UK Biobank, whose genotype is less likely to be confounded by cultural factors associated with the relatedness of their biological parents. For all 26 significant traits measured in this cohort, effect estimates are directionally consistent with the meta-analysis and 3 (height, walking pace and hearing acuity) reach replication significance ($p < 0.004$). In addition, a meta-analysis of the ratio $\widehat{\beta}_{F_{ROH\_ADOPTEE}} : \widehat{\beta}_{F_{ROH}}$ across all traits differs significantly from zero (Fig. 5c; average = 0.78, 95% CI 0.56–1.00, $p = 2 \times 10^{-12}$).

Finally, the effect of F_{ROH} was estimated in up to 118,773 individuals in sibships (full-sibling pairs, trios, etc.: $\widehat{\beta}_{F_{ROH\_wSibs}}$). F_{ROH} differences between siblings are caused entirely by Mendelian segregation, and are thus independent of any reasonable model of confounding. The variation of F_{ROH} among siblings is a small fraction of the population-wide variation[11] (Supplementary Data 5); nevertheless, 23 out of 29 estimates of $\widehat{\beta}_{F_{ROH\_wSibs}}$ are directionally consistent with $\widehat{\beta}_{F_{ROH}}$, and two (self-reported overall health and ever having children) reach replication

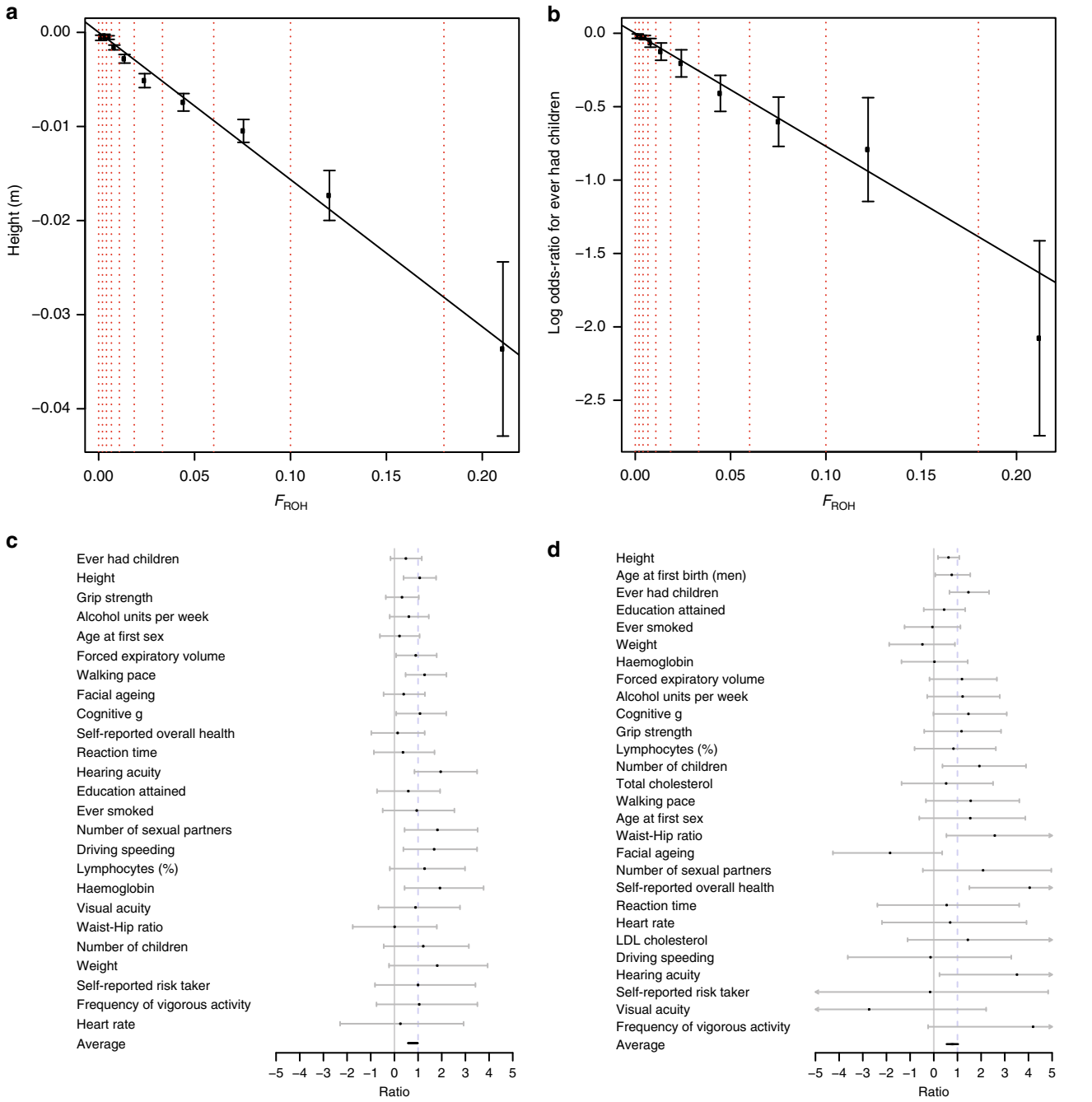

Fig. 5 Evidence ROH effects are un-confounded. **a** Linear decrease in height with increasing F_{ROH}. Average heights (in metres) is plotted in bins of increasing F_{ROH}. The limits of each bin are shown by red dotted lines, and correspond to the offspring of increasing degree unions left-to-right. The overall estimate of $\beta_{F_{ROH}}$ is shown as a solid black line. Subjects with kinship equal to offspring of full-sibling or parent-child unions are significantly shorter than those of avuncular or half-sibling unions who in turn are significantly shorter than those of first-cousin unions. **b** Linear decrease in odds of ever having children with increasing F_{ROH}. Linear model approximations of ln(Odds-Ratio) for ever having children (1 = parous, 0 = childless) are plotted in bins of increasing F_{ROH}. A strong relationship is evident, extending beyond the offspring of first cousins. **c** ROH effects are consistent in adoptees. The ratios of effect estimates, $\beta_{F_{ROH}}$, between adoptees and all individuals are presented by trait. All traits are directionally consistent and overall show a strongly significant difference from zero (average = 0.78, 95% CI 0.56–1.00, $p = 2 \times 10^{-12}$). FEV1 forced expiratory volume in one second. **d** ROH effects are consistent in full siblings. The ratios of effect estimates within full siblings to effects in all individuals ($\beta_{F_{ROH\_wSibs}} : \beta_{F_{ROH}}$) are presented by trait. Twenty-three of 29 estimates are directionally consistent and overall show a significant difference from zero (average = 0.78, 95% CI 0.53–1.04, $p = 7 \times 10^{-10}$). BMI body mass index. All errors bars represent 95% confidence intervals

significance. A meta-analysis of the ratio $\widehat{\beta}_{F_{\mathrm{ROH\_wSibs}}} : \widehat{\beta}_{F_{\mathrm{ROH}}}$ for all traits is significantly greater than zero (Fig. 5d; average = 0.78, 95% CI 0.53–1.04, $p = 7 \times 10^{-10}$), indicating a substantial fraction of these effects is genetic in origin. However, for both adoptees and siblings, the point estimates are less than one, suggesting that non-genetic factors probably contribute a small, but significant, fraction of the observed effects.

Discussion

Our results reveal inbreeding depression to be broad in scope, influencing both complex traits related to evolutionary fitness and others where the pattern of selection is less clear. While studies of couples show optimal fertility for those with distant kinship[25,26], fewer have examined reproductive success as a function of individual inbreeding. Those that did are orders of magnitude smaller in size than the present study, suffer the attendant drawbacks of pedigree analysis, and have found mixed results[27–29]. Our genomic approach also reveals that in addition to socio-demographic factors and individual choice, recessive genetic effects have a significant influence on whether individuals reproduce. The discordant effects on fertility and education demonstrate that this is not just a result of genetic correlations between the two domains[30].

The effects we see on fertility might be partially mediated through a hitherto unknown effect of autozygosity on decreasing the prevalence of risk-taking behaviours. Significant effects of autozygosity are observed for self-reported risk taking, speeding on motorways, alcohol and smoking behaviour, age at first sexual intercourse and number of sexual partners. Independent evidence for a shared genetic architecture between risk-taking and fertility traits comes from analysis of genetic correlations using LD-score regression in UKB (Supplementary Table 1). The core fertility traits, ever had children and number of children, are strongly genetically correlated ($r_G = 0.93$; $p < 10^{-100}$). Genetic correlations with ever-smoking and self-reported risk-taking are lower, but also significant: 0.23–0.27, $p < 10^{-10}$. Age at first sex is strongly genetically correlated both with the fertility traits, ($r_G =$ 0.53–0.57), and number of sexual partners, ever-smoking and risk-taking[30] ($r_G = 0.42$–0.60).

Reproductive traits are understandable targets of natural selection, as might be walking speed, grip strength, overall health, and visual and auditory acuity. While we cannot completely exclude reverse causality, whereby a less risk-taking, more conservative, personality is associated with greater likelihood of consanguineous marriage, we note that the effects are consistent for ROH < 5 Mb, which are less confounded with mate choice, due to their more distant pedigree origins (Supplementary Fig. 11a). This group of traits also shows similar evidence for unconfounded effects in the analysis of adoptees and full siblings (Fig. 5c, d; Supplementary Data 16) and the signals remained after correcting for religious activity or education.

On the other hand, for some traits that we expected to be influenced by ROH, we observed no effect. For example, birth weight is considered a key component of evolutionary fitness in mammals, and is influenced by genomic homozygosity in deer[31]; however, no material effect is apparent here (Supplementary Data 10). Furthermore, in one case, ROH appear to provide a beneficial effect: increasing F_{ROH} significantly decreases total and LDL-cholesterol in men, and may thus be cardio-protective in this regard.

Our multivariate models show that homozygosity at common SNPs outside of ROH has little influence on traits, and that the effect rather comes from ROH over 1.5 Mb in length. This suggests that genetic variants causing inbreeding depression are almost entirely rare, consistent with the dominance hypothesis[1]. The alternative hypothesis of overdominance, whereby positive selection on heterozygotes has brought alleles to intermediate frequencies, would predict that more common homozygous SNPs outside long ROH would also confer an effect. The differential provides evidence in humans that rare recessive mutations underlie the quantitative effects of inbreeding depression.

Previous studies have shown that associations observed between F_{ROH} and traits do not prove a causal relationship[14,24]. Traditional Genome-wide Association Studies (GWAS) can infer causality because, in the absence of population structure, genetic variants (SNPs) are randomly distributed between, and within, different social groups. However, this assumption does not hold in studies of inbreeding depression, where, even within a genetically homogeneous population, social groups may have differing attitudes towards consanguinity, and therefore different average F_{ROH} and, potentially, different average trait values. We therefore present a number of analyses that discount social confounding as a major factor in our results. Firstly, we show that the effects are consistent across diverse populations, including those where ROH burden is driven by founder effects rather than cultural practices regarding marriage. Effects are also consistent across a 20-fold range of F_{ROH}: from low levels, likely unknown to the subject, to extremely high levels only seen in the offspring of first-degree relatives. Secondly, we show that the effects of ROH are consistent in direction and magnitude among adopted individuals, and also for short ROH which are not informative about parental relatedness. Finally, we introduce a within-siblings method, independent of all confounders, that confirms a genetic explanation for most of the observed effects. Variation in F_{ROH} between siblings is caused entirely by random Mendelian segregation; we show that higher F_{ROH} siblings experience poorer overall health and lower reproductive success, as well as other changes consistent with population-wide estimates. Nevertheless, average effect sizes from both adoptees and siblings are 20% smaller than population-wide estimates, confirming the importance of accounting for social confounding in future studies of human inbreeding depression.

Our results reveal five large groups of phenotypes sensitive to inbreeding depression, including some known to be closely linked to evolutionary fitness, but also others where the connection is, with current knowledge, more surprising. The effects are mediated by ROH rather than homozygosity of common SNPs, causally implicating rare recessive variants rather than overdominance as the most important underlying mechanism. Identification of these recessive variants will be challenging, but analysis of regional ROH and in particular using whole-genome sequences in large cohorts with sufficient variance in autozygosity will be the first step. Founder populations or those which prefer consanguineous marriage will provide the most power to understand this fundamental phenomenon.

see Supplementary Data.

Methods

Overview. Our initial aim was to estimate the effect of F_{ROH} on 45 quantitative traits and to assess whether any of these effects differed significantly from zero. Previous work[7,11] has shown that inbreeding coefficients are low in most human populations, and that very large samples are required to reliably estimate the genetic effects of inbreeding[13]. To maximise sample size, a collaborative consortium (ROHgen[6]) was established, and research groups administering cohorts with SNP chip genotyping were invited to participate. To ensure that all participants performed uniform and repeatable analyses, a semi-automated software pipeline was developed and executed locally by each research group. This software pipeline required cohorts to provide only quality-controlled genotypes (in plink binary format) and standardised phenotypes (in plain-text) and used standard software (R, PLINK[12,32], KING[33]) to perform the analyses described below. Results from each cohort were returned to the central ROHgen analysts for meta-analysis.

During the initial meta-analysis, genotypes were released for >500,000 samples from the richly phenotyped UK Biobank (UKB)[10]. It was therefore decided to add a

further 34 quantitative phenotypes and 21 binary traits to the ROHgen analysis. Many of these additional traits were unique to UKB, although 7 were also available in a subset of ROHgen cohorts willing to run additional analyses. In total, the effect of F_{ROH} was tested on 100 traits and therefore experiment-wise significance was defined as 5×10^{-4} (=0.05/100).

Cohort recruitment. In total, 119 independent, genetic epidemiological study cohorts were contributed to ROHgen. Of these, 118 were studies of adults and contributed multiple phenotypes, while 1 was a study of children and contributed only birth weight. To minimise any potential confounding or bias caused by within-study heterogeneity, studies were split into single-ethnicity sub-cohorts wherever applicable. Each sub-cohort was required to use only one genotyping array and be of uniform ancestry and case-status. For example, if a study contained multiple distinct ethnicities, sub-cohorts of each ancestry were created and analysed separately. At minimum, ancestry was defined on a sub-continental scale (i.e. European, African, East Asian, South Asian, West Asian, Japanese, and Hispanic were always analysed separately) but more precise separation was used when deemed necessary, for example, in cohorts with large representation of Ashkenazi Jews. In case-control studies of disease, separate sub-cohorts were created for cases and controls and phenotypes associated with disease status were not analysed in the case cohort: for example, fasting plasma glucose was not analysed in Type 2 diabetes case cohorts. Occasionally, cohorts had been genotyped on different SNP genotyping microarrays and these were also separated into sub-cohorts. There was one exception (deCODE) to the single microarray rule, where the intersection between all arrays used exceeded 150,000 SNPs. In this cohort the genotype data from all arrays was merged since the correspondence between F_{ROH} for the individual arrays and F_{ROH} the intersection dataset was found to be very strong ($\beta_{merged,hap} = 0.98$, $r^2 = 0.98$; $\beta_{merged,omni} = 0.97$, r^2=0.97). Dividing studies using these criteria yielded 234 sub-cohorts. Details of phenotypes contributed by each cohort are available in Supplementary Data 4.

Ethical approval. Data from 119 independent genetic epidemiology studies were included. All subjects gave written informed consent for broad-ranging health and genetic research and all studies were approved by the relevant research ethics committees or boards. PubMed references are given for each study in Supplementary Data 2.

Genotyping. All samples were genotyped on high-density (minimum 250,000 markers), genome-wide SNP microarrays supplied by Illumina or Affymetrix. Genotyping arrays with highly variable genomic coverage (such as Exome chip, Metabochip, or Immunochip) were judged unsuitable for the ROH calling algorithm and were not permitted. Imputed genotypes were also not permitted; only called genotypes in PLINK binary format were accepted. Each study applied their own GWAS quality controls before additional checks were made in the common analysis pipeline: SNPs with >3% missingness or MAF <5% were removed, as were individuals with >3% missing data. Only autosomal genotypes were used for the analyses reported here. Additional, cohort-specific, genotyping information is available in Supplementary Data 2.

Phenotyping. In total, results are reported for 79 quantitative traits and 21 binary traits. These traits were chosen to represent different domains of health and reproductive success, with consideration given to presumed data availability. Many of these traits have been the subject of existing genome-wide association meta-analyses (GWAMA), and phenotype modelling, such as inclusion of relevant covariates, was copied from the relevant consortia (GIANT for anthropometry, EGG for birth weight, ICBP for blood pressures, MAGIC for glycaemic traits, CHARGE-Cognitive, -Inflammation & -Haemostasis working groups for cognitive function, CRP, fibrinogen, CHARGE-CKDgen for eGFR, CHARGE-ReproGen for ages at menarche and menopause, Blood Cell & HaemGen for haematology, GUGC for urate, RRgen, PRIMA, QRS & QT-IGC for electrocardiography, GLGC for classical lipids, CREAM for spherical equivalent refraction, Spirometa for lung function traits, and SSGAC for educational attainment and number of children ever born). Further information about individual phenotype modelling is available in Supplementary Note 1 and Supplementary Data 8.

ROH calling. Runs of homozygosity (ROH) of >1.5 Mb in length were identified using published methods[6,11]. In summary, SNPs with minor allele frequencies below 5% were removed, before continuous ROH SNPs were identified using PLINK with the following parameters: homozyg-window-snp 50; homozyg-snp 50; homozyg-kb 1500; homozyg-gap 1000; homozyg-density 50; homozyg-window-missing 5; homozyg-window-het 1. No linkage disequilibrium pruning was performed. These parameters have been previously shown to call ROH that correspond to autozygous segments in which all SNPs (including those not present on the chip) are homozygous-by-descent, not chance arrangements of independent homozygous SNPs, and inbreeding coefficient estimates calculated by this method (F_{ROH}) correlate well with pedigree-based estimates (F_{PED})[11]. Moreover, they have also been shown to be robust to array choice[6].

Calculating estimators of *F*. For each sample, two estimates of the inbreeding coefficient (F) were calculated, F_{ROH} and F_{SNP}. We also calculated three additional measures of homozygosity: $F_{ROH<5Mb}$, $F_{ROH>5Mb}$ and $F_{SNP\_outsideROH}$.

F_{ROH} is the fraction of each genome in ROH >1.5 Mb. For example, in a sample for which PLINK had identified n ROH of length l_i (in Mb), $i \in \{1..n\}$, then F_{ROH} was then calculated as

$$F_{ROH} = \frac{\sum_{i=1}^{n} l_i}{3Gb}, \quad (1)$$

where $F_{ROH<5Mb}$ and $F_{ROH>5Mb}$ are the genomic fractions in ROH of length >5 Mb, and in ROH of length <5 Mb (but >1.5 Mb), respectively, and the length of the autosomal genome is estimated at 3 gigabases (Gb). It follows from this definition that

$$F_{ROH} = F_{ROH>5Mb} + F_{ROH<5Mb}. \quad (2)$$

Single-point inbreeding coefficients can also be estimated from individual SNP homozygosity without any reference to a genetic map. For comparison with F_{ROH}, a method of moments estimate of inbreeding coefficient was calculated[34], referred to here as F_{SNP}, and implemented in PLINK by the command–het.

$$F_{SNP} = \frac{O(HOM) - E(HOM)}{N - E(HOM)}, \quad (3)$$

where O(HOM) is the observed number of homozygous SNPs, E(HOM) is the expected number of homozygous SNPs, i.e. $\sum_{i=1}^{N}(1 - 2p_iq_i)$, and N is the total number of non-missing genotyped SNPs.

