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Association of *OPRM1* functional coding variant with opioid use disorder: A genome-wide association analysis in 114,795 subjects

Subtitle: *OPRM1**A118G associated with OUD

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Key Points

Question: What is the genetic architecture of opioid use disorder (OUD) and how is OUD related to other traits?

Findings: Meta-analysis in 10,544 European ancestry cases and 72,163 opioid-exposed controls identified *OPRM1* functional variant rs1799971 as associated with OUD, with replication in two independent samples. No significant associations were detected in African-ancestry subjects (total n= 32,088). OUD was genetically correlated with 83 traits, and causal effects from 5 traits were detected.

Meaning: This GWAS study, by far the largest ever for this trait, identified a significant association of OUD, with replication.

Abstract

IMPORTANCE: With the current opioid crisis, we must improve our understanding of the biological mechanisms of opioid use disorder (OUD).

OBJECTIVE: Detect genetic risk variants for OUD, and determine genetic correlations and causal effects with OUD and other traits.

DESIGN, SETTING, AND PARTICIPANTS: A genome-wide association study (GWAS) of electronic health record (EHR)-defined OUD in the Million Veteran Program (MVP) sample was conducted, comprising 8,529 affected European-American (EA) subjects and 71,200 opioid-exposed EA controls (defined by EHR trajectory analysis), and 4,032 African-American (AA) cases and 26,029 controls. Participants were enrolled 2011-2018, with EHR data for OUD diagnosis 2000-2018. MVP results and additional OUD case-control GWAS results from the Yale-Penn and SAGE samples were meta-analyzed (total n's: EA, 10,544 OUD cases and 72,163 opioid-exposed controls; AA, 5,212 cases and 26,876 controls). Yale-Penn participants were collected 1999-2017, and SAGE, 1990-2007. The key result was replicated in two independent cohorts: proxy-phenotype 'buprenorphine treatment' in the UK Biobank, and newly genotyped Yale-Penn subjects. Genetic correlations between OUD and other traits were tested, and genetic causality contributed by related traits to the liability of OUD evaluated using Mendelian Randomization.

MAIN OUTCOME AND MEASURES: ICD-9/10-diagnosed OUD (MVP), and DSM-IV opioid dependence (Yale-Penn and SAGE).

RESULTS: 114,759 total subjects were included. In 82,707 EAs, a functional coding variant (rs1799971, encoding Asn40Asp) in *OPRM1* (*mu* opioid receptor gene, the main biological target for opioid drugs) reached genome-wide significance (G allele, beta=-0.066, se=0.012, $p=1.51\times10^{-8}$). The finding was replicated in two independent samples (each at $p<0.05$). SNP-based heritability of OUD=11.3% (se=0.018). OUD was genetically correlated with 83 traits, including multiple substance use traits, psychiatric illnesses, cognitive performance, and others. Mendelian Randomization revealed possible causal effects on OUD: risk of tobacco smoking, depression, neuroticism, and cognitive performance. No genome-wide significant association was detected in AAs or in trans-population meta-analysis.

CONCLUSION AND RELEVANCE: This GWAS study, by far the largest for this trait, identified significant association of OUD with an *OPRM1* variant, replicated in two independent samples. Post-GWAS analysis revealed novel pleiotropy and biology. Recruitment of additional OUD subjects for future studies – especially non-European ancestry – is a crucial next step in identifying additional significant risk loci.

Introduction

Opioid abuse, addiction, and overdose are at epidemic levels in the United States. Opioids are the leading cause of overdose deaths, and their use has increased dramatically in recent decades.[1] A multifaceted approach is needed to address the opioid crisis, including improving our understanding of the biological mechanisms of opioid addiction. Opioids exert their biological effects primarily by binding (mainly in brain and peripheral nervous tissues) to the opioid receptors *mu* (μ), *kappa* (κ), and *delta* (δ), which are encoded by *OPRM1*, *OPRK1*, and *OPRD1*, respectively.[2] Numerous candidate-gene association studies of these genes (especially *OPRM1*) and those encoding related proteins have been conducted in the past two decades (reviewed in ref 3,4), but prior studies have failed consistently to demonstrate association (e.g., studies on *OPRM1**rs1799971 are reviewed in ref 5).

Rs1799971 (A118G, encoding Asn40Asp),[5,6] a functional variant, is one of the most studied candidate variants for substance use traits. Several kinds of evidence support possible functional effects of this SNP: rs1799971 reportedly alters beta-endorphin binding and activity,[6] may be associated with cortisol response to naloxone blockade,[7] may be associated with neurobehavioral functions in a mouse model,[8,9] and modulates synaptic function in human induced pluripotent stem cell lines; alternate-allele protein products showing differential N-linked glycosylation.[10]

Several GWAS of DSM-IV opioid dependence [OD] yielded significant findings;[11-14] one included internal replication[13] but none reported clear external replication, probably due to the limited sample sizes available (the largest study so far included 2,015 OD cases[13]). The risk variants identified map to *APBB2*, *PARVA*, *KCNC1*, and *KCNC2*[11] in African-American (AA) samples, and *CNIH3*[12] and *RGMA*[13] in European-ancestry samples. There have also been GWAS of related traits including therapeutic opioid dose (that identified a genome-wide significant (GWS) variant upstream of the *OPRM1* locus in AAs),[15] and opioid overdose (which

identified one variant near *MCOLN1* in AAs).[16] Of these, only the study on opioid dosing included an external validation. No GWAS yet has been sufficiently powered to estimate the SNP-based heritability (h^2) of OD.

We conducted GWAS on ICD (International Classification of Diseases)–9/10-diagnosed opioid use disorder (OUD) and opioid-exposed controls in 79,729 European-Americans (EAs) and 30,061 AAs from the Million Veteran Program (MVP). Then we meta-analyzed for OUD combining MVP, Yale-Penn, and the Study of Addiction: Genetics and Environment (SAGE) samples.[17] The latter two EA samples were included in our previous publication,[13] but were reanalyzed here as a binary diagnostic trait rather than a criterion count for better congruence with available MVP information. Rs1799971 was the only variant that was GWS ($p=1.51\times10^{-8}$) in the EA meta-analysis. We then replicated the result in two independent samples.

Methods

MVP datasets. The MVP is a cross-sectional mega-biobank supported by the U.S. Department of Veterans Affairs (VA). Enrollment in MVP began in 2011 and is ongoing. Phenotypic data were collected using the VA electronic health record (EHR), and blood samples were obtained for genetic studies.[18] Two phases of genotypic data have been released according to their genotyping epochs and were included in this study. MVP phase1 contains 353,948 subjects, of whom 209,020 were defined previously as unrelated EAs, and 57,340 unrelated AAs.[19] MVP phase2 contains 108,416 subjects. We used the same process as in MVP phase1 for quality control and to define EAs and AAs (see eMethods);[19] this yielded 67,268 unrelated EA subjects and 18,214 unrelated AAs.

Cases were participants with at least one inpatient or two outpatient ICD-9/10 codes for OUD (eTable 1) between 2000 and 2018. In MVP phase1, there were 6,367 OUD EAs (3.04%

prevalence, among unrelated subjects) and 3,151 OUD AAs (prevalence=5.50%), and 2,162 OUD EAs (prevalence=3.21%) and 881 OUD AAs (prevalence=4.84%) in MVP phase2 were included in this study. Stringent criteria were applied to define incident opioid-exposed controls (see details in ref 20). In short, we started with all MVP participants and excluded subjects with exposure to a prescription opioid <7 consecutive days, or with VA follow-up less than 6 months after baseline, or with cancer diagnosed before or after baseline, or with baseline opioid dosage >90 mg morphine equivalent daily dose (MEDD), or with OUD diagnosis or OUD treatment at baseline. For the remaining participants, a latent growth mixture model was applied to identify the major classes of opioid dose (measured by MEDD) trajectories that assigned each individual to the trajectory with the highest probability of membership. Four resultant MEDD trajectories were designated as low, moderate, escalating, and rapidly escalating. To minimize the potential rate of false negatives in the control group (eTable 2), subjects assigned to the low- dose trajectory without an incident OUD diagnosis during follow-up were defined as controls, yielding 55,429 EA and 15,771 EA controls in MVP phase1 and MVP phase2, respectively; plus 20,254 AA and 5,775 AA controls, respectively.

Genotyping in MVP was performed using a customized Affymetrix Biobank Array. Imputation and quality control metrics for MVP phase1 were as described previously.[19] Similar processes were used for MVP phase2 (see eMethods). GWAS was then performed on the MVP datasets. We used logistic regression implemented in PLINK v1.90b4.4[21] for the OUD GWAS correcting for age, sex, and the first 10 principal components (PCs).

Ethics statement: The Central VA Institutional Review Board (IRB) and site-specific IRBs approved the MVP study. All relevant ethical regulations for work with human subjects were followed in the conduct of the study, and written informed consent was obtained from all participants.