F_{ROH} and F_{SNP} are strongly correlated, especially in cohorts with significant inbreeding, since both are estimates of F. To clarify the conditional effects of F_{ROH} and F_{SNP}, an additional measure of homozygosity,$F_{SNPoutsideROH}$, was calculated to describe the SNP homozygosity observed outside ROH.

$$F_{SNP_{outsideROH}} = \frac{O'(HOM) - E'(HOM)}{N' - E'(HOM)}, \quad (4)$$

where

$$O'(HOM) = O(HOM) - N_{SNP\_ROH}, \quad (5)$$

$$E'(HOM) = \left(\frac{N - N_{ROH}}{N}\right) * E(HOM), \quad (6)$$

$$N' = N - N_{ROH} \quad (7)$$

And N_{SNP_ROH} is the number of homozygous SNPs found in ROH. Note that:

$$F_{SNP\,outsideROH} \approx F_{SNP} - F_{ROH} \quad (8)$$

A further single point estimator of the inbreeding coefficient, described by Yang et al.[20] as $\widehat{F}^{III}$, is implemented in PLINK by the parameter –ibc (Fhat3) and was also calculated for all samples.

$$F_{GRM} = \widehat{F}^{III} = \frac{1}{N}\sum_{i=1}^{N} \frac{\left(x_i^2 - (1 + 2p_i)x_i + 2p_i^2\right)}{2p_i(1 - p_i)}, \quad (9)$$

where N is the number of SNPs, $_{pi}$ is the reference allele frequency of the ith SNP in the sample population and x_i is the number of copies of the reference allele.

Effect size estimates for quantitative traits. In each cohort of n samples, for each of the quantitative traits measured in that cohort, trait values were modelled by

$$y = \beta_{F_{ROH}} * \mathbf{F_{ROH}} + \mathbf{Xb} + \boldsymbol{\varepsilon}, \quad (10)$$

where $\mathbf{y}$ is a vector ($n \times 1$) of measured trait values, $\beta_{F_{ROH}}$ is the unknown scalar effect of F_{ROH} on the trait, $\mathbf{F_{ROH}}$ is a known vector ($n \times 1$) of individual F_{ROH}, $\mathbf{b}$ is a vector ($m \times 1$) of unknown fixed covariate effects (including a mean, μ), $\mathbf{X}$ in a known design matrix ($n \times m$) for the fixed effects, and $\boldsymbol{\varepsilon}$ is an unknown vector ($n \times 1$) of residuals.

The m fixed covariates included in each model were chosen with reference to the leading GWAMA consortium for that trait and are detailed in Supplementary Data 8. For all traits, these covariates included: age (and/or year of birth), sex, and at least the first 10 principal components of the genomic relatedness matrix (GRM). Where necessary, additional adjustments were made for study site, medications, and other relevant covariates (Supplementary Data 3).

For reasons of computational efficiency, it was decided to solve Eq. (10) in two steps. In the first step, the trait ($\mathbf{y}$) was regressed on all fixed covariates to obtain the maximum likelihood solution of the model:

$$\mathbf{y} = \mathbf{Xb} + \boldsymbol{\varepsilon}'. \quad (11)$$

All subsequent analyses were performed using the vector of trait residuals $\boldsymbol{\varepsilon}'$, which may be considered as the trait values corrected for all known covariates.

In cohorts with a high degree of relatedness, mixed-modelling was used to correct for family structure, although, because ROH are not narrow-sense heritable, this was considered less essential than in Genome-Wide Association Studies. Equation (11) becomes

$$\mathbf{y} = \mathbf{Xb} + \mathbf{u} + \boldsymbol{\varepsilon}', \quad (12)$$

where $\mathbf{u}$ is an unknown vector ($n \times 1$) of polygenic effects with multivariate normal distribution of mean 0 and covariance matrix $\sigma_g^2\mathbf{A}$, where $\mathbf{A}$ is the genomic relationship matrix (GRM). In these related cohorts, a GRM was calculated using PLINK v1.9 and Grammar+ residuals of Eq. (12) were estimated using GenABEL[35]. These Grammar+ residuals ($\boldsymbol{\varepsilon}'$) were used in subsequent analyses.

To estimate $\beta_{F_{\mathrm{ROH}}}$ for each trait, trait residuals were regressed on F_{ROH} to obtain the maximum likelihood (ML) solution of the model

$$\boldsymbol{\varepsilon}' = \mu + \beta_{F_{\mathrm{ROH}}} * \mathbf{F_{ROH}} + \boldsymbol{\varepsilon}. \quad (13a)$$

The sex-specific estimates of $\beta_{F_{\mathrm{ROH}}}$ (Supplementary Data 12) were obtained from Eq. (13) applied to the relevant sex.

For all traits, a corresponding estimates of $\beta_{F_{\mathrm{SNP}}}$ and $\beta_{F_{\mathrm{GRM}}}$ were obtained from the models

$$\boldsymbol{\varepsilon}' = \mu + \beta_{F_{\mathrm{SNP}}} * \mathbf{F_{SNP}} + \boldsymbol{\varepsilon}, \quad (13b)$$

$$\boldsymbol{\varepsilon}' = \mu + \beta_{F_{\mathrm{GRM}}} * \mathbf{F_{GRM}} + \boldsymbol{\varepsilon} \quad (14)$$

and the effects of different ROH lengths and of SNP homozygosity (Fig. 4b) were obtained from the model

$$\boldsymbol{\varepsilon}' = \mu + \left(\beta_1 * \mathbf{F_{SNP_{outsideROH}}}\right) + \left(\beta_2 * \mathbf{F_{ROH<5Mb}}\right) + \left(\beta_3 * \mathbf{F_{ROH>5Mb}}\right) + \boldsymbol{\varepsilon} \quad (15)$$

Effect size estimates for binary traits. Binary traits were analysed by two methods. The primary estimates of $\beta_{F_{\mathrm{ROH}}}$ (Fig. 3b and Supplementary Data 10) were obtained from full logistic models:

$$g(E[\mathbf{y}]) = \mathbf{Xb}, \quad (16)$$

where $g()$ is the link function (logit), and where F_{ROH} and all applicable covariates (Supplementary Datas 3, 8) were fitted simultaneously. Mixed modelling for family structure was not attempted in the logistic models since an accepted method was not apparent.

For all subsequent results, $\mathbf{y}$ was scaled by $1/\sigma_y^2$ and analysed by linear models, as for quantitative traits, including mixed-modelling where appropriate for family studies. This method of estimating binary traits with simple linear models gives asymptotically unbiased estimates of $\beta_{F_{\mathrm{ROH}}}$ and $\mathrm{se}(\beta_{F_{\mathrm{ROH}}})$ on the ln(Odds-Ratio) scale[36]. For all significant binary traits, a comparison of $\widehat{\beta}_{F_{\mathrm{ROH}}}$ from the full model with $\widehat{\beta}_{F_{\mathrm{ROH}}}$ from the linear model approximation is presented in Supplementary Fig. 8.

To give $\widehat{\beta}_{F_{\mathrm{ROH}}}$ a more tangible interpretation, effect estimates are frequently quoted in the text as $\beta_{0.0625}$, i.e. the estimated effect in the offspring of first cousins, where 6.25% of the genome is expected to be autozygous.

Religiosity and educational attainment as additional covariates. To assess the importance of potential social confounders, proxy measures of socio-economic status and religiosity were separately included in Eq. (13) as additional covariates. The modified effect estimates ($\widehat{\beta}'_{F_{\mathrm{ROH}}}$) were tested for significance (Supplementary Data 20) and compared to the uncorrected estimates ($\beta_{F_{\mathrm{ROH}}}$) (Supplementary Fig. 10a, b).

Since Educational Attainment (EA) was measured in many cohorts, this was chosen as the most suitable proxy for socio-economic status. However, since F_{ROH} is known to affect EA directly[6] any change in $\beta_{F_{\mathrm{ROH}}}$ when conditioning on EA cannot be assumed to be entirely due to environmental confounding.

The analysis of religiosity was only carried out in UKB, where a rough proxy was available. Although no direct questions about religious beliefs were included, participants were asked about their leisure activities. In response to the question *Which of the following do you attend once a week or more often? (You can select more than one)*, 15.6% of UKB participants selected *Religious Group* from one of the seven options offered. In the models described, religiosity was coded as 1 for those who selected *Religious Group* and 0 for those who did not. Although this is likely to be an imperfect measure of actual religious belief it is currently the best available in a large dataset.

Assortative mating. Humans are known to mate assortatively for a number of traits including height and cognition[37], and so we sought to investigate if this could influence our results, for example, by the trait extremes being more genetically similar and thus the offspring more homozygous. We see no evidence for an effect of assortative mating on autozygosity, however. Firstly, a polygenic risk score for height (see Supplementary Note 1), which explains 18.7% of the phenotypic variance in height, was not associated with F_{ROH} ($p = 0.77$; Supplementary Fig. 5). Secondly, linear relationships between traits and autozygosity extend out to very high F_{ROH} individuals (Supplementary Figs. 9a–f). Samples in the highest F_{ROH} group are offspring of genetically similar parents, very likely first or second degree relatives and, for example, the height of these samples is on average 3.4 cm [95% CI 2.5–4.3] shorter than the population mean. Assortative mating would suggest this height deficit has been inherited from genetically shorter parents, but this would require an implausibly strong relationship between short stature and a propensity to marry a very close relative. Thirdly, the sex-specific effects we observe could only be explained by assortative mating if the additive heritability of these traits also differed by gender.

Average trait values in groups of similar F_{ROH}. In each cohort individuals were allocated to one of ten groups of similar F_{ROH}. The bounds of these groups were the same for all cohorts, specifically {0, 0.002, 0.0041, 0.0067, 0.0108, 0.0186, 0.0333, 0.06, 0.10, 0.18 and 1.0}. Within each group the mean trait residual ($\boldsymbol{\varepsilon}'$) and mean F_{ROH} were calculated, along with their associated standard errors. Within each cohort the expectation of $\boldsymbol{\varepsilon}'$ is zero at the mean F_{ROH}, however as mean F_{ROH} varies between cohorts (Fig. 2, Supplementary Data 5) it was necessary to express $\boldsymbol{\varepsilon}'$ relative to a common F_{ROH} before meta-analysis. Hence, for this analysis only, the trait residuals ($\boldsymbol{\varepsilon}'$) were expressed relative to the $F_{\mathrm{ROH}} = 0$ intercept, i.e. by subtracting μ from Eq. (13).

Effect of F_{ROH} within adoptees. We compared $\beta_{F_{\mathrm{ROH\_ADOPTEE}}}$ to cross-cohort $\beta_{F_{\mathrm{ROH}}}$, not that from UKB alone, as we consider the latter to be a noisy estimate of the former; estimates in UKB are consistent with those from meta-analysis.

Effect of F_{ROH} within full-sibling families. In a subset of cohorts, with substantial numbers of related individuals, further analyses were performed to investigate the effect of F_{ROH} within full-sibling families. In each of these cohorts, all second-degree, or closer, relatives were identified using KING (parameters:–related–degree 2). Full-siblings were then selected as relative pairs with genomic kinship >0.175 and IBS0 >0.001. This definition includes monozygotic twins, who were intentionally considered as part of full-sibling families. Although monozygotic twins are expected to have identical F_{ROH}, they may not have identical trait values, and including additional trait measurements decreases the sampling error of the within-family variance estimate, hence increasing statistical power. Dizygotic twins were also included.

For each individual (j) with identified siblings, the values of F_{ROH} and trait residual ($\boldsymbol{\varepsilon}'$) were calculated relative to their family mean (and called $F_j^{\mathrm{ROH\_wSibs}}$ and $\varepsilon_j^{\mathrm{wSibs}}$, respectively), i.e. for individual j with n full-siblings S_k where $k \in \{1..n\}$

$$F_j^{\mathrm{ROHwSibs}} = F_j^{\mathrm{ROH}} - \frac{1}{(n+1)} \sum_{i \in \{j, S_k\}} F_i^{\mathrm{ROH}}, \quad (17)$$

$$\varepsilon_j^{\mathrm{wSibs}} = \varepsilon_j' - \frac{1}{(n+1)} \sum_{i \in \{j, S_k\}} \varepsilon'_i. \quad (18)$$

The effect of F_{ROH} within-full-siblings ($\beta_{F_{\mathrm{ROH}}\_\mathrm{wSibes}}$) was estimated by linear regression of $\boldsymbol{\varepsilon}^{\mathbf{wSibs}}$ on $\mathbf{F^{ROH\_wSibs}}$.

Importantly, the variation of F_{ROH} within full-siblings is entirely caused by differences in Mendelian segregation, and is therefore completely independent of all possible confounders. Hence, the effect estimates obtained by this method are estimates of the genetic effects of F_{ROH}, unbiased by any possible confounder. Since confounding by social factors is a major concern in this field, methods that can definitively exclude this possibility are of critical importance.

Between-cohort meta-analysis. As is typical in genome-wide association meta-analyses (GWAMA), genetic effects were estimated within single-ethnicity sub-cohorts, and meta-analysis of the within-cohort effect sizes was used to combine results[38]. This established method eliminates any potential confounding caused by between-cohort associations between F_{ROH} and traits.

Each cohort returned estimates and standard errors of: $\beta_{F_{\mathrm{ROH}}}$, $\beta_{F_{\mathrm{SNP}}}$, $\beta_{F_{\mathrm{ROH>Mb}}}$, $\beta_{F_{\mathrm{ROH<Mb}}}$, $\beta_{F\_\mathrm{outsideROH}}$, $\beta_{F_{\mathrm{ROH\_wSibs}}}$, as well as trait means ($\overline{\varepsilon'}$) and standard errors within each of 10 F_{ROH} bins. The between-cohort mean of each of these 16 estimates was then determined by fixed-effect, inverse-variance meta-analysis using the R package metafor[39]. Results shown in Figs. 3–5 are meta-analysed averages of the within-cohort effects.

The meta-analysis was also run for various subsets of cohorts, stratified by ancestry as defined in Supplementary Data 18. Meta-analysis estimates from these groupings are shown in Supplementary Fig. 1.

Median and 95% CI of a ratio. In the analyses of adoptees (Fig. 5c), siblings (Fig. 5d) and potential confounders (Supplementary Figs. 10a, b) we wished to compare the effect estimates ($\beta_{F_{\mathrm{ROH}}}$) from two different methods across a wide range of traits. The units of $\beta_{F_{\mathrm{ROH}}}$ differ by trait so, to allow comparison across all traits, the unitless ratio of effect size estimates was calculated (for example $\beta_{F_{\mathrm{ROH\_wSibs}}} : \beta_{F_{\mathrm{ROH}}}$). Figure 5c, d and Supplementary Figs. 10a, b show the medians and 95% CI of these ratios. These were determined empirically by bootstrap since, although formulae exist for the mean and standard error of a ratio[40], the assumption of normality is violated when $\beta_{F_{\mathrm{ROH}}}/\mathrm{se}(\beta_{F_{\mathrm{ROH}}})$ is not large.

Genetic correlations in UK Biobank. Genetic correlations were calculated using LD-Score Regression[41], implemented in LDSC v1.0.0 (https://github.com/bulik/ldsc). Summary statistics were parsed using default parameters in the LDSC

'munge_sumstats.py' script, extracting only variants present in the HapMap 3 reference panel.

Accuracy of F_{ROH} measures of inbreeding effects. A recent paper suggested that ROH may overestimate inbreeding effects by as much as 162%[42]; however, this could only be the case if F_{ROH} underestimates excess homozygosity at the causal loci by at least 162%. We do not believe this to be the case since the maximum F_{ROH} measured in many cohorts is around 0.25 (the expectation in the offspring off first-degree relatives), and the effect size estimates from these samples are consistent with the overall estimates (Fig. 5c, d and Supplementary Fig. 9a–f). We note that Yengo et al. applied the ROH calling parameters used here to imputed data. These parameters have been validated for called genotype data[6] but not, to our knowledge, for the higher SNP density and error rate of imputed data (see also Supplementary Note 4). The simple method for detecting ROH used here was well suited to our study, since it could be easily implemented on over one million samples, and most of the variation in F_{ROH} is caused by easily-identified long ROH.[43–45]

Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

The meta-analysed data which support these findings are available as Supplementary Data files. Cohort-level summary statistics underlying all figures and tables are available in a publicly accessible dataset (https://doi.org/10.6084/m9.figshare.9731087). In the majority of cases we do not have consent to share individual-level data, although for UK Biobank this is available on request from https://www.ukbiobank.ac.uk/.

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Additional information

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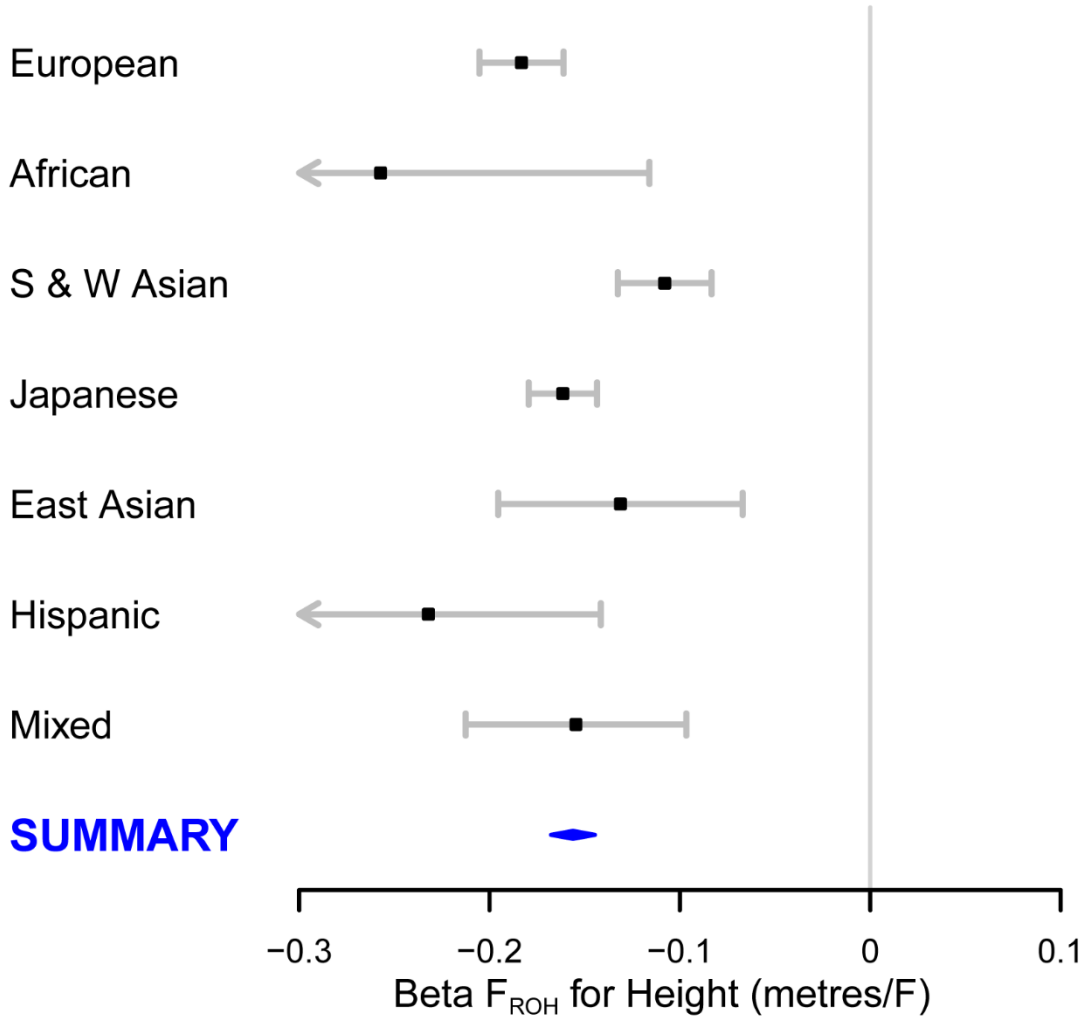
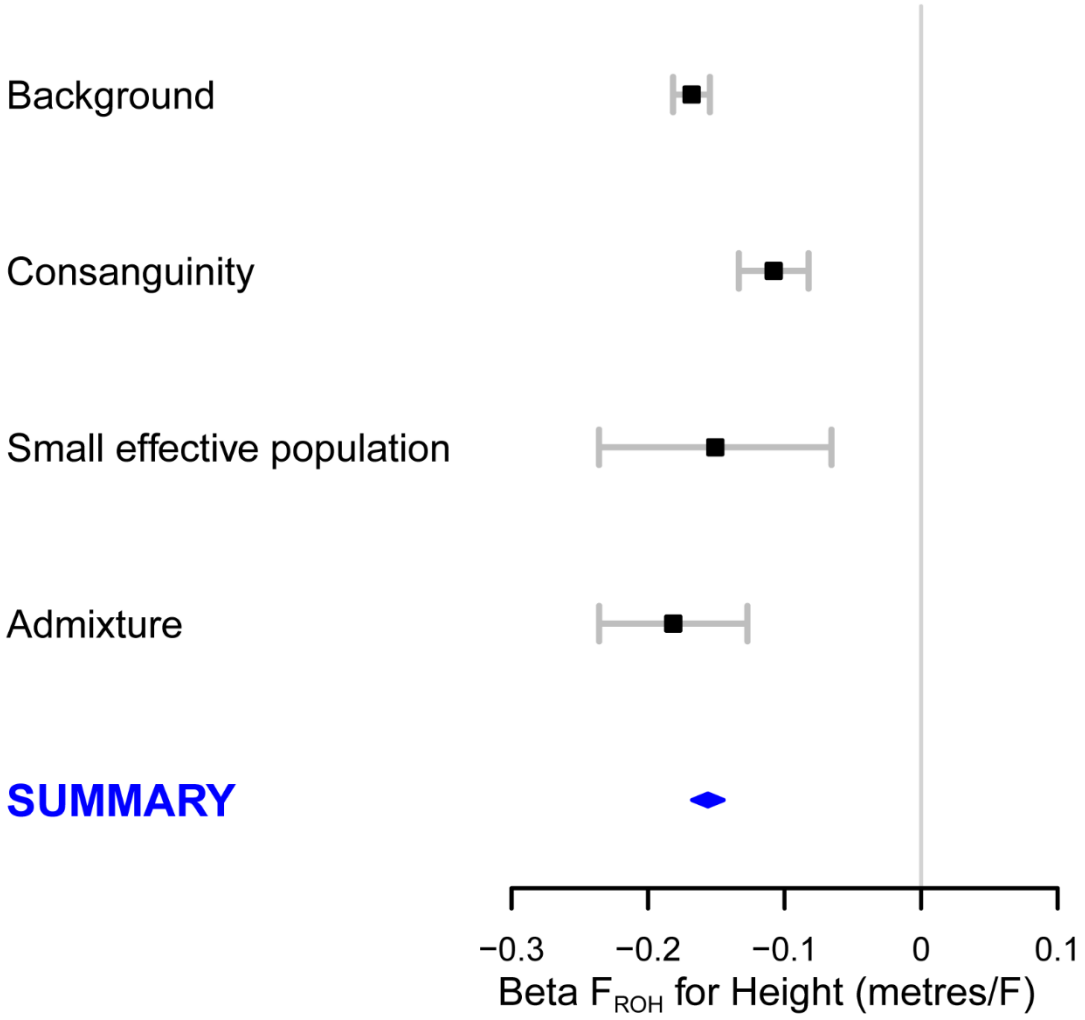
[285]University Hospital Schleswig-Holstein (UKSH), Campus Kiel, Kiel 24105, Germany. [286]Institute of Epidemiology and PopGen Biobank, University of Kiel, Kiel, Schleswig Holstein 24105, Germany. [287]Department of Statistics, University of Auckland, Auckland, New Zealand. [288]Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria. [289]Synlab Academy, Synlab Holding Deutschland GmbH, Mannheim, Germany. [290]Department of Genetics, King Faisal Specialist Hospital and Research Centre, Riyadh 11211, Saudi Arabia. [291]Institute for Molecular Bioscience, The University of Queensland, Brisbane, Queensland 4072, Australia. [292]Department of Public Health and Primary Care, Leiden University Medical Center, Leiden 2333 ZA, The Netherlands. [293]School of Biomedical Sciences, Institute of Health and Biomedical Innovation, Queensland University of Technology, Kelvin Grove, QLD 4059, Australia. [294]Department of Psychiatry, Interdisciplinary Center Psychopathology and Emotion Regulation, University of Groningen, University Medical Center Groningen, Groningen 9700 RB, The Netherlands. [295]Department of Medicine, Columbia University Medical Center, New York, New York, USA. [296]Pat Macpherson Centre for Pharmacogenetics and Pharmacogenomics, The School of Medicine, University of Dundee, Dundee DD1 9SY, UK. [297]School of Medicine and Public Health, Faculty of Medicine and Health, The University of Newcastle, Newcastle, New South Wales, Australia. [298]Division of Obstetrics and Gynaecology, The University of Western Australia, Perth, Western Australia/Australia 6009, Australia. [299]Department of kinesiology, Laval University, Quebec, QC G1V 0A6, Canada. [300]Institute of Nutrition and Functional Foods, Laval University, Quebec, QC G1V 0A6, Canada. [301]Institute of Genetic and Biomedical Research - Support Unity, National Research Council of Italy, Sassari 07100, Italy. [302]Department of Clinical Genetics, Amsterdam Neuroscience, VU Medical Centre, Amsterdam 1081HV, The Netherlands. [303]Cardiovascular Health Research Unit, Departments of Epidemiology, Medicine and Health Services, University of Washington, Seattle, WA 98101, USA. [304]Kaiser Permanente Washington Health Research Institute, Seattle, WA 98101, USA. [305]Department of Medicine, Faculty of Medicine, Université de Montréal, Montreal, Quebec H3T 1J4, Canada. [306]Laboratory of Experimental Cardiology, Division Heart & Lungs, University Medical Center Utrecht, University of Utrecht, Utrecht, Utrecht 3584 CX, Netherlands. [307]Oklahoma Center for Neuroscience, Oklahoma City, OK 73104, USA. [308]Institute of Nutritional Sciences, University of Potsdam, Nuthetal, Germany. [309]Deutsches Zentrum für Herz- und Kreislauferkrankungen (DZHK), Munich Heart Alliance, Munich 80636, Germany. [310]Regeneron Genetics Center, Regeneron Pharmaceuticals, Inc, Tarrytown, NY 10591-6607, USA. [311]Faculty of Health Studies, University of Bradford, Bradford, West Yorkshire BD7 1DP, UK. [312]Cardiovascular Health Research Unit, Division of Cardiology, University of Washington, Seattle, WA 98101, USA. [313]Duke-NUS Medical School, National University of Singapore, Singapore, Singapore 169857 SG, Singapore. [314]Institute for Community Medicine, University Medicine Greifswald, Greifswald 17475, Germany. [315]Department of Population Health Sciences, Bristol Medical School, University of Bristol, Bristol BS8 2PR, UK. [316]Avon Longitudinal Study of Parents and Children (ALSPAC), University of Bristol, Bristol BS8 2PR, UK. [317]Endocrinology, Abdominal Centre, University of Helsinki, Helsinki University Hospital, Helsinki, Finland. [318]Folkhalsan Research Center, Helsinki, Finland. [319]Research Program of Diabetes and Endocrinology, University of Helsinki, Helsinki, Finland. [320]Department of Medicine, Internal Medicine, Lausanne University Hospital, Lausanne 1011, Switzerland. [321]Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital of Philadelphia, Philadelphia, PA 19146, USA. [322]Unit of Genomics and Biomarkers, National Institute for Health and Welfare, Helsinki 00271, Finland. [323]National Heart and Lung Institute, Imperial College London, London W12 0NN, UK. [324]The Mindich Child Health and Development Institute, The Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA. [325]Roslin Institute and Royal (Dick) School of Veterinary Studies, University of Edinburgh, Easter Bush, Midlothian EH25 9RG, Scotland. [326]Program in Medical and Population Genetics, Broad Institute, Broad Institute, Cambridge, MASSACHUSETTS 02142, USA. [327]Deceased: Yucheng Jia, John M. Starr.

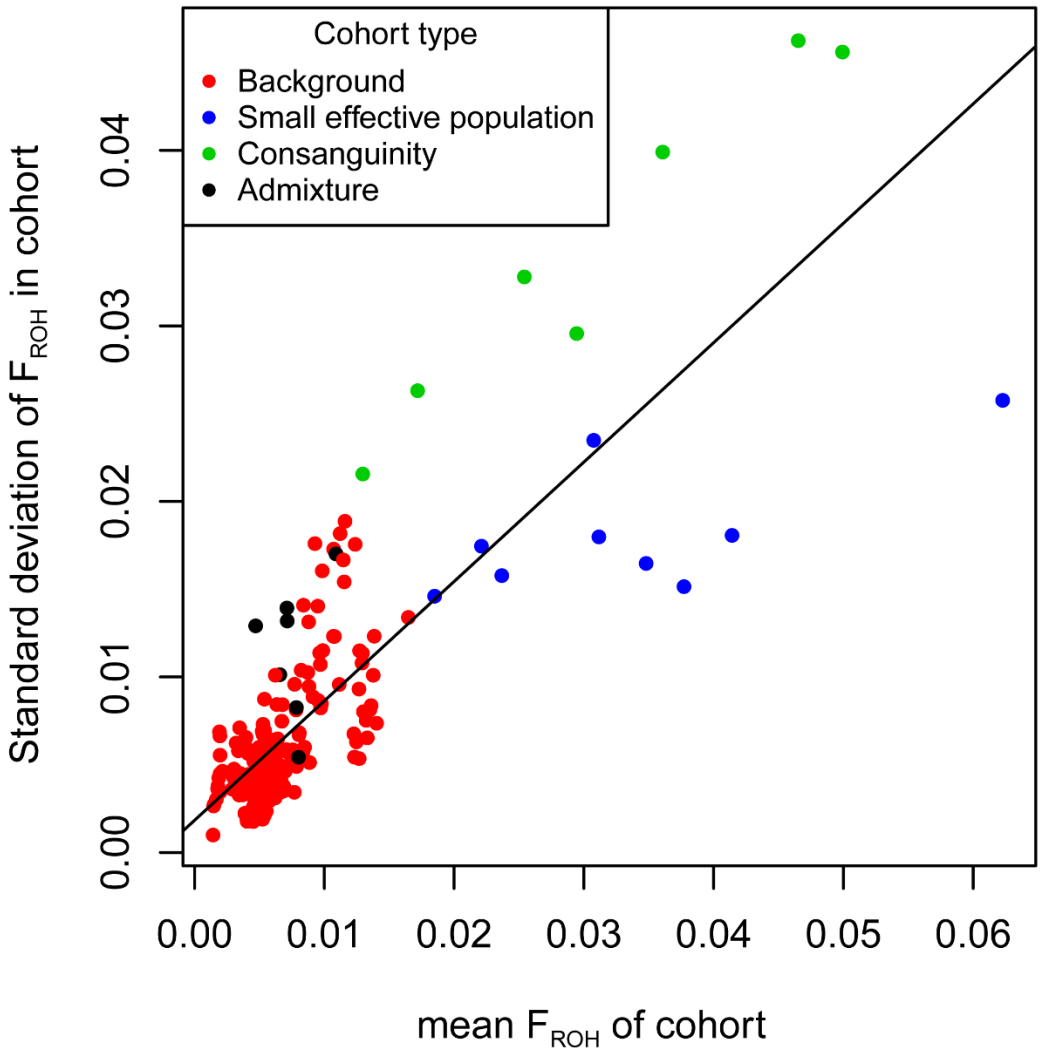
SUPPLEMENTARY FIGURES



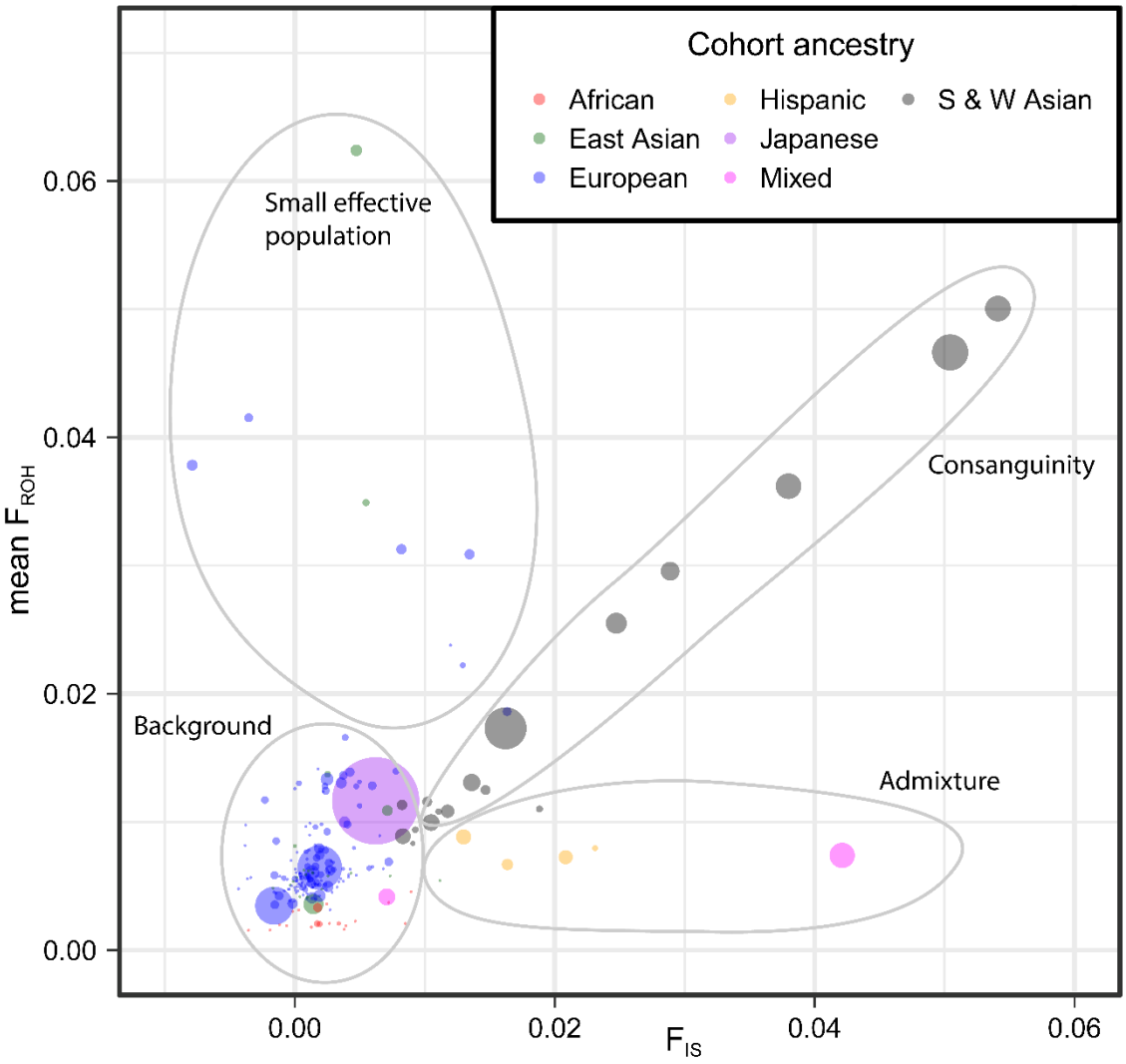
Supplementary Figure 1: Effect of F_{ROH} on height is robust to stratification by ancestral group. Cohorts were divided into eight broad ancestral groups (Supplementary Data Table 1) and meta-analysed separately. Although some heterogeneity is observed (heterogeneity *p*-value = 3 x 10^{-4}), $\beta_{F_{\mathrm{ROH}}}$ is directionally consistent and differs significantly from 0 in all ancestral groups. All errors bars represent 95% confidence intervals.