Yale-Penn and SAGE datasets. GWAS for DSM-IV OD criterion counts in EAs were performed previously, including three phases of Yale-Penn data, and the SAGE cohort (dbGaP study id phs000092.v1.p1).[13] We re-analyzed these data using OUD diagnosis. For AAs, the first two phases of Yale-Penn data were included (because Yale-Penn 3 has only 7 cases and SAGE has only 105 cases and 158 exposed controls, they were not included). See eMethods.

Meta-analyses. Sample-size-weighted meta-analyses were performed using METAL considering the differences of ethnicity, phenotype distribution, association model (linear v.s. linear mixed), or other sample characteristics.[22] Given the unbalanced ratios of cases to controls in MVP samples, effective sample sizes were calculated as follow:

$$n_{effective} = \frac{4}{\frac{1}{n_{case}} + \frac{1}{n_{control}}}.$$

The calculated effective sample sizes in MVP were used in meta-analyses and all downstream analyses. Only variants present at least in MVP phase1, which is the largest sample (~75% of the total EAs and ~78% of the total AAs), and with heterogeneity test p-value $>5\times10^{-8}$ were retained, leaving 6.91 M, 5.07 M, and 9.42 M variants for AAs, EAs, and trans-population meta-analyses, respectively.

Replication in independent EA samples. We genotyped 4,817 recently-added Yale-Penn subjects who were not included in any prior analysis. We used the Illumina Multi-Ethnic Genotyping Array (San Diego, CA) which includes ~1.7 M SNPs. Subjects with mismatched genotypic and phenotypic sex were removed, as were subjects with excessive heterozygosity. Duplicate subjects with respect to the Yale-Penn discovery samples were removed. The

remaining subjects were classified into population groups as for MVP. Among the 2,041 genetically classified EAs, 508 were diagnosed as DSM-IV OD cases, and 206 were opioid exposed controls. GEMMA[23] was used for an association test only for rs1799971 (i.e., no other markers were evaluated) and corrected for age, sex, and the first 10 PCs.

In the UK Biobank (UKB), we looked up the association between rs1799971 (only this marker, as for the other replication sample) and buprenorphine treatment (mostly used to treat OUD; treatment/medication code: 20003_1140871732) in the UKB. We examined GWAS summary data released by the Neale lab (information available at http://www.nealelab.is/uk-biobank) for 240 cases and 360,901 controls differentiated based on buprenorphine treatment.

SNP-based h^2. LD Score Regression (LDSC)[24] was used to estimate the SNP-based h^2 using 1000 Genomes Project Europeans or Africans[25] as the LD reference panel. The major histocompatibility complex (MHC) region (chr6: 26–34Mb) was excluded. Effective sample size was used in LDSC.

Genetic correlation. We estimated the genetic correlation (r_g) between OUD and 715 publicly available traits from LD-Hub[26] or other resources using LDSC (eTable 3).[27] Among the tested traits, 232 were published previously (including recent non-LD-hub studies), and 483 from the UKB were unpublished, but integrated in LD-Hub. Bonferroni correction was applied and correlation was considered significant at a p-value threshold of 6.99×10^{-5}.

Mendelian Randomization. We used Mendelian randomization (MR) to investigate whether exposures (based on 18 published traits that were significantly correlated with OUD [r_g

212 $p<6.99\times10^{-5}$]) have causal effects on the liability to OUD (unidirectional). After variant
213 harmonization and filtering, 12 exposures were analyzed. Weighted median,[28] inverse-variance
214 weighted (IVW, random-effects model),[29] and MR-Egger[30] were used for MR inference.
215 Evidence of pleiotropic effects was examined by the MR-Egger intercept test[30] (see eMethods).

216

217 **Results**

218 **Association results for opioid use disorder (OUD) in EAs**

219 When we meta-analyzed the 8,529 OUD cases and 71,200 controls within MVP (totaling 79,729
220 individuals, Table 1), no variant reached GWS ($p<5\times10^{-8}$, eFigure 1). The variant with the
221 smallest p-value was rs1799971 in *OPRM1* ($p=5.90\times10^{-8}$, $n_{effective}$=30,443; the minor G allele is
222 protective with beta=-0.142 and se=0.026).

223 We then meta-analyzed the MVP samples with Yale-Penn (three tranches) and SAGE
224 samples, bringing the total sample size to 82,707 (10,544 cases and 72,163 opioid-exposed
225 controls, Table 1). This represents a 24% increase in the number of cases. From the meta-
226 analysis, the SNP-based heritability (h^2) was 0.113 (se=0.018) estimated by LDSC. The
227 association of rs1799971 with OUD was GWS (beta=-0.066, se=0.012, $p=1.51\times10^{-8}$,
228 $n_{effective}$=33,421, Figure 1, eFigures 2 and 3). The LD structure around rs1799971 is complex[31]
229 (eFigure 3). The effects were all in the same direction except for SAGE, which might be due to
230 its limited sample size. There were no significant results from gene-based association and
231 gene-set analyses.

232

233 **Replication in independent EA samples**

234 In total, we analyzed 714 EAs (508 OD cases and 206 opioid-exposed controls) from the new

Yale-Penn samples, and rs1799971*G was associated with reduced OD risk (i.e., in the same direction as the discovery meta-analysis) (beta=-0.074, se=-0.038, p=0.049). In the UKB, rs1799971*G was negatively associated with buprenorphine treatment status (240 cases and 360,901 controls, beta=-1.90×10^{-4}, se=9.13×10^{-5}, p=0.038), also consistent with the direction of effect in the discovery sample. A meta-analysis of discovery and replication cohorts for this variant yielded a p-value of 7.81×10^{-10} (beta=-0.070, se=0.011).

Genetic correlations with other traits in EAs

OUD was significantly correlated with 83 of the 715 traits tested (eTable 3). Figure 2 depicts 18 correlated traits from published literature (eMethods). Among the correlated substance use-related traits, "ever smoked regularly" showed the highest correlation with OUD (r_g=0.51, se=0.06, p=3.37×10^{-19}), followed by "opioid medication use" in UKB (r_g=0.48, se=0.07, p=1.61×10^{-11}). Both alcohol dependence and "alcohol use quantity" (measured by drinks per week) showed high genetic correlations with OUD. "Unable to stop smoking" (current *vs.* former smoker), and "earlier age of smoking initiation" were also correlated with OUD. However, correlations with AUDIT-C (Alcohol Use Disorders Identification Test–Consumption), total AUDIT, cigarettes per day, and lifetime cannabis use were not significant after Bonferroni correction. Several psychiatric traits were correlated with OUD, including attention deficit hyperactivity disorder (ADHD, r_g=0.36, se=0.07, p=6.78×10^{-7}), major depressive disorder (MDD, r_g=0.35, se=0.06, p=1.62×10^{-10}), schizophrenia (r_g=0.29, se=0.05, p=1.93×10^{-8}), neuroticism (r_g=0.27, se=0.05, p=8.65×10^{-8}), and neuroticism subclusters. OUD was positively correlated with risk-taking behavior and insomnia, and negatively correlated with cognitive traits and age of first birth. These finding are consistent with the known adverse medical, psychiatric, and social consequences of OUD.

Mendelian Randomization in EAs

Using MR, we explored possible causal effects of exposures on OUD (Table 2). Among the 12 tested exposures, five supported a possible causal effect on liability to OUD by at least one method and were without evidence of horizontal pleiotropy (MR-Egger intercept p>0.05): positively with ever smoked regularly, MDD, neuroticism and worry neuroticism subcluster, and negatively with educational attainment. There was weak evidence of a causal effect of drinks per week on OUD risk by the IVW method, but the estimate could be biased due to horizontal pleiotropy.

Association results for OUD in AAs and trans-population meta-analysis

For AAs, 4,032 OUD cases and 26,029 controls within MVP were meta-analyzed; no variant reached GWS (Table 1, eFigure 4). We then meta-analyzed the MVP samples with Yale-Penn (two tranches), bringing the total sample size to 32,088 (5,212 cases and 26,876 opioid-exposed controls); no association was detected (eFigure 5). There was insufficient power for a robust estimate for SNP-based heritability (h^2= 0.065, se= 0.052).

Trans-population meta-analysis combining all datasets was conducted in 114,795 subjects. No significant association was detected (eFigure 6).

Discussion

Opioid use is at epidemic levels in the United States and is a major cause of death and disability worldwide. Understanding the genetic architecture of OUD might provide clinically useful clues about its biology. However, only a few risk variants have been identified by GWAS so far, and none has had clear external replication. Several factors contribute to this situation: 1). OUD is a

complex psychiatric disease with relatively low heritability, and there is no single variant with large effect size that can be detected in small cohorts (contrary to, for example, alcohol dependence[32] with *ADH1B*, and nicotine dependence with the chromosome 15 nicotine receptor cluster[33]); 2). Previous OUD GWAS were relatively small compared to those for legal substance use disorders (e.g., the number of alcohol use disorder cases reached 57,564 in a large meta-analysis[34]); 3). In published work relevant to opioid use, there was considerable phenotypic heterogeneity across samples. The ascertainment of OUD cases (e.g., ICD-diagnosed OUD in the EHR, DSM-IV-assessed OD, patients receiving opioid substitution therapy, and daily injectors of illicit opioids) and controls (e.g., opioid exposed, or random population with unknown opioid exposure status) differ by study. One way to reach a better understanding of OUD genetics is increasing the sample size in a homogeneous cohort.