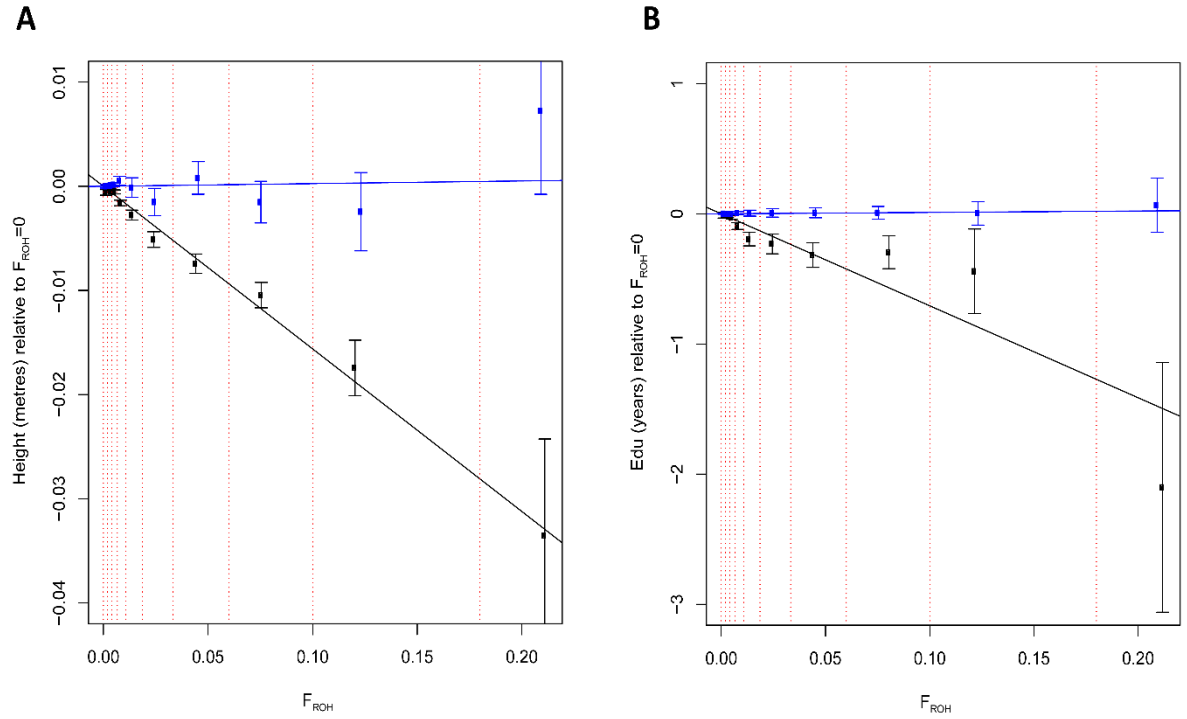
Supplementary Figure 2: Effect of F_{ROH} on height is robust to stratification by inferred demographic history. Cohorts were divided by inferred demographic history (Supplementary Fig. 4, Supplementary Data Table 1) and meta-analysed separately. A small amount of heterogeneity is observed (heterogeneity *p*-value = 0.008), but $\beta_{F_{\mathrm{ROH}}}$ 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, $\beta_{F_{\mathrm{ROH}}}$ [-0.15, 95% CI -0.07 -0.23, *p*-value 3 x 10^{-4}] is consistent with the global estimate. All errors bars represent 95% confidence intervals.



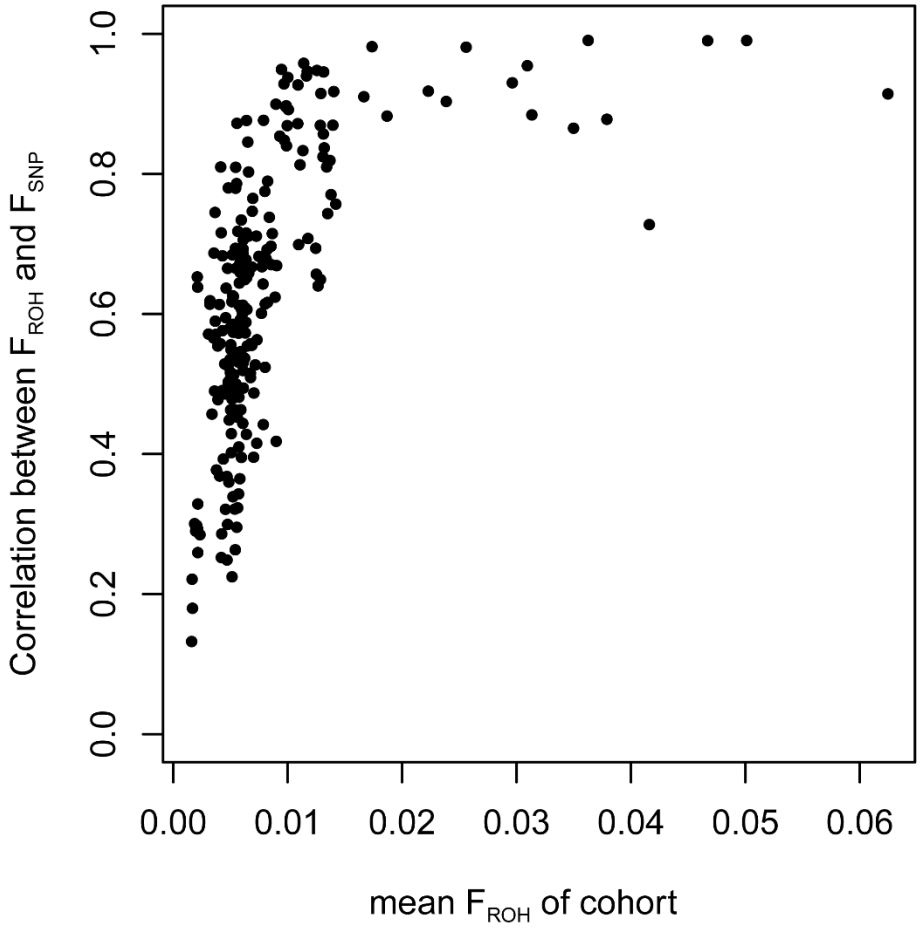
Supplementary Figure 3: A strong correlation (r=0.82, p-value = 9 x 10^{-103}) is observed between $\sigma_{F_{\mathrm{ROH}}}$ and mean F_{ROH}. The standard deviation of F_{ROH} ($\sigma_{F_{\mathrm{ROH}}}$) is plotted against mean F_{ROH} for all cohorts. In regressions on F_{ROH} the statistical power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



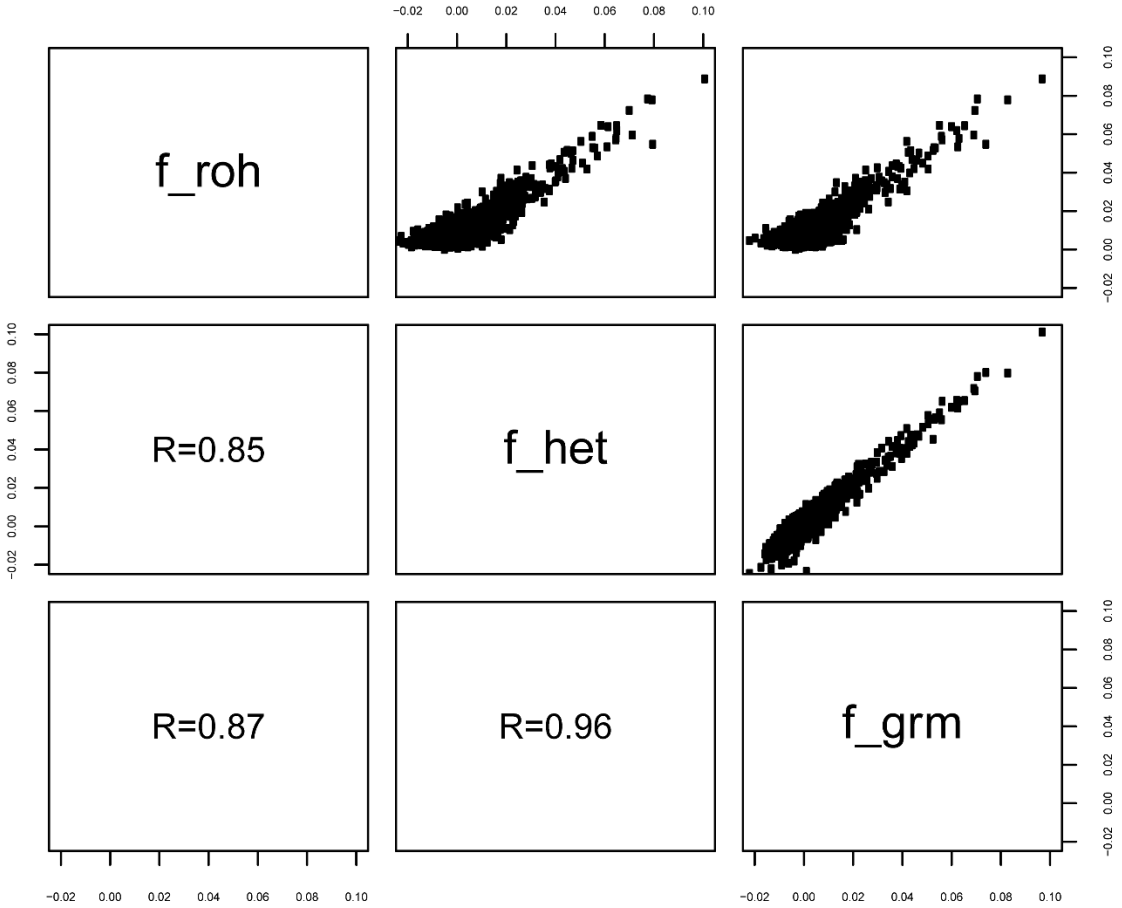
Supplementary Figure 4: Assignment of cohorts to one of four inferred demographic histories. Fig. 2 is replicated (see also Fig. 2 legend) and used to empirically assign cohorts to one of four inferred demographic histories. In cohorts where $F_{IS} > 0.1$, but the Cartesian distance to the 1:1 line 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 consider 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*.



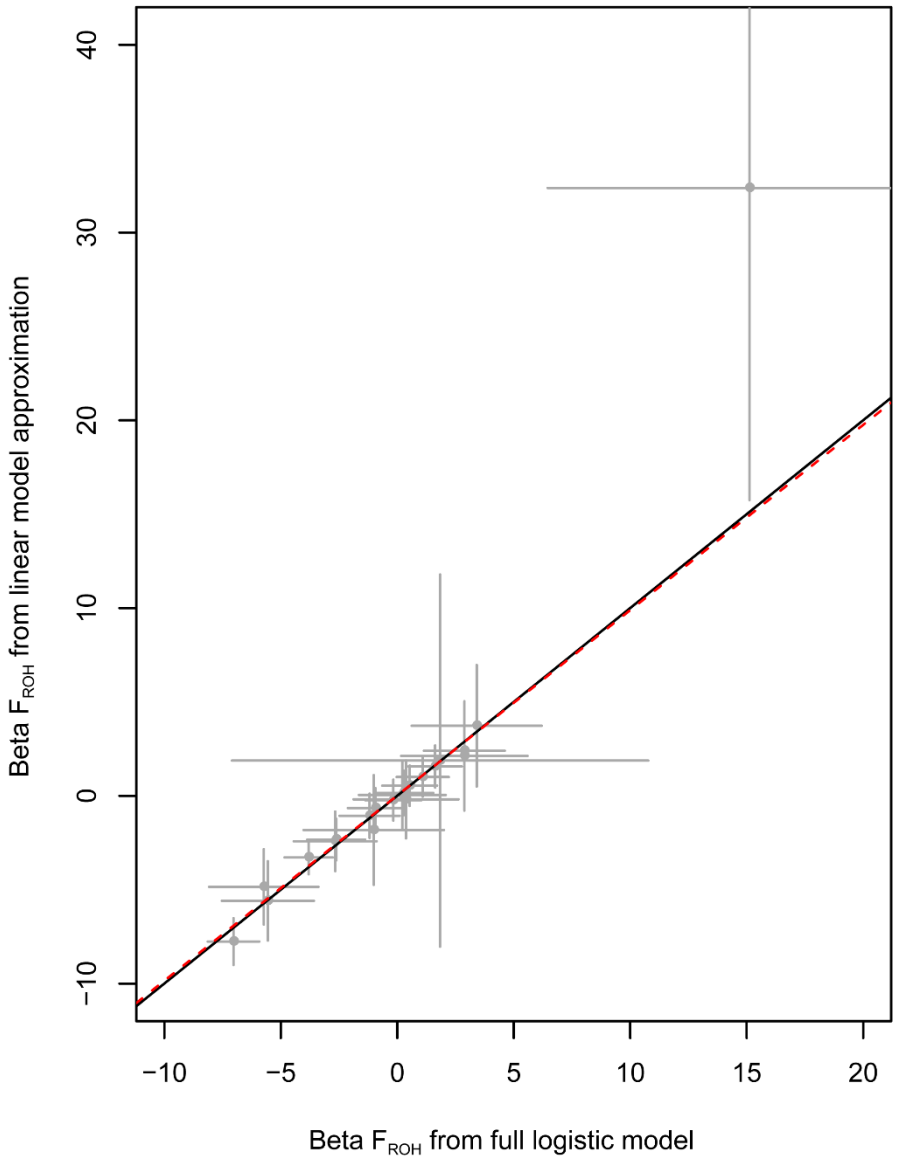
Supplementary Figure 5: Effect of assortative mating on height and educational attainment (a): Linear decrease in height with increasing F_{ROH} but no decrease in a polygenic score for height. In black, average height (in metres) is plotted in bins of increasing F_{ROH}. In blue, averages of a polygenic 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_{ROH} and F_{SNP} are observed in cohorts with high average F_{ROH}. The correlation between F_{ROH} and F_{SNP} is plotted against mean F_{ROH} for all cohorts. In low autozygosity cohorts the correlation between F_{ROH} and F_{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_{ROH} and F_{SNP} is stronger.

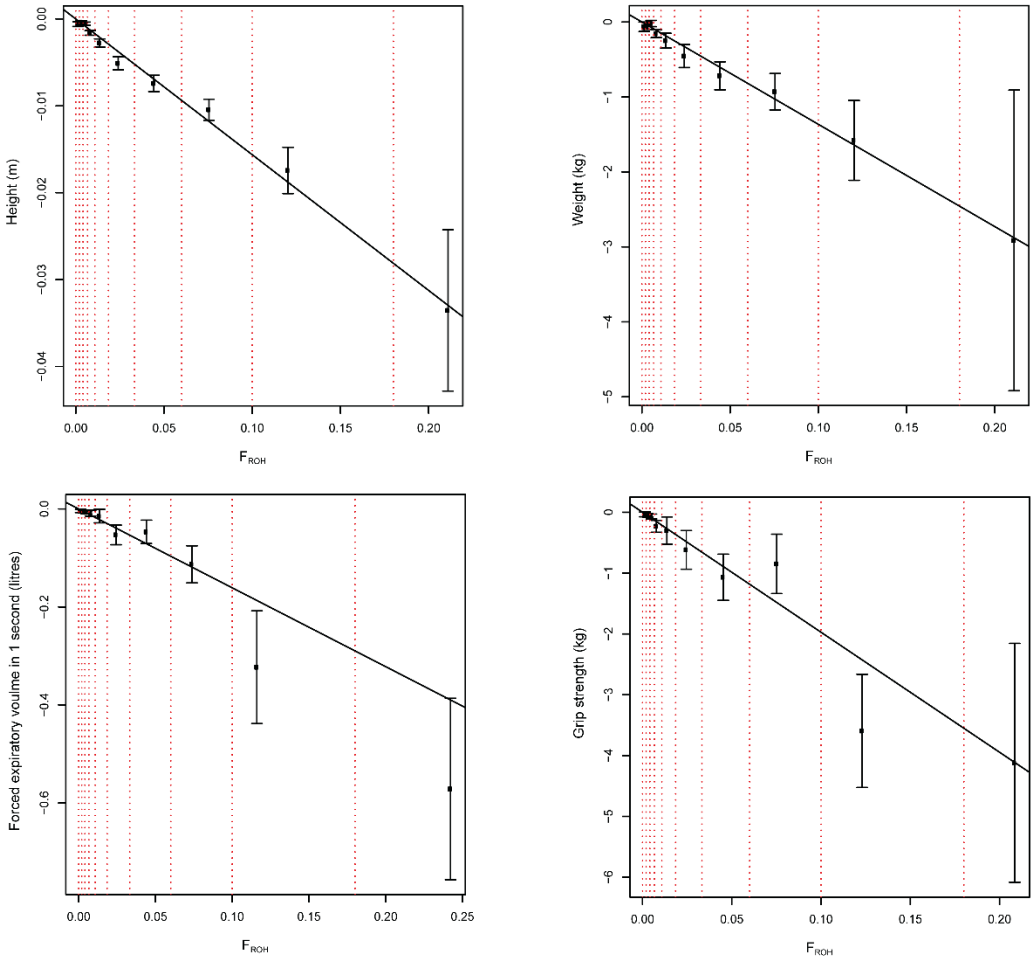


Supplementary Figure 7: Scatter plots of F_{ROH} plotted against F_{SNP} and F_{GRM} in a single cohort (VIKING). Scatter plots of three estimates of inbreeding coefficient (F_{ROH}, F_{SNP} and F_{GRM}) are shown in the upper right panels. The correlation between these estimates is shown in the lower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

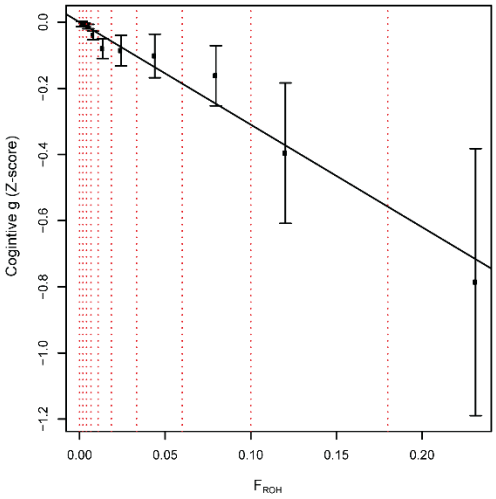


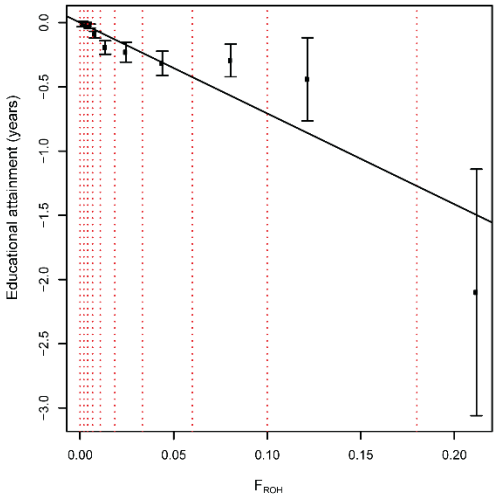
Supplementary Figure 8: A linear model approximation of the full logistic model gives relatively unbiased estimates of $\boldsymbol{\beta}_{\boldsymbol{F}_{\mathbf{ROH}}}$. For all 22 binary traits analysed, estimates obtained from a two-step linear model approximation are plotted against estimates obtained from the full logistic model (See Methods). Estimates of $\boldsymbol{\beta}_{\boldsymbol{F}_{\mathbf{ROH}}}$ 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 $\boldsymbol{\beta}_{\boldsymbol{F}_{\mathbf{ROH}}}$. 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 $\boldsymbol{\beta}_{\boldsymbol{F}_{\mathbf{ROH}}}$. 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.

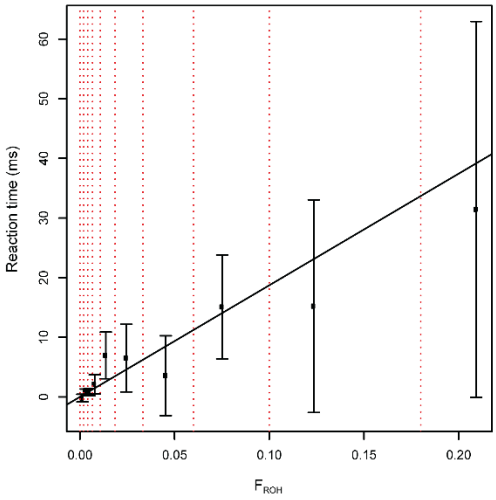
9a


Height (m)
0.00
−0.01
−0.02
−0.03
−0.04
0.00
0.05
0.10
0.15
0.20
F_ROH
Weight (kg)
0
−1
−2
−3
−4
−5
0.00
0.05
0.10
0.15
0.20
F_ROH
Forced expiratory voulme in 1 second (litres)
0.0
−0.2
−0.4
−0.6
0.00
0.05
0.10
0.15
0.20
0.25
F_ROH
Grip strength (kg)
0
−1
−2
−3
−4
−5
−6
0.00
0.05
0.10
0.15
0.20
F_ROH

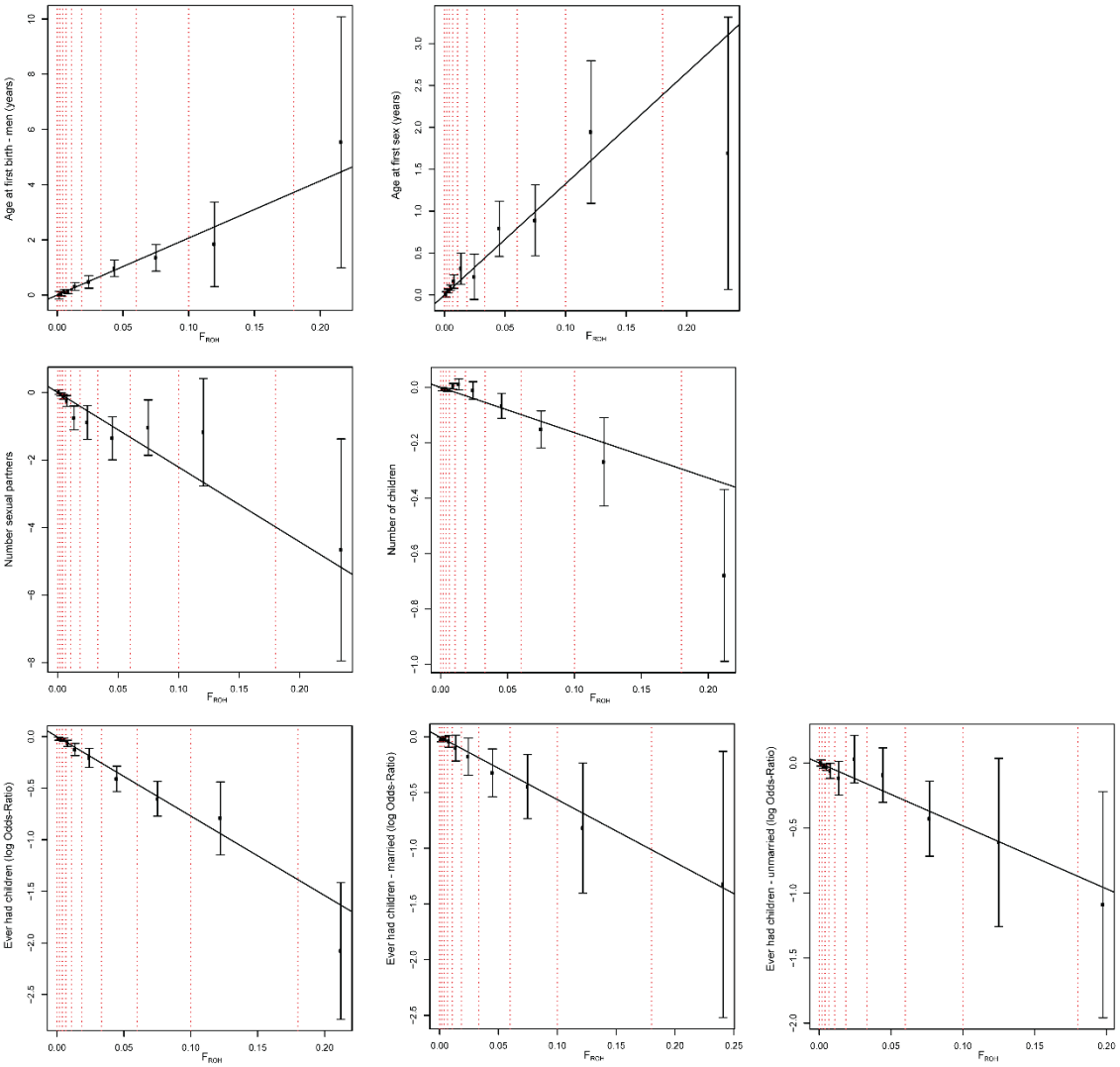
9b


Cogintive g (Z-score)
0.0
−0.2
−0.4
−0.6
−0.8
−1.0
−1.2
0.00
0.05
0.10
0.15
0.20
F_ROH

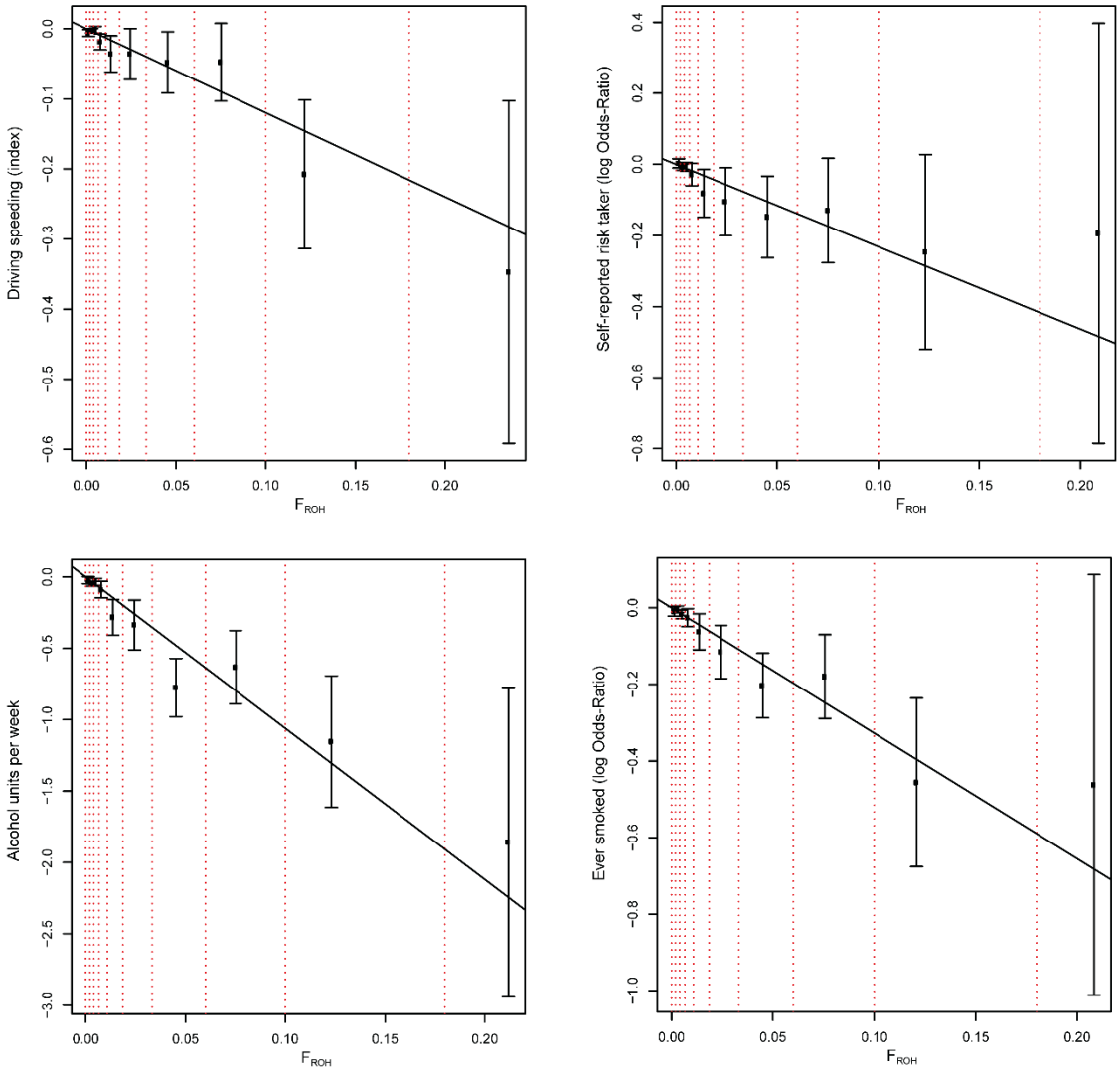

Educational attainment (years)
0.0
−0.5
−1.0
−1.5
−2.0
−2.5
−3.0
0.00
0.05
0.10
0.15
0.20
F_ROH


Reaction time (ms)
60
50
40
30
20
10
0
0.00
0.05
0.10
0.15
0.20
F_ROH

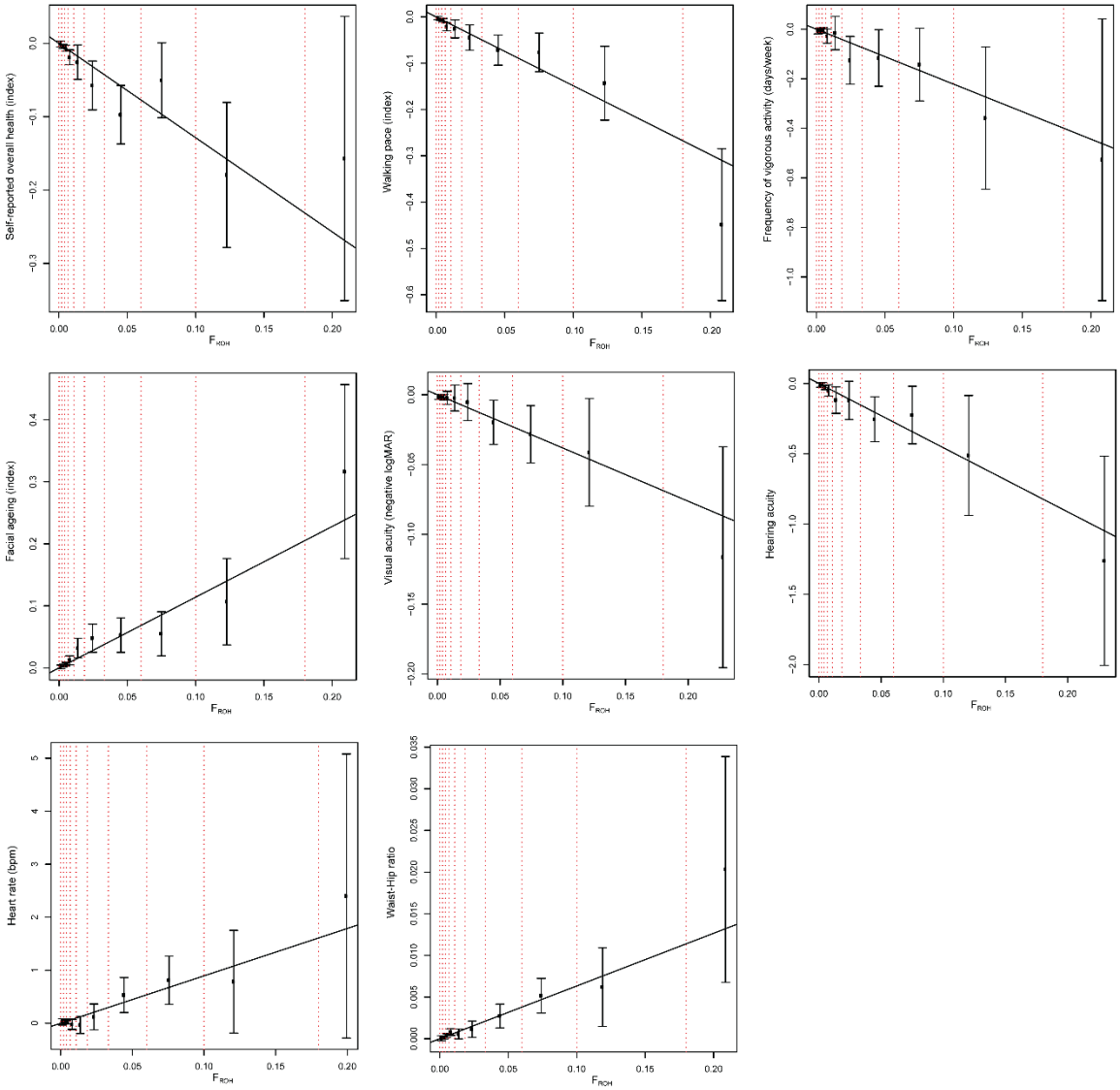
9c


Age at first birth - men (years)
Age at first sex (years)
Number sexual partners
Number of children
Ever had children (log Odds-Ratio)
Ever had children - married (log Odds-Ratio)
Ever had children - unmarried (log Odds-Ratio)
F_ROH

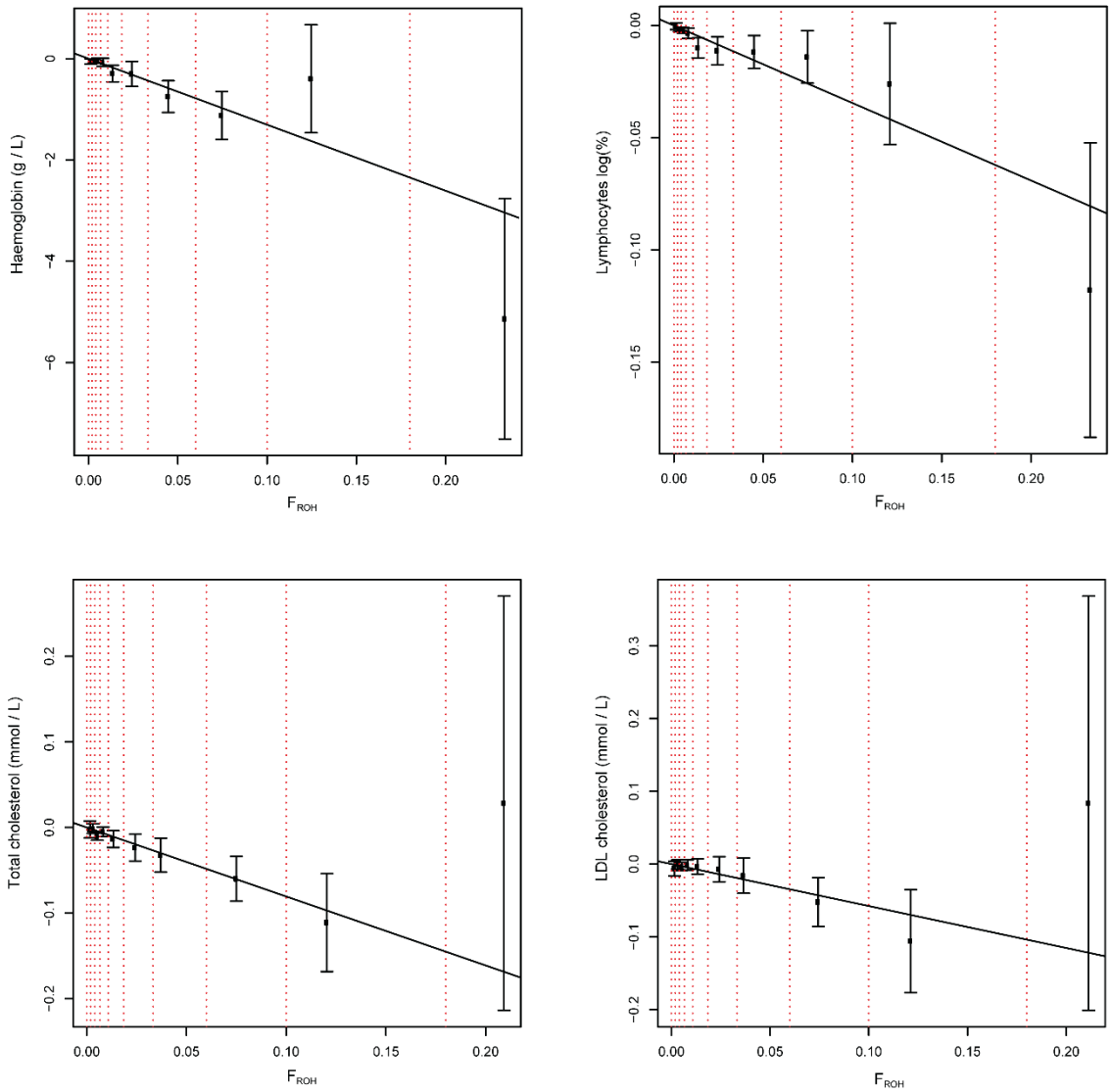
9d


Driving speeding (index)
Self-reported risk taker (log Odds-Ratio)
Alcohol units per week
Ever smoked (log Odds-Ratio)
F_ROH
0.00
0.05
0.10
0.15
0.20