For EAs, we conducted a GWAS of OUD in a large cohort, the MVP, comprising 8,529 cases and 71,200 opioid-exposed controls. Most previously reported variants associated with a wide range of opioid-related traits were not significant in MVP (cf. summary statistics). For some, this reflects lack of marker information or LD proxies in the MVP; some associations were previously reported in African-ancestry populations only;[11] others were reported in EAs, but relevant variants are missing in the MVP data (e.g., rs12442183 near *RGMA* reported by Cheng et al.[13] was filtered by low genotype call rate in imputation). No variant reached GWS in this largest-ever cohort individually; *OPRM1**rs1799971 was nominally significantly associated with OUD ($p=5.90\times10^{-8}$). We meta-analyzed MVP samples with Yale-Penn and SAGE (re-analyzed to match the available phenotype from the MVP more closely), increasing total sample size to 82,707 (10,544 cases and 72,163 opioid-exposed controls). By adding four samples from Yale-Penn and SAGE, rs1799971 reached GWS. The final meta-analyzed p-value for this marker is 1.51×10^{-8} (excluding independent replications). Rs1799971 was genotyped directly (not imputed) in all samples, discovery and replication. No association was detected in AAs or in trans-

307 population meta-analyses.

308 Rs1799971 (A118G) maps to exon 1 of the mu opioid receptor (*OPRM1*) gene, causing
309 an amino acid change (Asn40Asp). Extensive candidate studies of this variant with a wide range
310 of addictive and other behavioral traits have been conducted over two decades.[5,35,36]
311 Associations between rs1799971 and opioid-related traits have been inconsistent (reviewed in
312 ref 5). We conducted hypothesis-free, genome-wide analyses for OUD and detected association
313 at rs1799971 by almost quintupling the number of cases compared to any previous study.[5,13]
314 Our increment in exposed controls, often even more limiting than affected OUD subjects in
315 previous studies, is even greater. Since many individuals exposed to opioids become
316 dependent, an unassessed control group is not an ideal alternative to an opioid-exposed control
317 group even if greater numbers of subjects can be achieved – because the former group is more
318 correctly "diagnosis unknown" including many subjects genetically predisposed to OUD who
319 would express that phenotype had they been exposed. We sought replication in two
320 independent EA samples. One included newly genotyped Yale-Penn subjects, and the other, a
321 proxy-phenotype buprenorphine treatment sample from the UKB. The association was
322 replicated in each of these samples.

323 Multiple substance use-related traits including smoking, alcohol, and opioid use and
324 psychiatric traits were among the top correlates. Several smoking traits were positively
325 correlated with OUD, consistent with the strong correlation between nicotine use and opioid use
326 disorder.[37,38] MR analysis provided evidence (weak, since not supported by all the three tested
327 methods) that the genetic liability to substance use related traits has causal effects on
328 susceptibility to OUD. Medical opioid use is correlated with OUD, as expected. Alcohol
329 dependence and drinking quantity are also genetically correlated with OUD. Thus, it may be
330 feasible for prevention or treatment efforts directed at legal substance use to reduce the burden
331 of consequent opioid dependence. Psychiatric traits including ADHD, MDD, schizophrenia, and

neuroticism are genetically correlated with OUD, consistent with phenotypic evidence.[39,40] Weak evidence from MR analyses also indicated possible causal effects on OUD risk of MDD and neuroticism.

Limitations

The sample size, though a major improvement from prior studies, is still not as large as what can be obtained for legal substance use-related traits, and this limited power to detect more GWS signals and to obtain insight into OUD biological mechanisms. Legal substance use traits are more common, and data pertinent to these traits are collected more commonly than for illegal traits in biobanks and EHRs. Second, the phenotypes in the samples we studied were not identical. The MVP used ICD 9/10-diagnosed OUD. There may be false negatives in a sample like the MVP, owing to stigma and OUD diagnoses not recorded by treatment teams concentrating mostly on medical illness, but few false positives. Third, the replication samples are small (508 OD cases in the new Yale-Penn sample and 240 buprenorphine treatment cases in UKB), and the associations only nominally significant (p~0.05); only a single variant was tested in the replication samples. The phenotype in UKB is a proxy phenotype–buprenorphine treatment. Buprenorphine is a first-line drug for OUD treatment, but it could have been used for other purposes in the UKB population, including pain management; but if this is true to any considerable extent, it should reduce our power to detect an association, rather than lead to a false positive finding. Fourth, there has been a lack of recruitment for non-European populations globally, e.g., only a few GWASs have been conducted in AAs[11,15] in smaller cohorts. Meta-analysis of AAs combining MVP and Yale-Penn was underpowered to detect significant signals.

In summary, we report here the largest GWAS and the largest meta-analysis for OUD so far. This finding may not have direct implications for personalized medicine – because the

relevant gene is already the main physiological target of all opioids, illegal and therapeutic; providing, at least, a “proof of principle” of relevance of the finding. OUD is genetically correlated with substance use traits, other psychiatric traits, insomnia, and cognitive performance. Among these, ever smoked regularly, MDD, neuroticism, and cognitive performance have potential causal or protective effects on the liability of OUD, which provides clues for future prevention efforts. Recruitment of additional OUD subjects – especially of non-European ancestry – is a crucial next step. Considering the general lack of private foundation funding for study of substance use disorders, it is likely that government-supported funding agencies will be required to accomplish this goal.

Data availability

The full summary-level association data from the meta-analyses are available through dbGaP: [https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001672.v3.p1] (accession number phs001672.v3.p1).

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The publicly available dataset of Study of Addiction: Genetics and Environment (SAGE) used for the analysis was obtained from dbGaP at https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000092.v1.p1. Funding support for SAGE was provided through the NIH (U01 HG004422). SAGE is one of the genome-wide association studies funded as part of the Gene Environment Association Studies (GENEVA) under Genes, Environment and Health Initiative (GEI). Assistance with phenotype harmonization and genotype cleaning, as well as with general study coordination, was provided by the GENEVA Coordinating Center (U01 HG004446).

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Figure legends

Figure 1. Associations between rs1799971*G and OUD in EAs. [a]Logistic regression was applied based on unrelated case/control samples in MVP, log(OR) is presented; [b]a linear mixed model was applied on complex family-based samples, beta is presented; [c]effective sample size weighted meta-analysis was applied, and beta is presented.

Figure 2. Genetic correlations between OUD and published traits. Listed are the 18

published traits significantly correlated with OUD. *N02A: Opioid*: self-reported medication-use of opioid drugs (Anatomical Therapeutic Chemical [ATC] Classification code: N02A) in UK Biobank; *PGC*: Psychiatric Genomics Consortium; *AUDIT-P*: the Alcohol Use Disorders Identification Test–Problems; *ADHD*: attention deficit hyperactivity disorder, *MDD*: major depressive disorder; *Depressed affect subcluster*: depressed affect neuroticism subcluster; *Worry subcluster*: worry neuroticism subcluster.

Figure 3. Causal effects on OUD by MR. P-values in bold are significant after multiple testing correction (significance threshold, $0.05/36=1.39\times10^{-3}$). Traits labeled in bold are those having a causal effect on OUD by at least one method without evidence of horizontal pleiotropy (MR-Egger intercept p>0.05). IVW: inverse-variance weighted (IVW) linear regression.

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Table 1. Demographics – discovery sample.

	European-Americans				African-Americans			
Samples	**# Cases**	**# Controls**	**Age (mean±SD)**	**%female**	**# Cases**	**# Controls**	**Age (mean±SD)**	**%female**
MVP phase1	6,367	55,429	61.2 (13.0)	9.3	3,151	20,254	57.0 (11.1)	14.5
MVP phase2	2,162	15,771	61.2 (13.7)	9.7	881	5,775	58.0 (11.2)	15.5
Sub-total	8,529	71,200	61.2 (13.2)	9.4	4,032	26,029	57.2 (11.1)	14.7
Yale-Penn 1	1,043	294	36.9 (10.3)	40.5	831	573	42.2 (7.9)	38.0
Yale-Penn 2	724	243	36.4 (11.4)	33.0	349	274	42.3 (10.2)	27.3
Yale-Penn 3	54	44	33.6 (11.6)	41.8	-	-	-	-
SAGE	194	382	35.8 (9.1)	33.9	-	-	-	-
Sub-total	2,015	963	36.4 (10.5)	36.8	1,180	847	42.3 (8.6)	34.7
Total	10,544	72,163			5,212	26,876		