9e

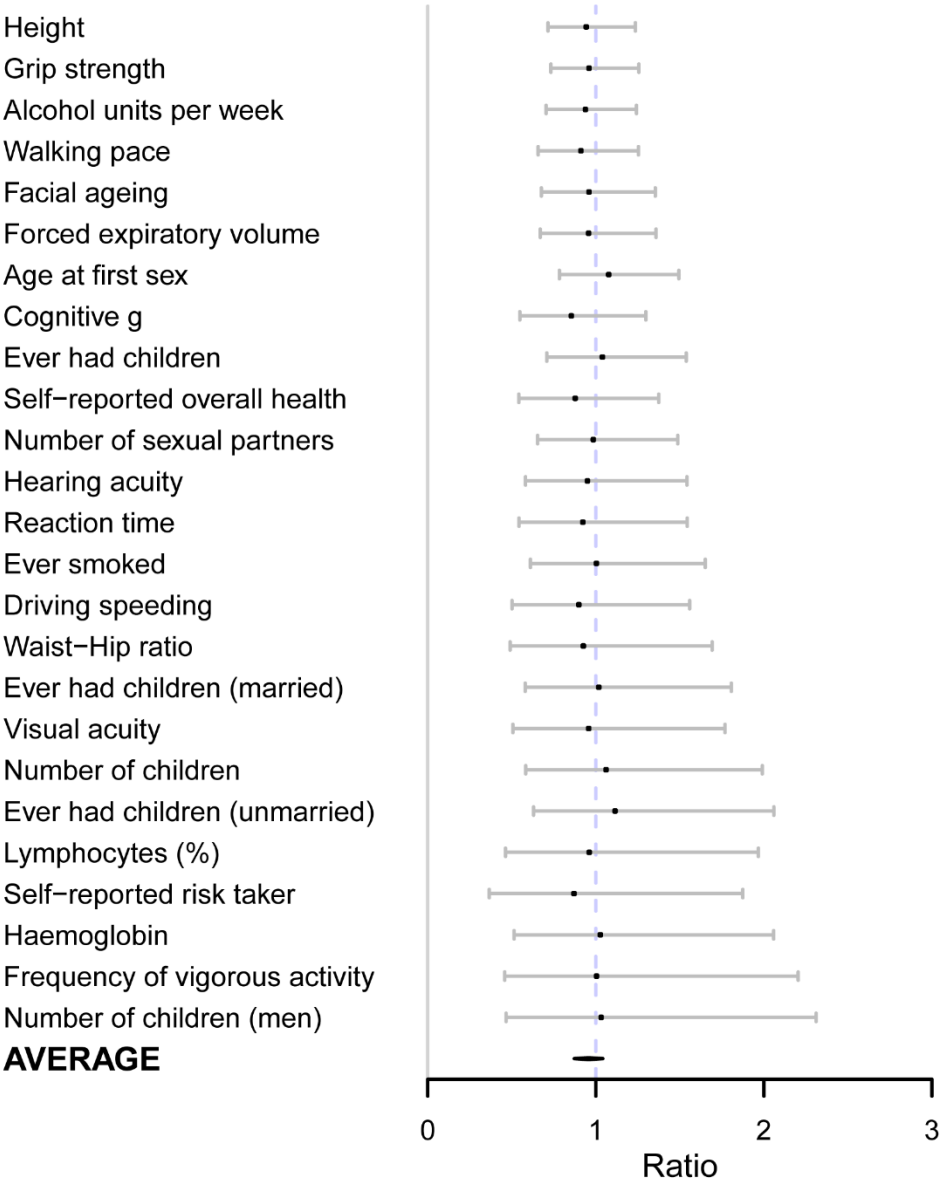

Self-reported overall health (index)
Walking pace (index)
Frequency of vigorous activity (days/week)
Facial ageing (index)
Visual acuity (negative logMAR)
Hearing acuity
Heart rate (bpm)
Waist-Hip ratio
F_ROH

9f

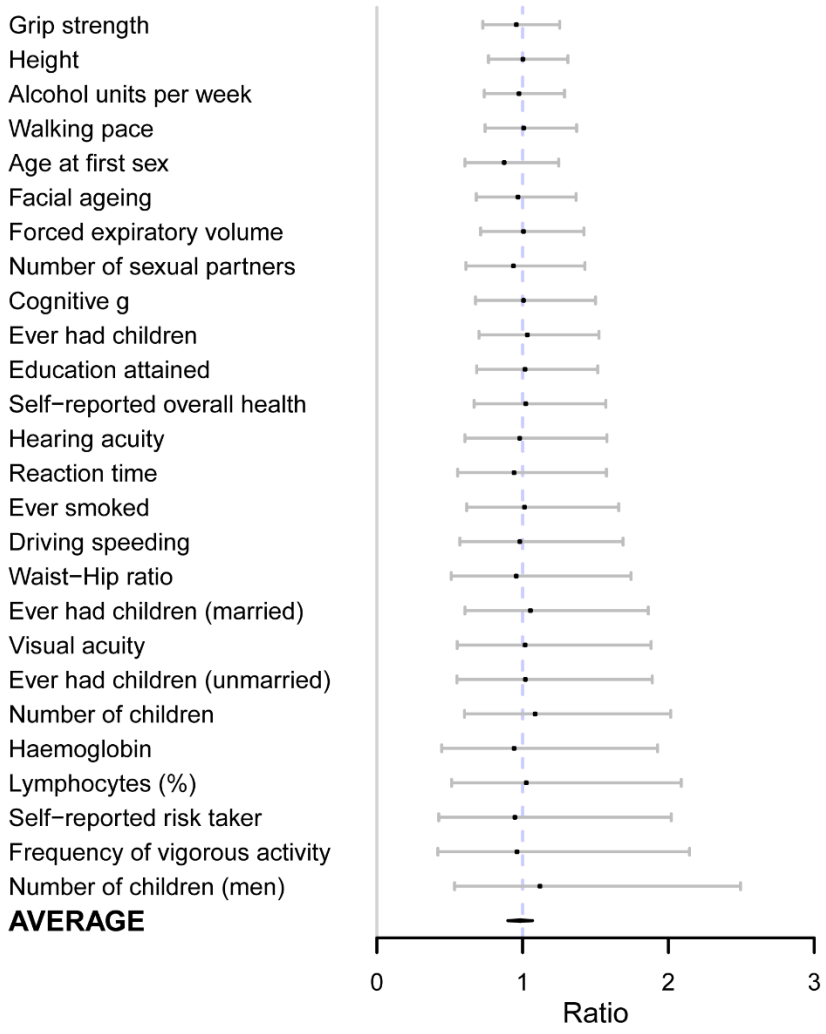


Supplementary Figure 9: Significant traits show a dosed response to increasing F_{ROH}. For all traits that reach experiment-wise significance in the meta-analysis, mean trait residuals are plotted in bins of increasing F_{ROH} (Methods) as also shown for height and Ever had children in Fig. 5a, b. Traits 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 x 10^{-8}, Educational Attainment heterogeneity *p*-value = 2 x 10^{-8}, Number ever born heterogeneity *p*-value = 7 x 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

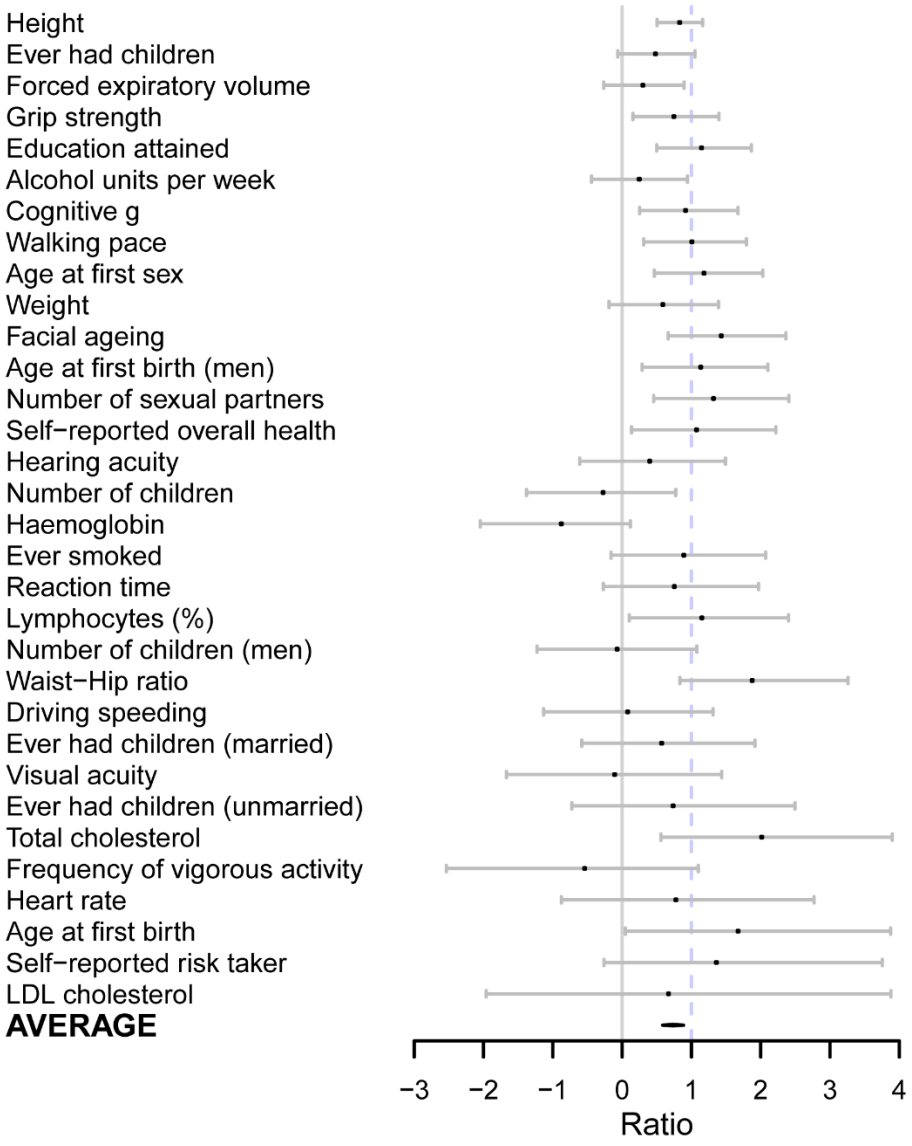

Height
Grip strength
Alcohol units per week
Walking pace
Facial ageing
Forced expiratory volume
Age at first sex
Cognitive g
Ever had children
Self−reported overall health
Number of sexual partners
Hearing acuity
Reaction time
Ever smoked
Driving speeding
Waist−Hip ratio
Ever had children (married)
Visual acuity
Number of children
Ever had children (unmarried)
Lymphocytes (%)
Self−reported risk taker
Haemoglobin
Frequency of vigorous activity
Number of children (men)
AVERAGE
0
1
2
3
Ratio

10b

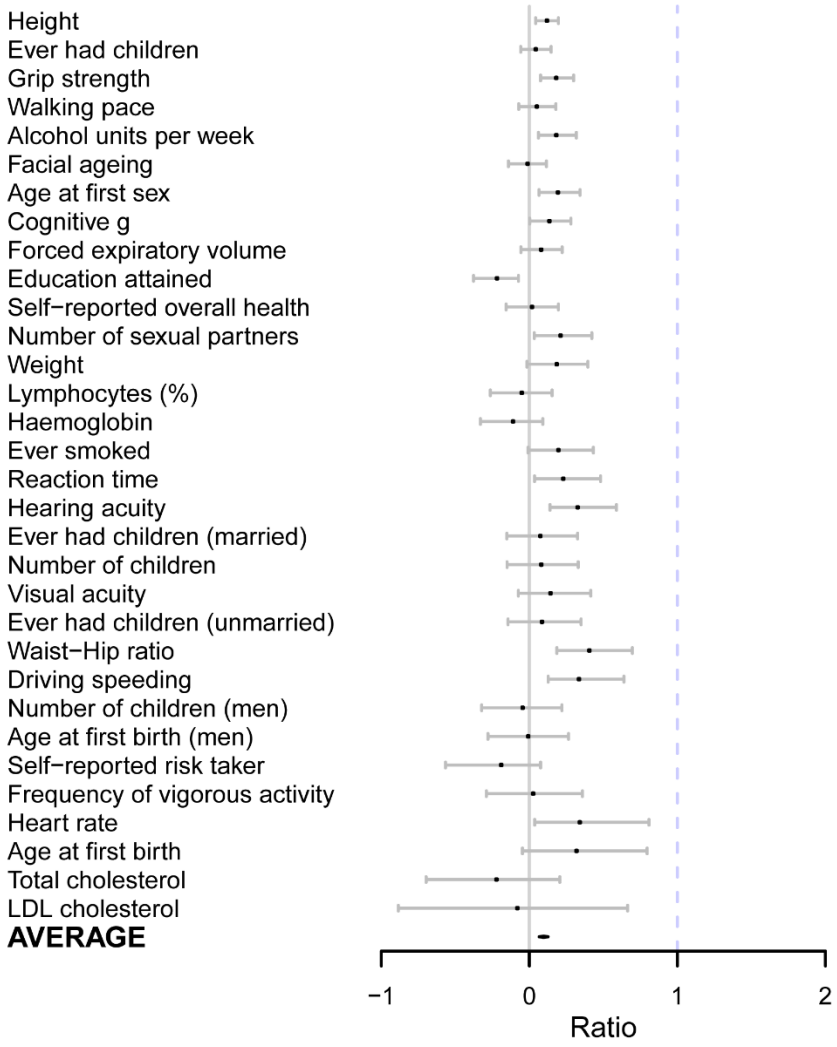


Supplementary Figure 10: Effect of fitting potential confounders as covariates. (a) Educational Attainment. For all traits that reach significance in UK Biobank, the ratio of effect size estimates with Educational Attainment (EA) fitted as an additional covariate ($\beta_{F_{\mathrm{ROH}}}^{+\mathrm{EA}}$) to the corresponding effect size estimates without EA ($\beta_{F_{\mathrm{ROH}}}$) are shown. The largest change is seen in Cognition (g) where fitting EA reduces $\beta_{F_{\mathrm{ROH}}}$ 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 $\beta_{F_{\mathrm{ROH}}}$ 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 ($\beta_{F_{\mathrm{ROH}}}^{+\mathrm{R}}$) to the corresponding effect size estimates without religious participation ($\beta_{F_{\mathrm{ROH}}}$) are shown. The largest reductions in $\beta_{F_{\mathrm{ROH}}}$ 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 $\beta_{F_{\mathrm{ROH}}}$ for 14 of 26 traits, again including number and likelihood of having children. All errors bars represent 95% confidence intervals.

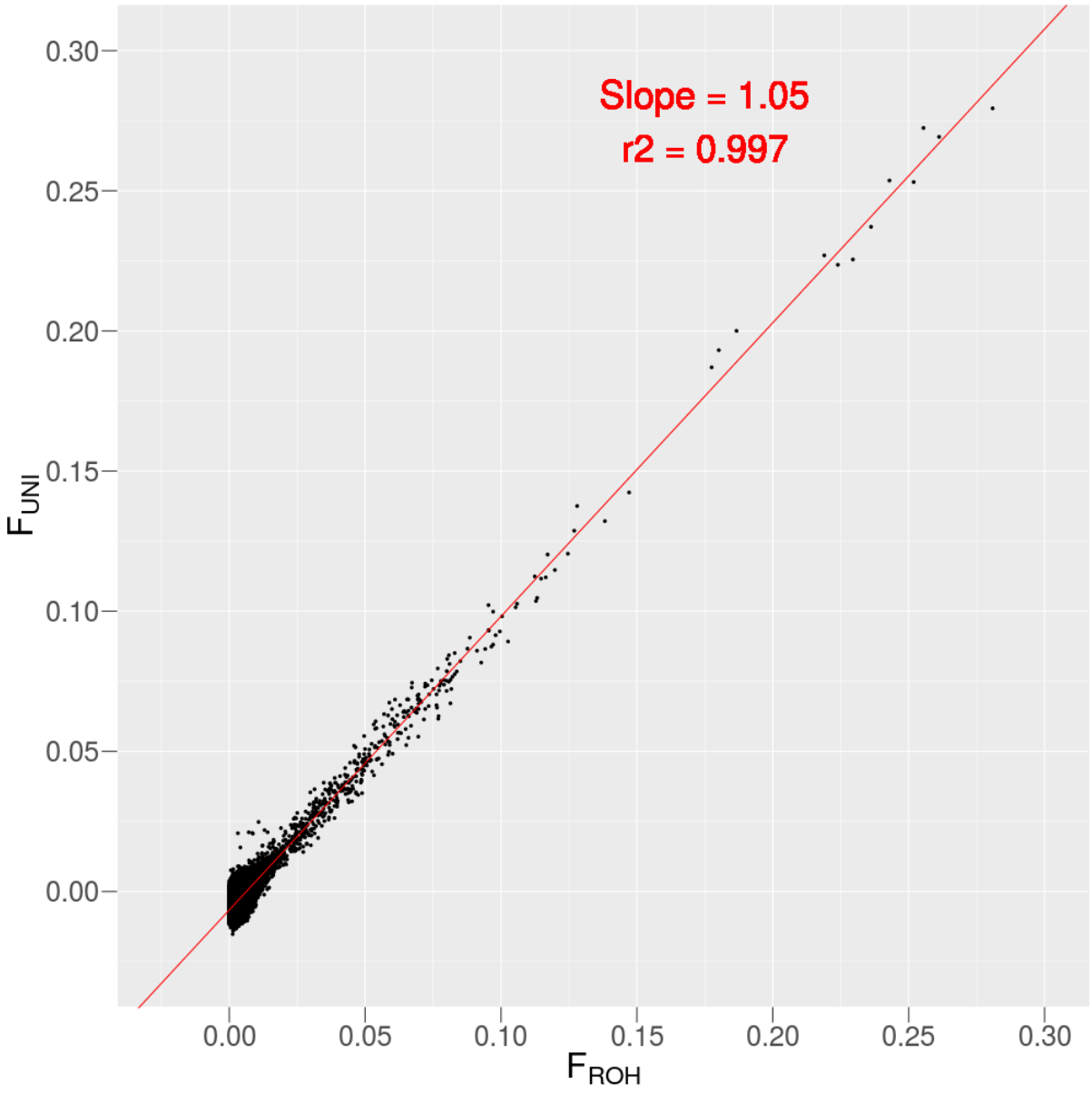
11a


Height
Ever had children
Forced expiratory volume
Grip strength
Education attained
Alcohol units per week
Cognitive g
Walking pace
Age at first sex
Weight
Facial ageing
Age at first birth (men)
Number of sexual partners
Self−reported overall health
Hearing acuity
Number of children
Haemoglobin
Ever smoked
Reaction time
Lymphocytes (%)
Number of children (men)
Waist−Hip ratio
Driving speeding
Ever had children (married)
Visual acuity
Ever had children (unmarried)
Total cholesterol
Frequency of vigorous activity
Heart rate
Age at first birth
Self−reported risk taker
LDL cholesterol
AVERAGE
−3
−2
−1
0
1
2
3
4
Ratio

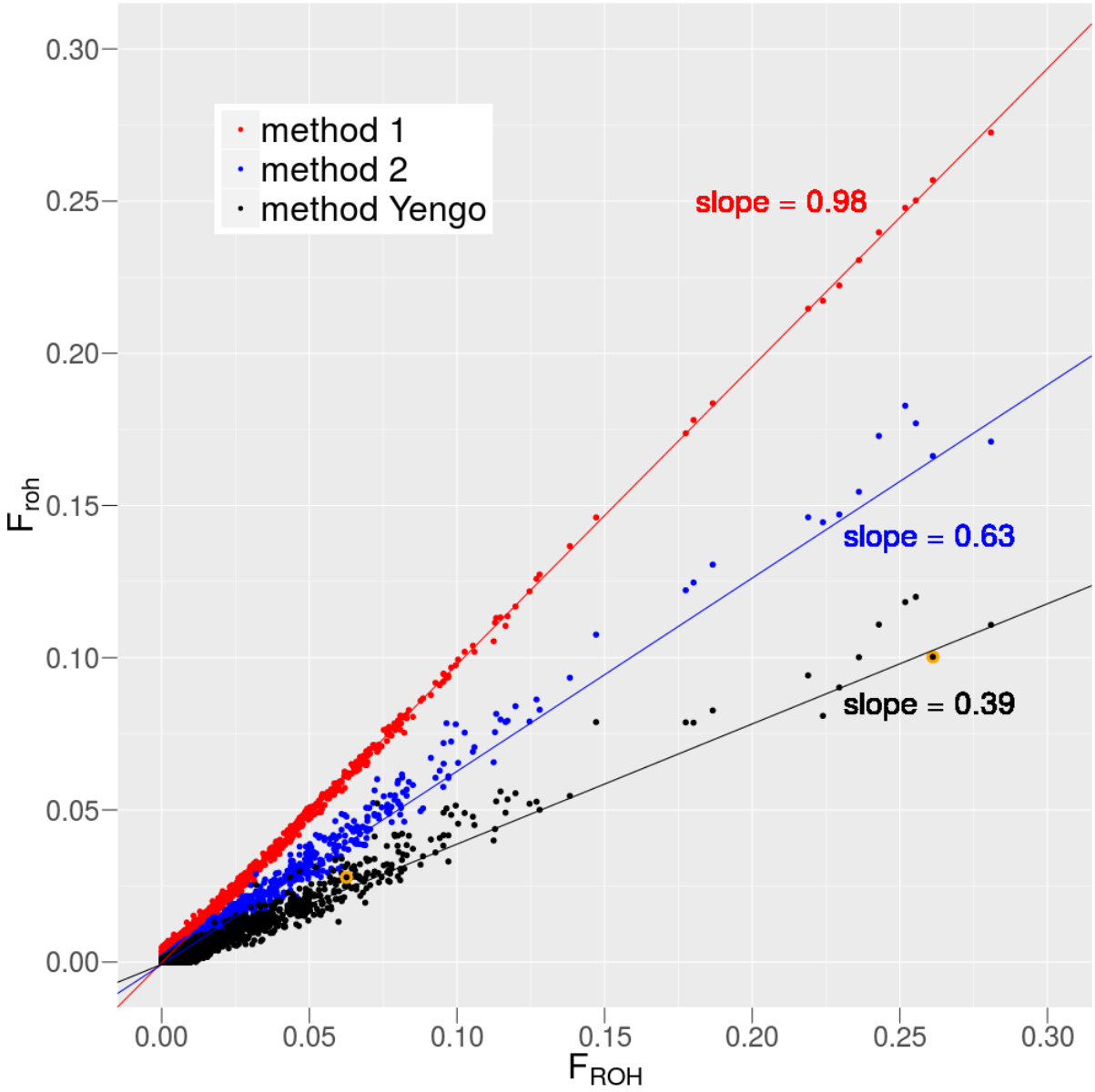
11b



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: $F_{\text{SNP\_OusideROH}}$, $F_{\text{ROH<5Mb}}$ and $F_{\text{ROH>5Mb}}$ (See Methods). **(a) Relative effect of ROH < 5Mb**. The conditional effect of $F_{\text{ROH<5Mb}}$ 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 x 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 $F_{\text{SNP\_OusideROH}}$ 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 $F_{\text{SNP\_OusideROH}}$ is significantly less than the effect of F_{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 x 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.

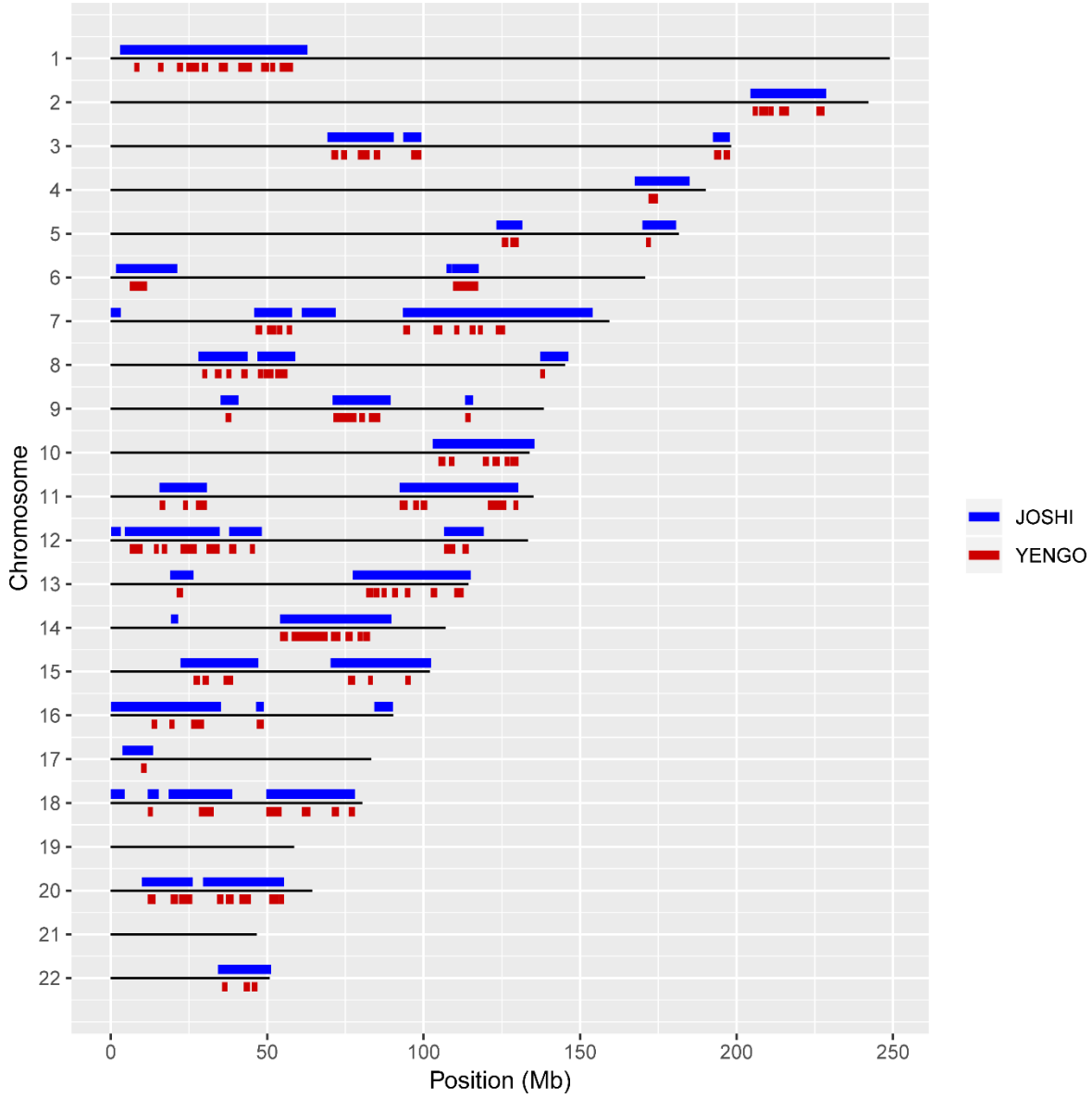


Supplementary Figure 12: Good correspondence between F_{UNI} and F_{ROH}. For 141,774 British samples in UK Biobank F_{UNI}, calculated from excess homozygosity of imputed genotypes, is plotted against F_{ROH}, calculated from SNP array genotypes. A weighted linear regression line is shown in red. Because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

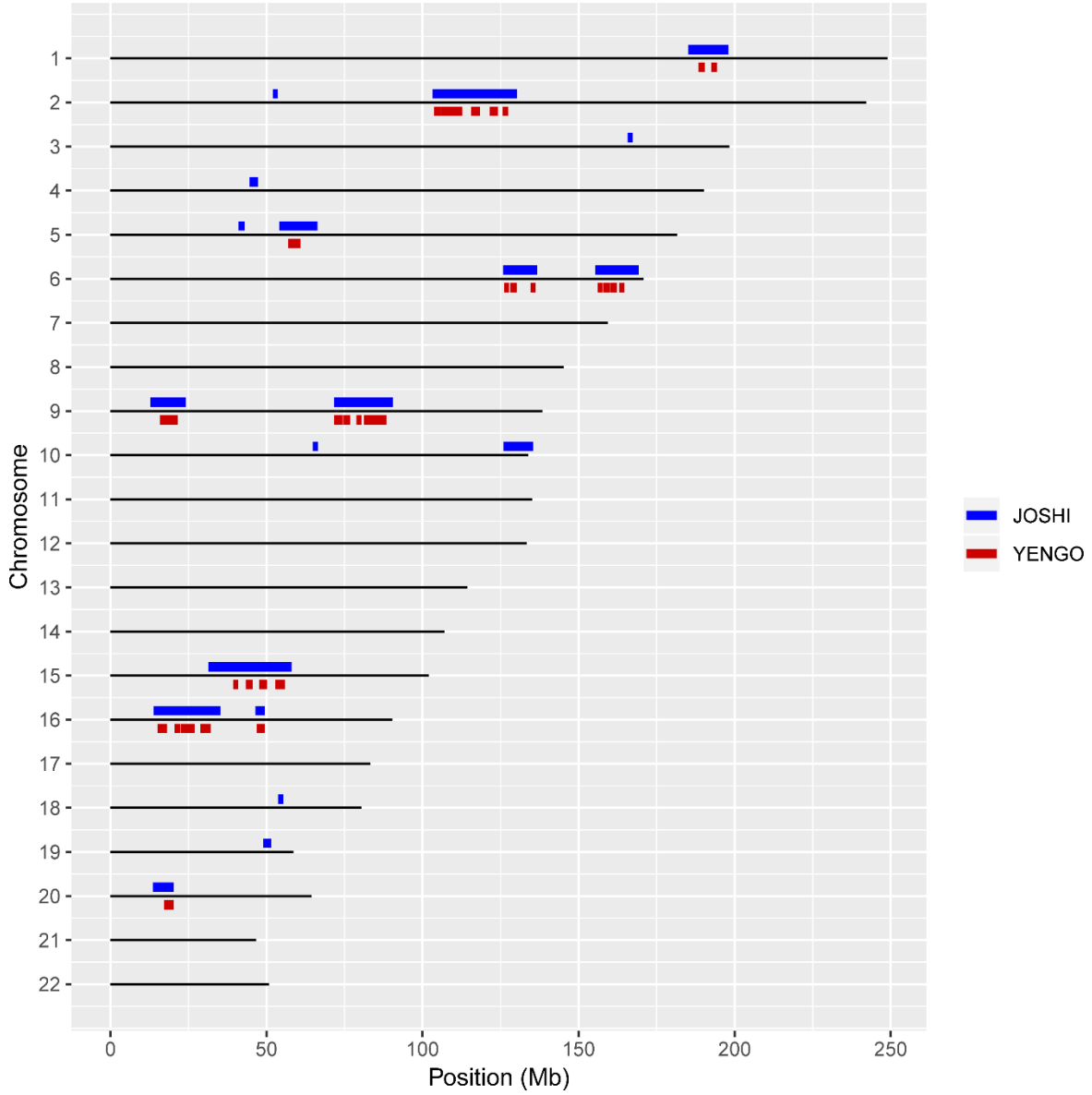


Supplementary Figure 13: Comparison of F_{roh} from imputed data and F_{ROH} from SNP array genotypes. For 141,774 British samples in UK Biobank, F_{roh} calculated from imputed genotypes is plotted against F_{ROH} calculated from SNP array genotypes for three methods of imputed genotype preparation. 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

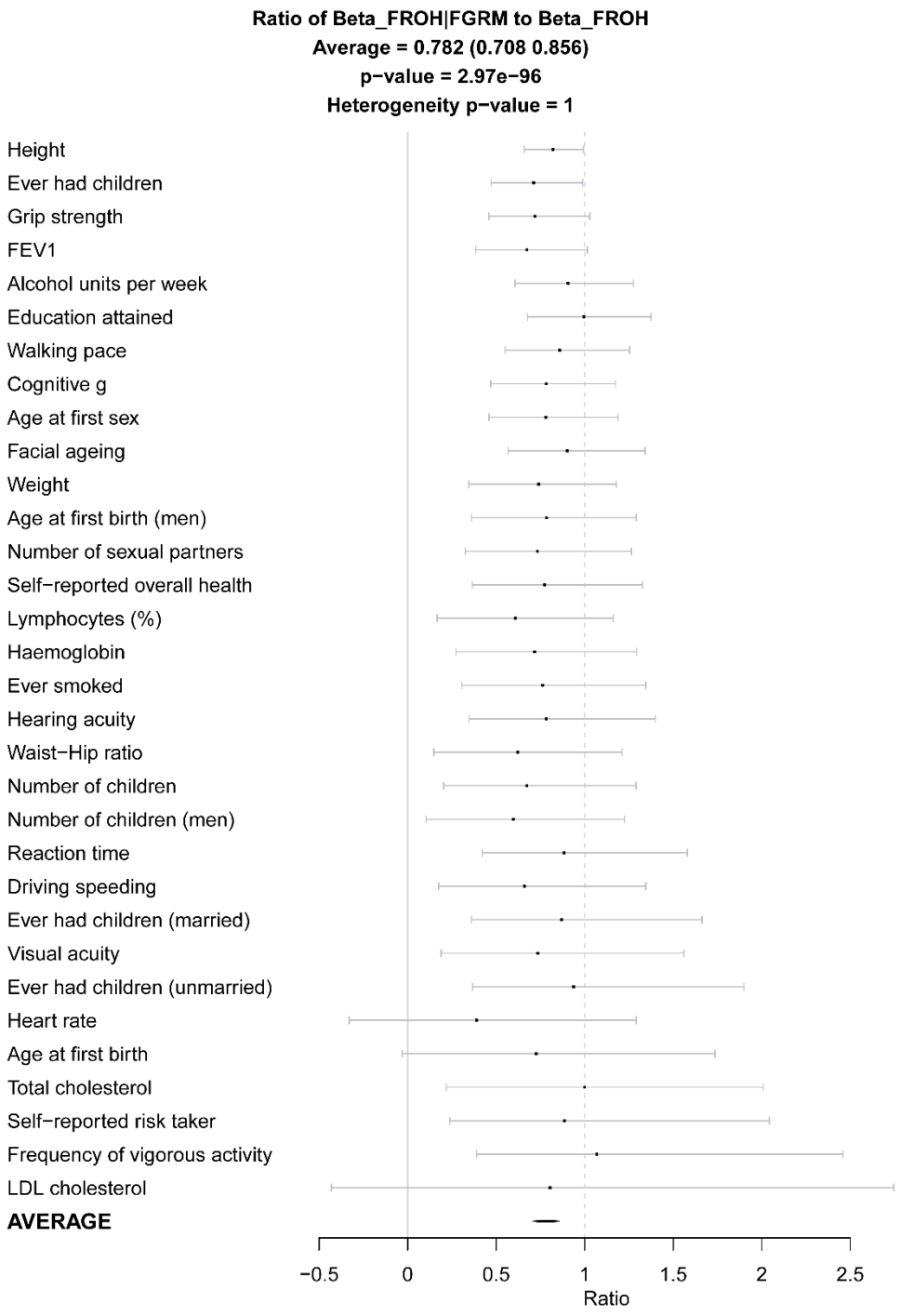

Chromosome
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
0
50
100
150
200
250
Position (Mb)
JOSHI
YENGO

14b

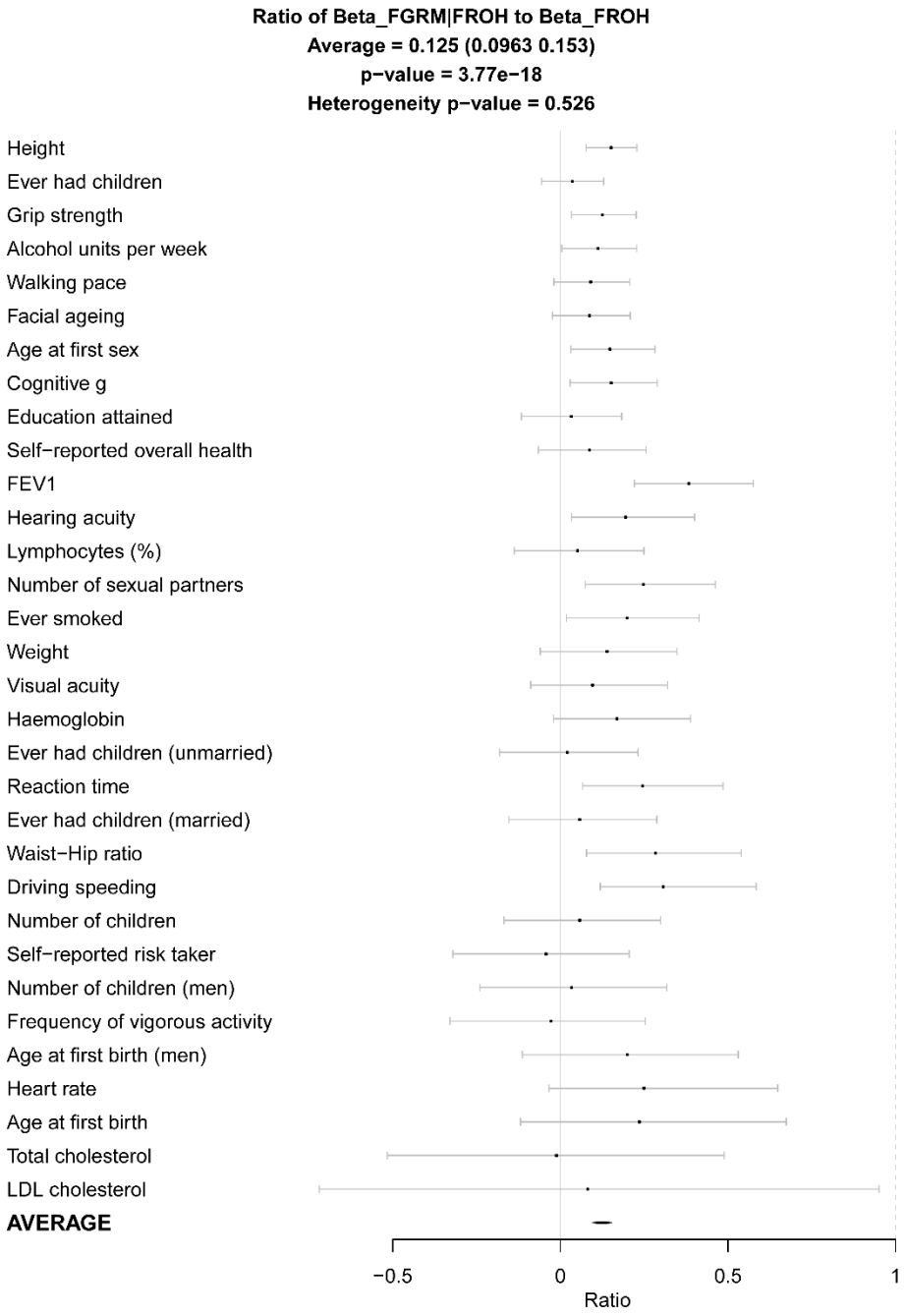


Supplementary Figure 14: Comparing ROH calling from SNP array genotypes and imputed dosages. For two high F_{ROH} individuals, the locations of called ROH are compared for two methods. The method shown in blue calls ROH from SNP array genotypes using the parameters used in Joshi et al. (2015). The method 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 $F_{\mathrm{ROH}} = 0.261$ thought to be offspring of first-degree relatives. (b) Individual with $F_{\mathrm{ROH}} = 0.0626$ thought to be offspring of third-degree relatives.**