Figure 1

Samples	N (#case)	Estimate (95% CI)	p
MVP phase1[a]	61,796 (6,367)	-0.116 (0.030)	1.14×10^{-4}
MVP phase2[a]	17,933 (2,162)	-0.227 (0.054)	2.49×10^{-5}
Yale−Penn 1[b]	1,337 (1,043)	-0.015 (0.025)	0.558
Yale−Penn 2[b]	967 (724)	-0.061 (0.030)	0.039
Yale−Penn 3[b]	98 (54)	-0.080 (0.104)	0.440
SAGE[b]	576 (192)	0.017 (0.042)	0.698
meta−analysis[c]	**82,707 (10,544)**	-0.066 (0.012)	**1.51×10^{-8}**

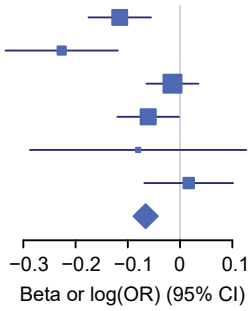


Figure 2

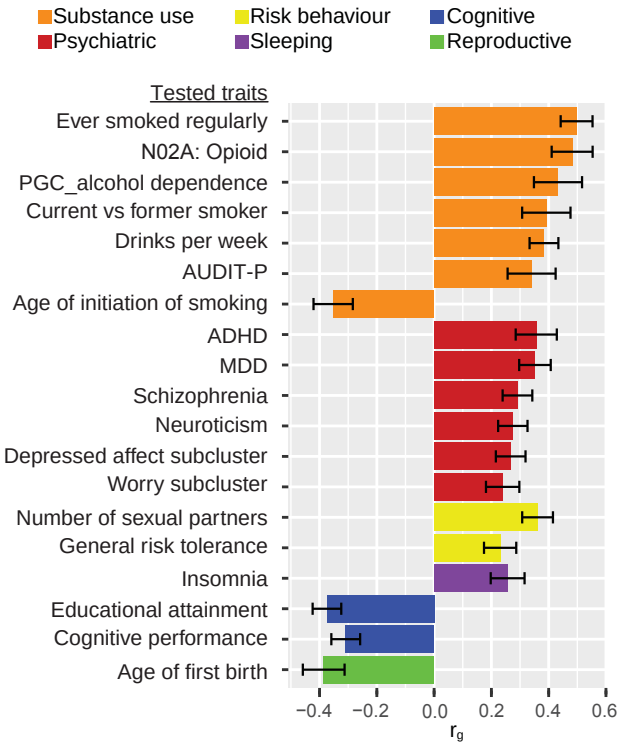
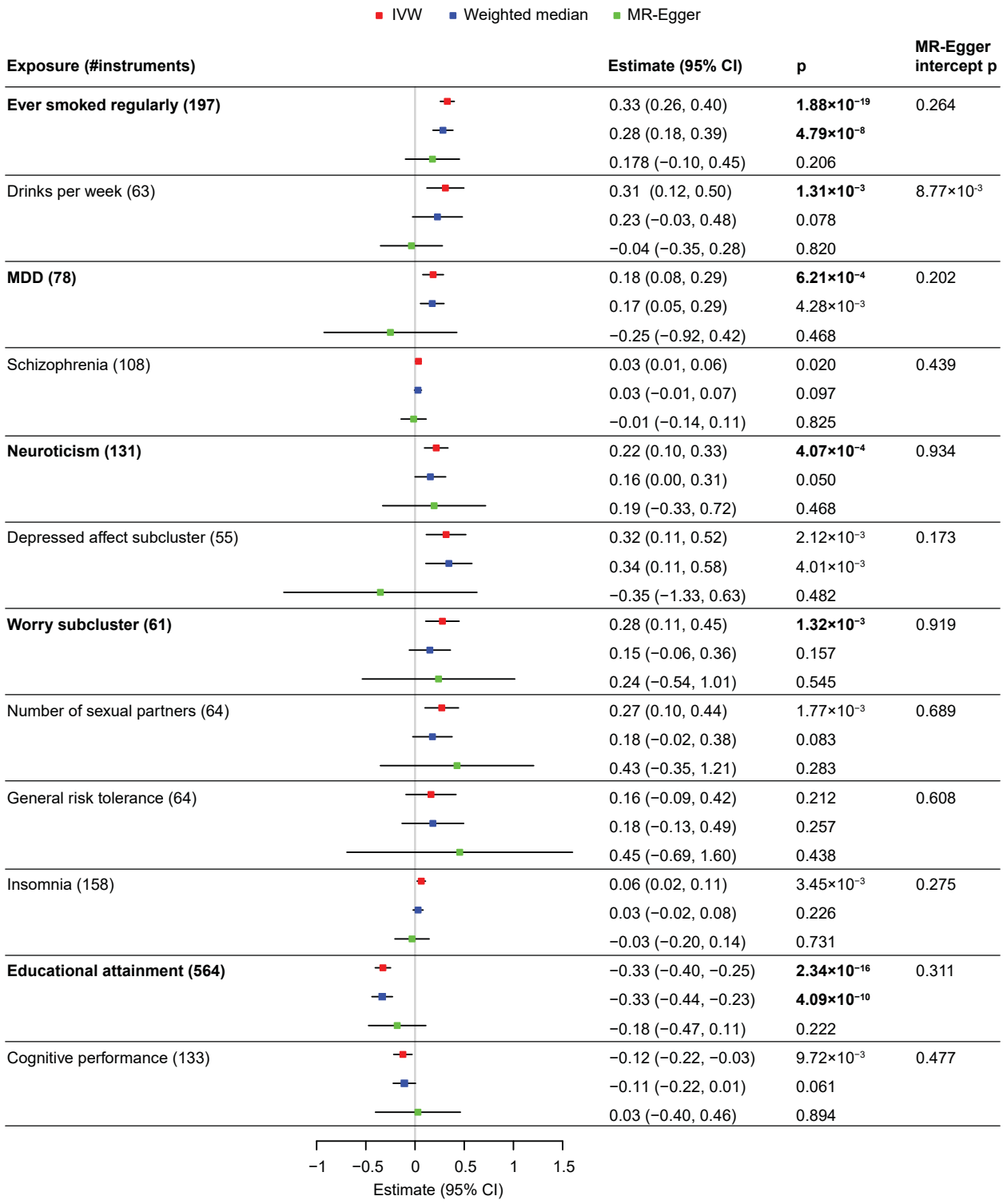

Substance use
Risk behaviour
Cognitive
Psychiatric
Sleeping
Reproductive
Tested traits
Ever smoked regularly
N02A: Opioid
PGC_alcohol dependence
Current vs former smoker
Drinks per week
AUDIT-P
Age of initiation of smoking
ADHD
MDD
Schizophrenia
Neuroticism
Depressed affect subcluster
Worry subcluster
Number of sexual partners
General risk tolerance
Insomnia
Educational attainment
Cognitive performance
Age of first birth
−0.4
−0.2
0.0
0.2
0.4
0.6
r_g

Figure 3


IVW
Weighted median
MR-Egger
Exposure (#instruments)
Estimate (95% CI)
p
MR-Egger intercept p
Ever smoked regularly (197)
0.33 (0.26, 0.40)
1.88×10−19
0.264
0.28 (0.18, 0.39)
4.79×10−8
0.178 (−0.10, 0.45)
0.206
Drinks per week (63)
0.31 (0.12, 0.50)
1.31×10−3
8.77×10-3
0.23 (−0.03, 0.48)
0.078
−0.04 (−0.35, 0.28)
0.820
MDD (78)
0.18 (0.08, 0.29)
6.21×10−4
0.202
0.17 (0.05, 0.29)
4.28×10−3
−0.25 (−0.92, 0.42)
0.468
Schizophrenia (108)
0.03 (0.01, 0.06)
0.020
0.439
0.03 (−0.01, 0.07)
0.097
−0.01 (−0.14, 0.11)
0.825
Neuroticism (131)
0.22 (0.10, 0.33)
4.07×10−4
0.934
0.16 (0.00, 0.31)
0.050
0.19 (−0.33, 0.72)
0.468
Depressed affect subcluster (55)
0.32 (0.11, 0.52)
2.12×10−3
0.173
0.34 (0.11, 0.58)
4.01×10−3
−0.35 (−1.33, 0.63)
0.482
Worry subcluster (61)
0.28 (0.11, 0.45)
1.32×10−3
0.919
0.15 (−0.06, 0.36)
0.157
0.24 (−0.54, 1.01)
0.545
Number of sexual partners (64)
0.27 (0.10, 0.44)
1.77×10−3
0.689
0.18 (−0.02, 0.38)
0.083
0.43 (−0.35, 1.21)
0.283
General risk tolerance (64)
0.16 (−0.09, 0.42)
0.212
0.608
0.18 (−0.13, 0.49)
0.257
0.45 (−0.69, 1.60)
0.438
Insomnia (158)
0.06 (0.02, 0.11)
3.45×10−3
0.275
0.03 (−0.02, 0.08)
0.226
−0.03 (−0.20, 0.14)
0.731
Educational attainment (564)
−0.33 (−0.40, −0.25)
2.34×10−16
0.311
−0.33 (−0.44, −0.23)
4.09×10−10
−0.18 (−0.47, 0.11)
0.222
Cognitive performance (133)
−0.12 (−0.22, −0.03)
9.72×10−3
0.477
−0.11 (−0.22, 0.01)
0.061
0.03 (−0.40, 0.46)
0.894
−1
−0.5
0
0.5
1
1.5
Estimate (95% CI)

Supplementary Note for "*Association of OPRM1 functional coding variant with opioid use disorder: A genome-wide association analysis in 114,795 subjects*"

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eMethods

MVP Dataset Quality Control. First, we removed subjects with mismatched genotypic and phenotypic sex and one subject randomly from each pair of related individuals (kinship coefficient ≥0.0884[1]), leaving 107,438 phase2 subjects for subsequent analyses. Then we ran principal components analysis (PCA) on 74,827 common SNPs (MAF >0.05) shared by MVP and the 1000 Genomes phase 3 reference panels[2] using FastPCA.[3] Next, we clustered each participant into the nearest reference population according to the Euclidean distances between the participant and the centers of the 5 reference populations (African, admixed American, East Asian, European, and South Asian) using the first 10 PCs. A second PCA was performed for participants who were clustered with the European reference population (EUR), or who were clustered with the African reference population (AFR), and outliers were removed if any of the first 10 PCs were >3 standard deviations from the mean, leaving 67,268 European-American (EA) and 18,214 African-American (AA) unrelated subjects.

MVP phase2 Imputation. Imputation was performed with EAGLE2[4] and Minimac3[5] using 1000 Genomes Project phase 3 data[2] as the reference panel. Imputed genotypes with posterior probability ≥0.9 were transferred to best-guess genotypes (the rest were treated as missing genotype calls). A total of 5.1 M SNPs in EAs and 6.9 M in AAs with imputation INFO scores ≥0.7, genotype call rates or best-guess rates >0.95, Hardy-Weinberg Equilibrium p-value $>1\times10^{-6}$, and minor allele frequency (MAF) >0.01 were retained for analysis.

Yale-Penn and SAGE datasets. To match the available diagnosis of MVP, the same EA datasets from Cheng et al.[6] were re-analyzed for OD status (case *vs.* control) using logistic regression in this study. AA and EA subjects from Yale-Penn in previously published studies[7]

and newly-genotyped samples were analyzed. All subjects were opioid exposed. Subjects with OD diagnosis information (either affected or not) were included. For EAs, Yale-Penn 1 contains 1,043 cases and 294 controls; Yale-Penn 2 contains 724 cases and 243 controls; Yale-Penn 3 contains 54 cases and 44 controls; SAGE contains 194 cases and 382 controls. For AAs, Yale-Penn 1 contains 831 cases and 573 controls and Yale-Penn 2 contains 349 cases and 274 controls. We used GEMMA[8] for association analyses taking relatedness into account, and correcting for age, sex, and the first 10 PCs.

Gene-based association and gene-set analyses. We performed gene-based association and gene-set analyses for OUD using MAGMA implemented in FUMA.[9,10] The summary data of the OUD meta-analysis was the input for FUMA. For each analysis, Bonferroni corrected p-value <0.05 was set as the significance threshold.

18 correlated traits from published GWASs. Those traits include 'ever smoked regularly', 'current *vs.* former drinker', 'drinks per week', and 'age of initiation of smoking' from GSCAN,[11] 'N02A: Opioid',[12] alcohol dependence from PGC,[13] AUDIT-P,[14] ADHD,[15] MDD,[16] schizophrenia,[17] neuroticism, depressed affect subcluster of neuroticism, and worry subcluster of neuroticism,[18] number of sexual partners and general risk tolerance,[19] insomnia,[20] educational attainment and cognitive performance,[21] and age of first birth.[22]

Mendelian Randomization. For instrumental variants missing in the OUD summary data, we used the results of the best proxy variant in highest LD (r^2>0.8) with the missing variant. If the MAF of the missing variant was <0.01, or none of the variants within 200 kb had LD r^2>0.8, we removed the instrumental variant from the analysis. Palindromic SNPs (A/T or G/C alleles) with

MAF [0.4, 0.5] in the OUD summary data were also removed or replaced with the best proxy variant. For robust causal effect inference, we limited the traits studied to those with >30 available instruments. Accordingly, 12 exposures were analyzed. Multiple testing correction was applied for tested exposures and methods (significance threshold, $0.05/36=1.39\times10^{-3}$). There is only one available instrument in the current OUD study, so unidirectional MR from exposures to OUD was tested. We used weighted median,[23] inverse-variance weighted (IVW, random-effects model),[24] and MR-Egger,[25] implemented in the R package "MendelianRandomization v0.3.0"[26] for MR inference. Evidence of pleiotropic effects was examined by the MR-Egger intercept test, where a non-zero intercept ($p<0.05$) indicates directional pleiotropy.[25] Whereas MR analyses require the beta (effect size) and standard error, we calculated these using Z-scores (z), allele frequency (p) and sample size (n) from the OUD meta-analyses:[27]

$$beta = z \Big/ \sqrt{2p(1-p)(n+z^2)}$$
$$SE = 1 \Big/ \sqrt{2p(1-p)(n+z^2)}.$$

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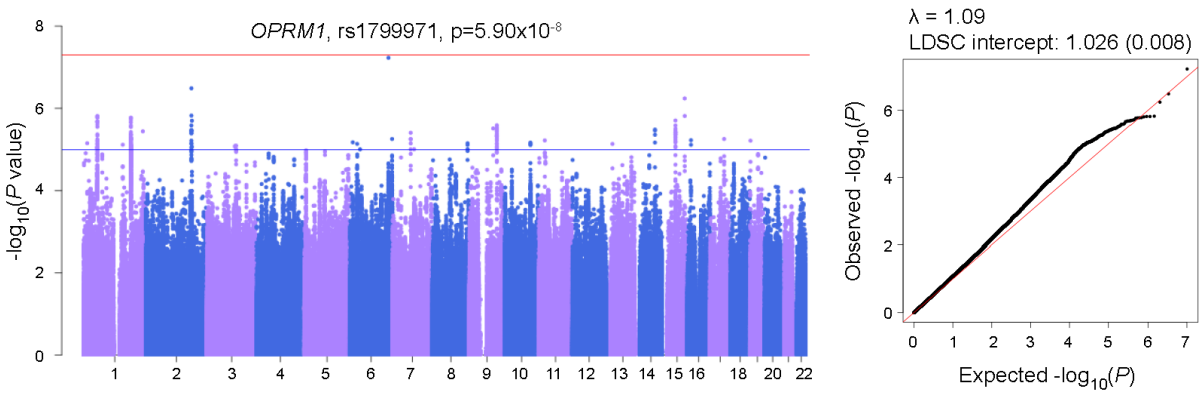
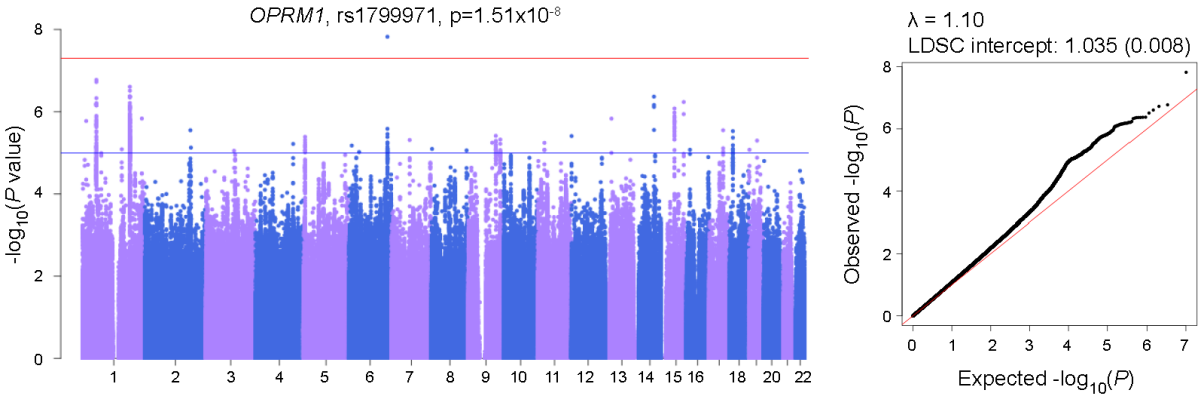
- Wm. Jennings Bryan Dorn VA Medical Center (Kathlyn Sue Haddock)
- VA North Texas Health Care System (Sujata Bhushan)
- Hampton VA Medical Center (Pran Iruvanti)
- Hunter Holmes McGuire VA Medical Center (Michael Godschalk)
- Iowa City VA Health Care System (Zuhair Ballas)
- Jack C. Montgomery VA Medical Center (Malcolm Buford)
- James A. Haley Veterans' Hospital (Stephen Mastorides)
- Louisville VA Medical Center (Jon Klein)
- Manchester VA Medical Center (Nora Ratcliffe)
- Miami VA Health Care System (Hermes Florez)
- Michael E. DeBakey VA Medical Center (Alan Swann)
- Minneapolis VA Health Care System (Maureen Murdoch)
- N. FL/S. GA Veterans Health System (Peruvemba Sriram)
- Northport VA Medical Center (Shing Shing Yeh)
- Overton Brooks VA Medical Center (Ronald Washburn)
- Philadelphia VA Medical Center (Darshana Jhala)
- Phoenix VA Health Care System (Samuel Aguayo)
- Portland VA Medical Center (David Cohen)
- Providence VA Medical Center (Satish Sharma)
- Richard Roudebush VA Medical Center (John Callaghan)
- Salem VA Medical Center (Kris Ann Oursler)
- San Francisco VA Health Care System (Mary Whooley)
- South Texas Veterans Health Care System (Sunil Ahuja)
- Southeast Louisiana Veterans Health Care System (Amparo Gutierrez)