15a

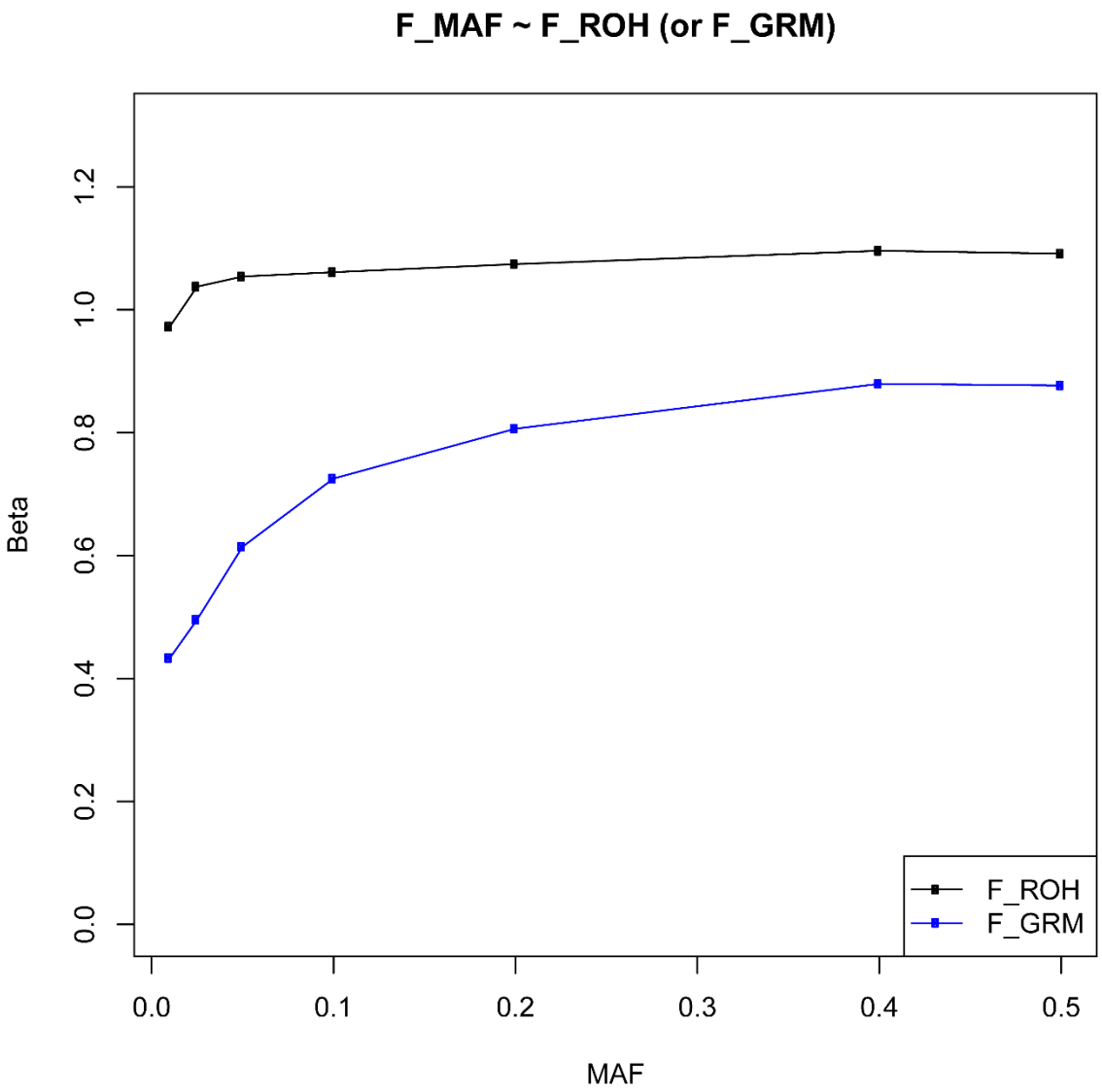

Ratio of Beta_FROH|FGRM to Beta_FROH
Average = 0.782 (0.708 0.856)
p−value = 2.97e−96
Heterogeneity p−value = 1
Height
Ever had children
Grip strength
FEV1
Alcohol units per week
Education attained
Walking pace
Cognitive g
Age at first sex
Facial ageing
Weight
Age at first birth (men)
Number of sexual partners
Self−reported overall health
Lymphocytes (%)
Haemoglobin
Ever smoked
Hearing acuity
Waist−Hip ratio
Number of children
Number of children (men)
Reaction time
Driving speeding
Ever had children (married)
Visual acuity
Ever had children (unmarried)
Heart rate
Age at first birth
Total cholesterol
Self−reported risk taker
Frequency of vigorous activity
LDL cholesterol
AVERAGE
−0.5
0
0.5
1
1.5
2
2.5
Ratio

15b

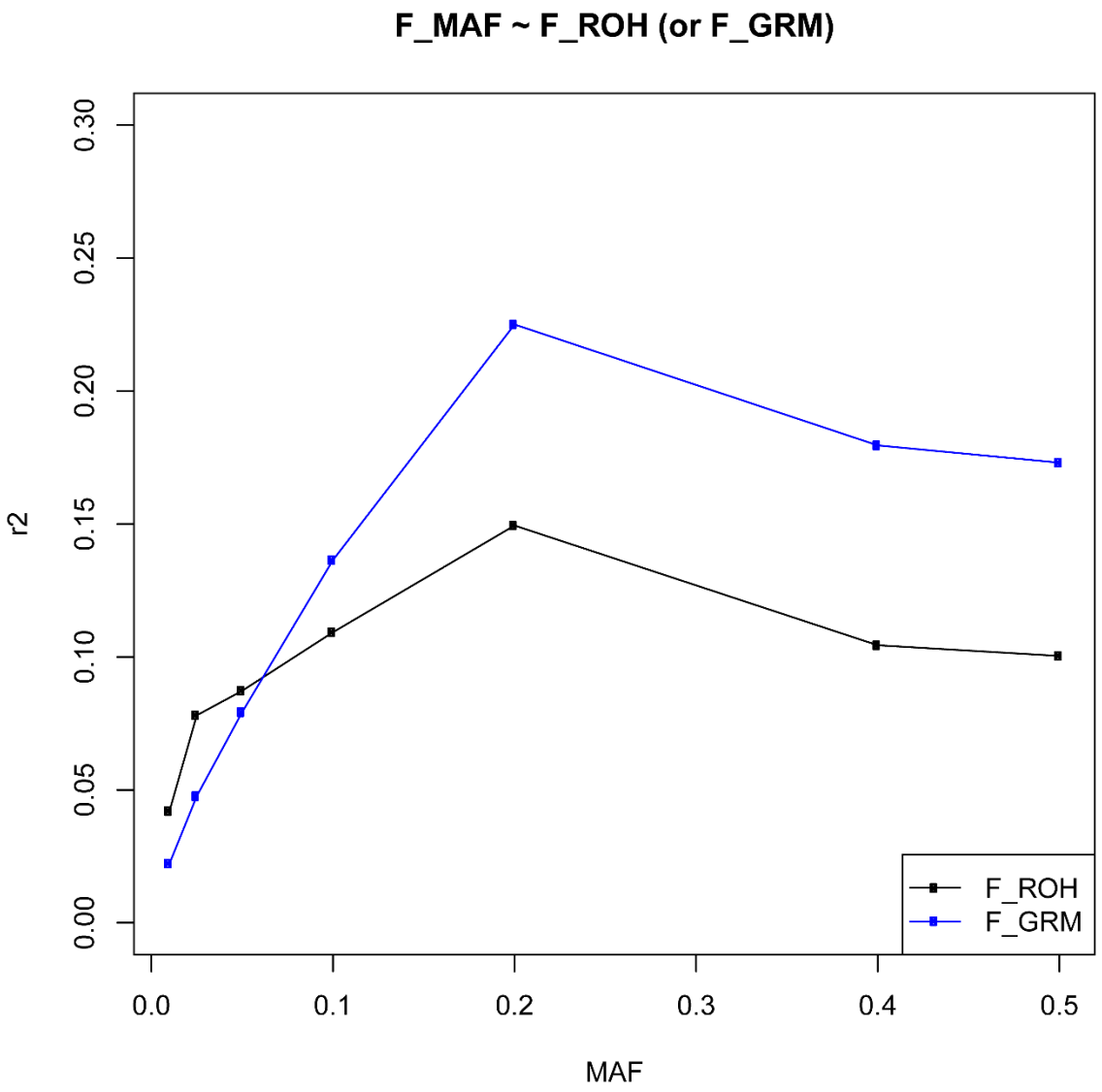


Supplementary Figure 15: Comparing effect estimates from bivariate models to the equivalent univariate estimates. For all significant traits, effect estimates were obtained from bivariate models of $Trait \sim F_{\mathrm{ROH}} + F_{\mathrm{GRM}}$ and compared to univariate estimates from the model $Trait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


F_MAF ~ F_ROH (or F_GRM)
Beta
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.0
0.1
0.2
0.3
0.4
0.5
MAF
F_ROH
F_GRM

16b



Supplementary Figure 16: Univariate relationships between estimates of inbreeding coefficient ($\boldsymbol{F_{ROH}}$, $\boldsymbol{F_{GRM}}$) 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 $\boldsymbol{F_{ROH}}$ and $\boldsymbol{F_{GRM}}$ on $\boldsymbol{F_{MAF}}$.** Univariate models of F_{MAF}~F_{ROH} and F_{MAF}~F_{GRM} were fitted at each allele frequency. A one unit increases 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 $\boldsymbol{F_{ROH}}$, $\boldsymbol{F_{GRM}}$ and $\boldsymbol{F_{MAF}}$.** Univariate models of F_{MAF}~F_{ROH} and F_{MAF}~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	***Earlier*** age at first sex	Number of sexual partners	Alcohol units	Ever smoked	Driving speed
Number of children	Rg	0.93						
	P	0						
Earlier 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_{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_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 – 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.

fev1perfvc – 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 – $mmolL^{-1}$. Known diabetic subjects were excluded, as were subjects with fpg > 7 or 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 – gL^{-1}. Concentration of haemoglobin. Values less than 0 or greater than 500 were set to NA.

hba1c – Glycosylated haemoglobin – % of hb (DCCT)[2]. Set to NA for known diabetics and all subjects for whom HbA1c > 6.5 or 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 – $mmolL^{-1}$. 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 exclude 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 – $mmolL^{-1}$. 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 – $mLmin^{-1}1.73m^{-2}$. Glomerular filtration rate was estimated from measured creatinine (in $mgdL^{-1}$) using the formula $186*creatinine^{-1.154}*age^{-0.203}$. 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 – $pmolL^{-1}$. Known diabetic samples, as well as samples with fpg > 7 or HbA1c < 6.5 were excluded. Values of fasting insulin greater than 1000 were set to NA.

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

log.hscrp – high sensitivity C-reactive protein – $nmolL^{-1}$. Serum levels of C-reactive protein (CRP) detected with high sensitivity systems (lower detection limit around 1 $nmolL^{-1}$). 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 $nmolL^{-1}$.

log.il6 – Interleukin-6 – $pgmL^{-1}$. 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 $pgmL^{-1}$.

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^{-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 100 pgmL^{-1}.

log.triglyc – Triglycerides – mmolL^{-1}. 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^{-1} were set to NA.

log.wbc – White blood cell count – 10^9 per Litre. Values greater than 30 x 10^9 per Litre were excluded.

log10.alt – Alanine transaminase – IUper 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 - 10^9 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^{-1}. 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^{-1} were set to NA.

uric – Uric acid – umolL^{-1}. Serum urate concentration. Values greater than 1190 umolL^{-1} 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_parous – 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 P*refer 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*, Stom*ach 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*, Mod*erately 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 encode 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 – mML^{-1}. 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 – mML^{-1}. 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 (β_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_{HOM}, F_{UNI}) and methods that identify autozygous genomic segments from unbroken tracts of homozygous genotypes, which are unlikely to occur by chance (e.g. F_{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, $MSE(\hat{F} - F) \ll var(F)$. Extensive comparisons of different estimators have been made by previous studies. Many of these conclude that F_{ROH} calculated from appropriately parameterized ROH calling gives estimates of F with minimal bias and lower variance than independent SNP methods[1–4]. In contrast, Yengo et al. (PNAS 2017) claim that $\hat{\beta}_{F_{\mathrm{ROH}}}$ may be upwardly biased by as much as 162%, and provide apparent evidence of this in both simulated and real data[5]. Furthermore, Yengo et al. show, in both theory and simulation, that two independent SNP methods (F_{UNI} and F_{HOM}) give unbiased estimates of β_F when causal SNPs are a random subset of all genotyped SNPs. This would cast doubt on the validity of using F_{ROH} to estimate β_F, and suggests F_{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_{UNI} was calculated by the formula presented by Yang et al. (2011)[6] as $\hat{F}^{III}$ (implemented in PLINK[7] by parameters --ibc Fhat3) and ROH were called by two PLINK parameterizations, including the values proposed in Joshi et al. (2015)[8]. 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_{ROH} calculated from SNP chip genotypes agrees well with F_{UNI} indicating minimal bias. We followed the method described in Yengo et al. to calculate both F_{UNI} and F_{ROH} from the UKB imputation, but initially compared Yengo's F_{UNI} to our F_{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_{UNI} and F_{ROH} (Supplementary Fig. 12). Since F_{UNI} is believed to be an unbiased estimator of F, the correspondence between F_{UNI} and F_{ROH} places limits on the possible bias of F_{ROH}. Specifically, if we model F_{ROH} as $F_i^{\mathrm{ROH}} = \Theta F_i + \epsilon_i$, then

$$\frac{r^2}{\beta_{F_{\mathrm{UNI}},F_{\mathrm{ROH}}}} \leq \Theta \leq \frac{1}{\beta_{F_{\mathrm{UNI}},F_{\mathrm{ROH}}}} \qquad (19)$$

(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_{UNI} and F_{ROH} limits the potential error in F_{ROH} to a small downward bias. This very small underestimate of F may be caused by autozygosity not captured in F_{ROH}, namely ROH of less than 1.5 Mb length or ROH in sparsely genotyped regions.

Calculating F_{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 ϵ [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_{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_{roh} with an expected value of just 0.39 of the F_{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_{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 $F_{\mathrm{ROH}} =$

0.261, amongst the highest observed in UKB, and is most likely the progeny of 1st degree relatives where $E[F] = 0.25$. Individual 2 has $F_{\mathrm{ROH}} = 0.0626$ and is most likely the offspring of first cousins (3nd 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_{roh} is sufficient to explain an upward bias of up to 156% (1/0.39) in $\hat{\beta}_{F_{\mathrm{roh}}}$.

In summary, calculating F_{ROH} from dense SNP chip genotypes, with the parameters used in this study, gives valid estimates of inbreeding coefficients. In contrast, calculating F_{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_{roh} in that study.

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

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

In summary, Yengo et al showed that $\hat{\beta}_{F_{\mathrm{UNI}}}$ 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_{ROH} (Supplementary Fig 16a).

Comparison of genomic measures of inbreeding with genealogy. As a further assessment of the relative abilities of F_{ROH}, F_{SNP} and F_{GRM} to capture inbreeding, we analysed Pearson's product-moment correlations between the genomic inbreeding measures and pedigree inbreeding (F_{PED}) for 47,927 Icelanders with mostly-complete (info score > 0.6)[9] 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 ($F_{\mathrm{ROH}} > 0.05$ & $F_{\mathrm{SNP}} < 0.001$) 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 $\boldsymbol{Trait \sim F_{ROH} + F_{GRM}}$ 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 ($Trait \sim F_{\mathrm{ROH}} + F_{\mathrm{GRM}}$) 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[10] 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 $\boldsymbol{F_{ROH}}$, $\boldsymbol{F_{GRM}}$ 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.

$$ID_i = \sum_{i=1}^{m} \delta_i = \beta_F * F_{\mathrm{QTL}} \tag{38}$$

Where

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

and

$$w_i = \frac{2p_iq_id_i}{\frac{1}{m}\sum_{i=1}^{m} 2p_iq_id_i} \tag{40}$$

We note that the unweighted form of equation (39) is identical to $\hat{F}^{III}$ introduced by Yang et al (2011)[6], 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*MAF < AF < 1.1*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 ($F_{\mathrm{MAF}} \sim F_{\mathrm{ROH}}$ and $F_{\mathrm{MAF}} \sim F_{\mathrm{GRM}}$) and bivariate models ($F_{\mathrm{MAF}} \sim F_{\mathrm{ROH}} + F_{\mathrm{GRM}}$) 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 $Trait \sim F_{\mathrm{ROH}} + F_{\mathrm{GRM}}$, 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

$$F_{\mathrm{UNI}} = F + \varepsilon \tag{20}$$

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

$$F_{\mathrm{ROH}} = \Theta F + \Theta\varepsilon' \tag{21}$$

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

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

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

$$\beta = \frac{\Theta var(F)}{\Theta^2 var(F) + \Theta^2 var(\varepsilon')} \tag{22}$$

Rearranging (22) gives

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

The range of $\frac{var(\varepsilon')}{var(F)}$ is limited by the correlation between F_{UNI} and F_{ROH}, and we can put $\left(1 + \frac{var(\varepsilon')}{var(F)}\right)^{-1}$ in terms $\frac{var(\varepsilon)}{var(\varepsilon')}$ of by considering that

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

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

$$\frac{\Theta^2 var(F) + \Theta^2 var(\varepsilon')}{var(F) + var(\varepsilon)} = \frac{r^2}{\beta^2} \tag{25}$$

Rearranging (25) gives

$$\frac{var(\varepsilon')}{var(F)} = \frac{\Theta^2\beta^2 - r^2}{r^2\frac{var(\varepsilon)}{var(\varepsilon')} - \Theta^2\beta^2} \tag{26}$$

Substituting equation (26) into equation (23)

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

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

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

$$\Theta = \frac{r^2}{\beta} \tag{29}$$

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

$$\Theta = \frac{1}{\beta} \tag{30}$$

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

$$\frac{r^2}{\beta_{F_{\mathrm{UNI}},F_{\mathrm{ROH}}}} \leq \Theta \leq \frac{1}{\beta_{F_{\mathrm{UNI}},F_{\mathrm{ROH}}}} \tag{31}$$

SUPPLEMENTARY NOTE 7: Expected attenuation bias in $\widehat{\boldsymbol{\beta}}_{\boldsymbol{F_{\mathrm{GRM}}}}$

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

$$F_{\mathrm{GRM}} = F_{\mathrm{ROH}} + \varepsilon \tag{32}$$

And

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

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

Because ε has no effect on the trait (y)

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

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

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

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

If $x_i \epsilon [0,1,2]$ 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 (β) is

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

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.

$$\beta F_{\mathrm{QTL}} = \sum_{i=1}^{m} \delta_i \tag{42}$$

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

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

Rearranging equation (43) gives

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

Substituting for β from equation (41) gives

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

Where

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

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