- Southern Arizona VA Health Care System (Ronald Schifman)
- Sioux Falls VA Health Care System (Jennifer Greco)
- St. Louis VA Health Care System (Michael Rauchman)
- Syracuse VA Medical Center (Richard Servatius)
- VA Eastern Kansas Health Care System (Mary Oehlert)
- VA Greater Los Angeles Health Care System (Agnes Wallbom)
- VA Loma Linda Healthcare System (Ronald Fernando)
- VA Long Beach Healthcare System (Timothy Morgan)
- VA Maine Healthcare System (Todd Stapley)
- VA New York Harbor Healthcare System (Scott Sherman)
- VA Pacific Islands Health Care System (Gwenevere Anderson)
- VA Palo Alto Health Care System (Philip Tsao)
- VA Pittsburgh Health Care System (Elif Sonel)
- VA Puget Sound Health Care System (Edward Boyko)
- VA Salt Lake City Health Care System (Laurence Meyer)
- VA San Diego Healthcare System (Samir Gupta)
- VA Southern Nevada Healthcare System (Joseph Fayad)
- VA Tennessee Valley Healthcare System (Adriana Hung)
- Washington DC VA Medical Center (Jack Lichy)
- W.G. (Bill) Hefner VA Medical Center (Robin Hurley)
- White River Junction VA Medical Center (Brooks Robey)
- William S. Middleton Memorial Veterans Hospital (Robert Striker)

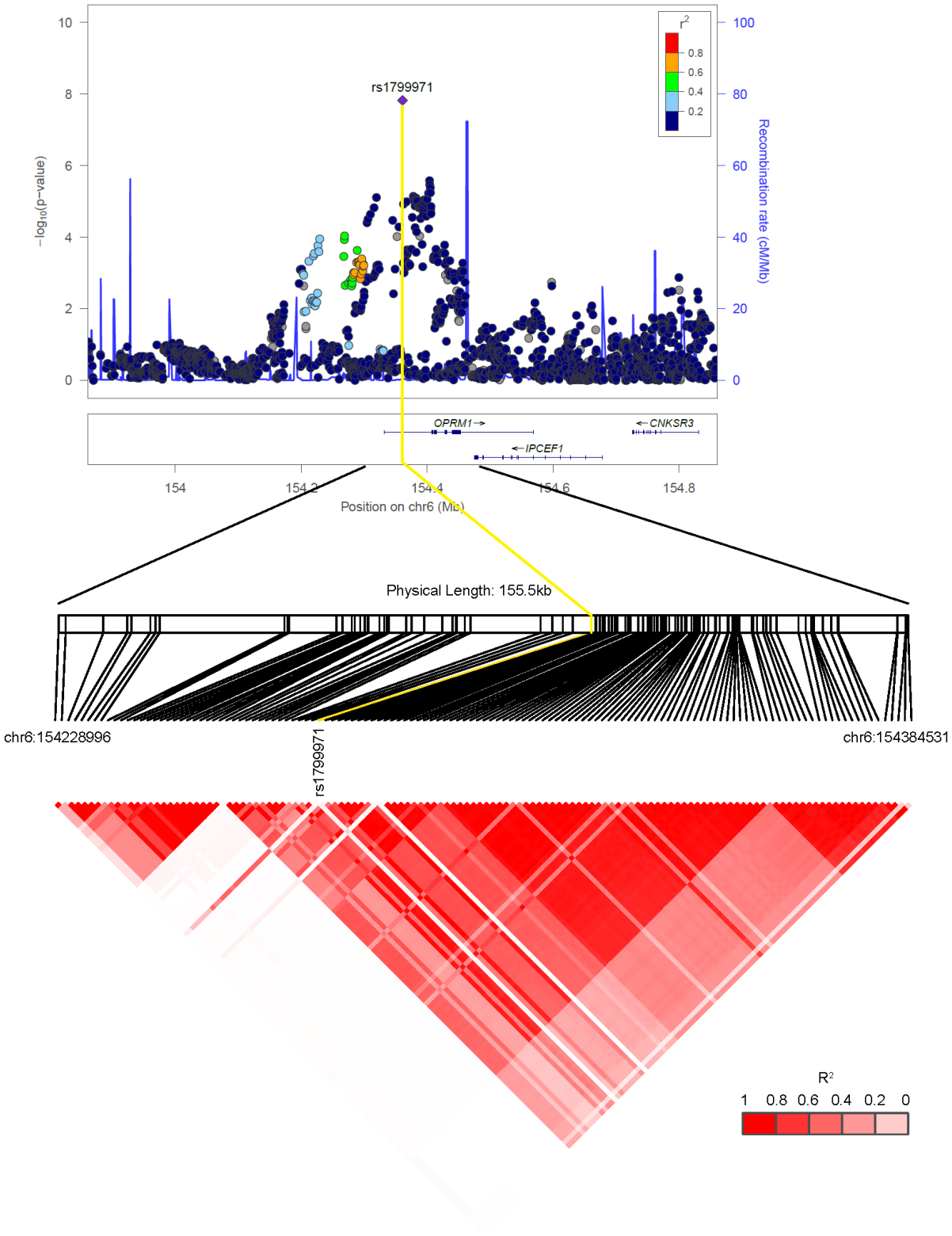
eFigure 1. Manhattan and QQ plots for OUD meta-analysis in MVP EAs (without Yale-Penn or SAGE).



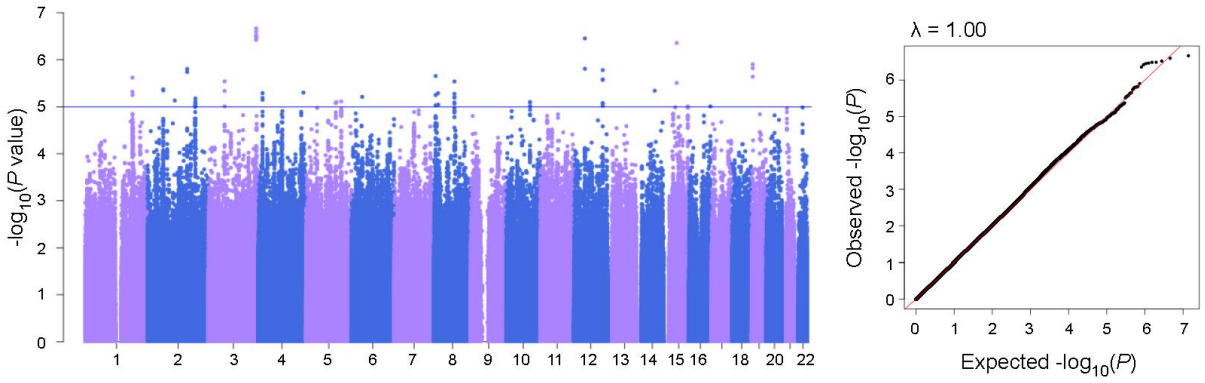
eFigure 2. Manhattan and QQ plots for OUD in the meta-analysis of EAs including all cohorts.



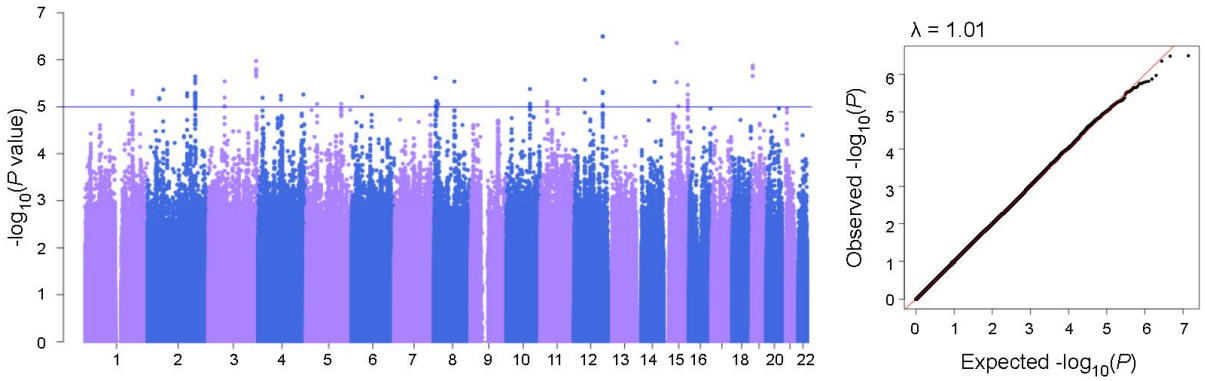
eFigure 3. Regional Manhattan plot for the *OPRM1* region including rs1799971, and LD matrix in 1000 Genome European reference. Pair-wise LD was calculated for SNPs with p<0.001 within ±200kb. 131 SNPs are presented ranging 155.5kb. The yellow line links the position of rs1799971 in the three panels.



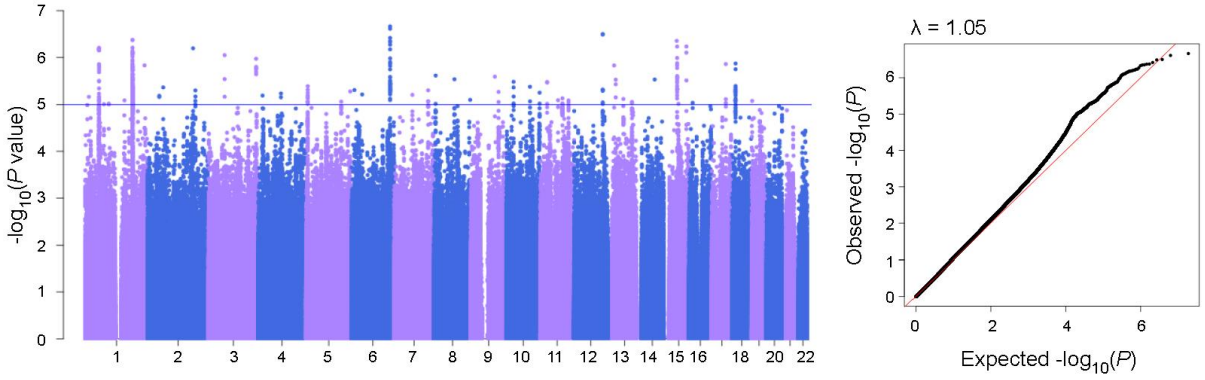
eFigure 4. Manhattan and QQ plots for OUD meta-analysis in MVP AAs (without Yale-Penn).



eFigure 5. Manhattan and QQ plots for OUD in the meta-analysis of AAs including all cohorts.



eFigure 6. Manhattan and QQ plots for OUD in the trans-population meta-analysis.



eTable 1. ICD-9/10 codes for OUD in MVP.

Domain	Code	Name
ICD-9	304.00	Opioid type dependence, Unspecified
	304.01	Opioid type dependence, Continuous
	304.02	Opioid type dependence Episodic
	304.03	Opioid type dependence in remission
	304.70	Combinations of opioid type drug with any other drug dependence, unspecified
	304.71	Combinations of opioid type drug with any other drug dependence, continuous
	304.72	Combinations of opioid type drug with any other drug dependence, episodic use
	304.73	Combinations of opioid type drug with any other drug dependence, in remission
	305.50	Opioid abuse Unspecified
	305.51	Opioid abuse Continuous
	305.52	Opioid abuse Episodic
	305.53	Opioid abuse in remission
ICD-10	F11.10	Opioid abuse uncomplicated
	F11.11	Opioid abuse in remission
	F11.120	Opioid abuse with intoxication uncomplicated
	F11.121	Opioid abuse with intoxication delirium
	F11.122	Opioid abuse with intoxication with perceptual disturbance
	F11.129	Opioid abuse with intoxication unspecified
	F11.14	Opioid abuse with opioid-induced mood disorder
	F11.150	Opioid abuse with opioid-induced psychotic disorder with delusions
	F11.151	Opioid abuse with opioid-induced psychotic disorder with hallucinations
	F11.159	Opioid abuse with opioid-induced psychotic disorder unspecified
	F11.181	Opioid abuse with opioid-induced sexual dysfunction
	F11.182	Opioid abuse with opioid-induced sleep disorder
	F11.188	Opioid abuse with other opioid-induced disorder
	F11.19	Opioid abuse with unspecified opioid-induced disorder
	F11.20	Opioid dependence uncomplicated
	F11.21	Opioid dependence in remission
	F11.220	Opioid dependence with intoxication uncomplicated
	F11.221	Opioid dependence with intoxication delirium
	F11.222	Opioid dependence with intoxication with perceptual disturbance
	F11.229	Opioid dependence with intoxication unspecified
	F11.23	Opioid dependence with withdrawal
	F11.24	Opioid dependence with opioid-induced mood disorder
	F11.250	Opioid dependence with opioid-induced psychotic disorder with delusions
	F11.251	Opioid dependence with opioid-induced psychotic disorder with hallucinations
	F11.259	Opioid dependence with opioid-induced psychotic disorder unspecified
	F11.281	Opioid dependence with opioid-induced sexual dysfunction
	F11.282	Opioid dependence with opioid-induced sleep disorder
	F11.288	Opioid dependence with other opioid-induced disorder
	F11.29	Opioid dependence with unspecified opioid-induced disorder

eTable 2. OUD cases by opioid use trajectory in MVP.

MEDD trajectory groups	Group 1	Group 2	Group 3	Group 4
EA				
#subjects[a]	72,483	36,452	8,285	2,491
#OUD (%)[b]	1,283 (1.77)	1,495 (4.10)	1,035 (12.5)	580 (23.3)
AA				
#subjects[a]	26,853	11,238	1,699	319
#OUD (%)[b]	824 (3.1)	528 (4.70)	197 (11.6)	67 (21.0)

Note: [a]Subjects with OUD before baseline were excluded from trajectory analysis;
[b]Subjects with OUD during follow up were all defined as cases for GWAS analysis.

eTable 3. Genetic correlations between OUD and 715 traits using LDSC. Traits labeled in bold are $p_{Bonferroni} < 0.05$.

Trait2	PMID	Category	Ethnicity	rg	se	p
Ever smoked regularly	30643251	substance use	European	0.4975	0.0556	3.37E-19
Maternal smoking around birth	0	ukbb	European	0.6797	0.0776	2.0569E-18
Age completed full time education	0	ukbb	European	-0.5085	0.0623	3.1703E-16
Qualifications: A levels/AS levels or equivalent	0	ukbb	European	-0.4714	0.0596	2.6778E-15
Qualifications: None of the above	0	ukbb	European	0.4452	0.0582	2.1099E-14
Drinks per week	30643251	substance use	European	0.3836	0.0503	2.43E-14
Past tobacco smoking - less smoked	0	ukbb	European	-0.4132	0.055	5.6473E-14
Educational attainment	30038396	cognitive	European	-0.3742	0.05	7.20E-14
Alcohol usually taken with meals	0	ukbb	European	-0.4635	0.0628	1.5509E-13
Qualifications: College or University degree	0	ukbb	European	-0.3685	0.0532	4.1808E-12
Qualifications: O levels/GCSEs or equivalent	0	ukbb	European	-0.449	0.0652	5.5469E-12
Exposure to tobacco smoke at home	0	ukbb	European	0.7198	0.1052	7.8857E-12
N02A: Opioids	31015401	substance use	European	0.4819	0.0715	1.61E-11
Number of sexual partners	30643258	risk behaviour	European	0.3612	0.0537	1.81E-11
Seen a psychiatrist for nerves_ anxiety_ tension or depression	0	ukbb	European	0.5019	0.0747	1.8909E-11
MDD	30718901	psychiatric	European	0.3521	0.0551	1.62E-10
Overall health rating - poorer rating	0	ukbb	European	0.3571	0.0566	2.7505E-10
Cognitive performance	30038396	cognitive	European	-0.3086	0.0503	8.61E-10
Tense / highly strung	0	ukbb	European	0.3986	0.0652	9.5507E-10
Townsend deprivation index at recruitment	0	ukbb	European	0.4812	0.0787	9.6454E-10
Current employment status: Unable to work because of sickness or disability	0	ukbb	European	0.5614	0.0939	2.2132E-09
Pain type(s) experienced in last month: Back pain	0	ukbb	European	0.4462	0.0747	2.33E-09
Average weekly beer plus cider intake	0	ukbb	European	0.3938	0.0681	7.2646E-09
Medication for pain relief_ constipation_ heartburn: None of the above	0	ukbb	European	-0.3627	0.0633	1.0258E-08
Types of physical activity in last 4 weeks: Heavy DIY (eg: weeding_ lawn mowing_ carpentry_ digging)	0	ukbb	European	-0.4109	0.073	1.8393E-08
Schizophrenia	25056061	psychiatric	European & East Asian	0.291	0.0518	1.9273E-08
Seen doctor (GP) for nerves_ anxiety_ tension or depression	0	ukbb	European	0.3534	0.0633	2.3186E-08
Pain type(s) experienced in last month: None of the above	0	ukbb	European	-0.3903	0.0705	3.1101E-08
Neuroticism	29942085	psychiatric	European	0.2748	0.0513	8.65E-08
Taking other prescription medications	0	ukbb	European	0.3529	0.0661	9.5303E-08
Age of first birth	27798627	reproductive	European	-0.3855	0.0729	1.2541E-07
Medication for pain relief_ constipation_ heartburn: Paracetamol	0	ukbb	European	0.373	0.0708	1.3869E-07
Wheeze or whistling in the chest in last year	0	ukbb	European	0.3448	0.0658	1.5793E-07
Blood clot_ DVT_ bronchitis_ emphysema_ asthma_ rhinitis_ eczema_ allergy diagnosed by doctor: Emphysema/chronic bronchitis	0	ukbb	European	0.5332	0.102	1.7093E-07
Mood swings	0	ukbb	European	0.3227	0.0619	1.8768E-07
Types of physical activity in last 4 weeks: Light DIY (eg: pruning_ watering the lawn)	0	ukbb	European	-0.3754	0.0722	1.9664E-07
Depressed affect subcluster	29942085	psychiatric	European	0.2673	0.0518	2.47E-07
Exposure to tobacco smoke outside home	0	ukbb	European	0.4325	0.084	2.5957E-07
PGC-Alcohol dependence	30482948	substance use	European	0.7335	0.1425	2.65E-07
Age of initiation of smoking	30643251	substance use	European	-0.3525	0.0686	2.78E-07
Frequency of depressed mood in last 2 weeks	0	ukbb	European	0.3777	0.0736	2.8555E-07
Qualifications: Other professional qualifications eg: nursing_ teaching	0	ukbb	European	-0.3489	0.0695	5.1998E-07
Number of incorrect matches in round	0	ukbb	European	0.3267	0.0654	5.9481E-07
Frequency of tenseness / restlessness in last 2 weeks	0	ukbb	European	0.331	0.0666	6.6551E-07
Light smokers_ at least 100 smokes in lifetime	0	ukbb	European	0.4251	0.0856	6.7726E-07
ADHD	30478444	psychiatric	European	0.3566	0.0718	6.78E-07
Mouth/teeth dental problems: None of the above	0	ukbb	European	-0.3707	0.0749	7.3639E-07
Job involves heavy manual or physical work	0	ukbb	European	0.329	0.0667	8.2765E-07
Job involves mainly walking or standing	0	ukbb	European	0.3207	0.0653	8.9916E-07

Medication for pain relief_ constipation_ heartburn: Laxatives (e.g. Dulcolax_ Senokot)	0	ukbb	European	0.5513	0.1123	9.135E-07
Mouth/teeth dental problems: Dentures	0	ukbb	European	0.3445	0.0705	1.0173E-06
Number of treatments/medications taken	0	ukbb	European	0.2949	0.0605	1.1085E-06
Frequency of unenthusiasm / disinterest in last 2 weeks	0	ukbb	European	0.3499	0.0718	1.1097E-06
Smoking/smokers in household	0	ukbb	European	0.7133	0.1465	1.1278E-06
Ever had hysterectomy (womb removed)	0	ukbb	European	0.6415	0.1327	1.3312E-06
Frequency of tiredness / lethargy in last 2 weeks	0	ukbb	European	0.3175	0.0667	1.9011E-06
Risk taking	0	ukbb	European	0.2843	0.06	2.1819E-06
Diagnoses - main ICD10: M54 Dorsalgia	0	ukbb	European	0.5985	0.1265	2.2525E-06
Noisy workplace	0	ukbb	European	0.3727	0.079	0.000002371
Pain type(s) experienced in last month: Neck or shoulder pain	0	ukbb	European	0.3419	0.0725	2.4133E-06
Medication for pain relief_ constipation_ heartburn: Omeprazole (e.g. Zanprol)	0	ukbb	European	0.4232	0.0899	2.4745E-06
Current vs former smoker	30643251	substance use	European	0.3918	0.0844	3.40E-06
Fed-up feelings	0	ukbb	European	0.2834	0.0612	0.000003627
Ever used hormone-replacement therapy (HRT)	0	ukbb	European	0.3942	0.086	4.6246E-06
Age started oral contraceptive pill	0	ukbb	European	-0.3981	0.0871	4.8321E-06
Pain type(s) experienced in last month: Stomach or abdominal pain	0	ukbb	European	0.397	0.0883	6.8597E-06
Time spent using computer	0	ukbb	European	-0.2578	0.0575	7.2478E-06
Duration walking for pleasure	0	ukbb	European	-0.4	0.0902	9.2916E-06
Miserableness	0	ukbb	European	0.2761	0.0626	0.000010416
Illnesses of mother: Chronic bronchitis/emphysema	0	ukbb	European	0.6303	0.1436	0.000011336
Prospective memory result - second attempt	0	ukbb	European	0.4478	0.1029	0.000013391
Insomnia	30804565	sleeping	European	0.2567	0.0591	1.41E-05
Types of transport used (excluding work): Walk	0	ukbb	European	-0.2971	0.0686	0.000015056
Age at last live birth	0	ukbb	European	-0.3132	0.0732	0.00001898
Health satisfaction -unhappy	0	ukbb	European	0.3112	0.0741	0.000026397
Usual walking pace	0	ukbb	European	-0.2416	0.058	0.000030754
Illnesses of father: Lung cancer	0	ukbb	European	0.4832	0.1163	0.000032783
Sensitivity / hurt feelings	0	ukbb	European	0.2514	0.061	0.000037743
Worry subcluster	29942085	psychiatric	European	0.2393	0.0583	4.10E-05
General risk tolerance	30643258	risk behaviour	European	0.2305	0.0563	4.18E-05
AUDIT-P	30336701	substance use	European	0.3404	0.0838	4.84E-05
Ever unenthusiastic/disinterested for a whole week	0	ukbb	European	0.3761	0.0926	0.000048757
Number of self-reported non-cancer illnesses	0	ukbb	European	0.2153	0.0536	0.000058778
Number of full sisters	0	ukbb	European	0.3749	0.0944	0.000071949
Pain type(s) experienced in last month: Hip pain	0	ukbb	European	0.3549	0.0895	0.000073493
Chest pain or discomfort walking normally	0	ukbb	European	0.4479	0.1148	0.000095773
Illness_ injury_ bereavement_ stress in last 2 years: Financial difficulties	0	ukbb	European	0.2904	0.0746	0.000099488
Forced expiratory volume in 1-second (FEV1)_ predicted percentage	0	ukbb	European	-0.219	0.0571	0.0001
Guilty feelings	0	ukbb	European	0.2519	0.0656	0.0001
Non-cancer illness code_ self-reported: emphysema/chronic bronchitis	0	ukbb	European	0.4098	0.1057	0.0001
Number of live births	0	ukbb	European	0.3015	0.0786	0.0001
Job involves shift work	0	ukbb	European	0.35	0.0955	0.0002
Time spent watching television (TV)	0	ukbb	European	0.1964	0.0531	0.0002
Why stopped smoking: None of the above	0	ukbb	European	-0.4202	0.1134	0.0002

Adopted as a child	0	ukbb	European	0.522	0.1441	0.0003
Illnesses of father: None of the above (group 2)	0	ukbb	European	-0.4439	0.1226	0.0003
Average weekly fortified wine intake	0	ukbb	European	-0.5485	0.1545	0.0004
Frequency of walking for pleasure in last 4 weeks	0	ukbb	European	0.2795	0.0803	0.0005
Long-standing illness_ disability or infirmity	0	ukbb	European	0.2009	0.0575	0.0005
Medication for cholesterol_ blood pressure_ diabetes_ or take exogenous hormones: Hormone replacement therapy	0	ukbb	European	0.4168	0.119	0.0005
Types of physical activity in last 4 weeks: Walking for pleasure (not as a means of transport)	0	ukbb	European	-0.2204	0.0634	0.0005
Worrier / anxious feelings	0	ukbb	European	0.2028	0.0579	0.0005
Diagnoses - main ICD10: R10 Abdominal and pelvic pain	0	ukbb	European	0.3761	0.1095	0.0006
Non-cancer illness code_ self-reported: gastro-oesophageal reflux (gord) / gastric reflux	0	ukbb	European	0.4233	0.1234	0.0006
Depressive symptoms	27089181	psychiatric	European	0.2758	0.0818	0.0007
Average weekly red wine intake	0	ukbb	European	-0.2449	0.0726	0.0007
Impedance of leg (left)	0	ukbb	European	0.1392	0.0415	0.0008
Types of physical activity in last 4 weeks: Other exercises (eg: swimming_ cycling_ keep fit_ bowling)	0	ukbb	European	-0.2321	0.0695	0.0008
Ever depressed for a whole week	0	ukbb	European	0.2829	0.0853	0.0009
Irritability	0	ukbb	European	0.1975	0.0595	0.0009
Number of unsuccessful stop-smoking attempts	0	ukbb	European	0.3933	0.1183	0.0009
Nap during day	0	ukbb	European	0.1759	0.0535	0.001
Suffer from nerves	0	ukbb	European	0.2256	0.0693	0.0011
Diagnoses - main ICD10: K29 Gastritis and duodenitis	0	ukbb	European	0.4354	0.1363	0.0014
Pain type(s) experienced in last month: Pain all over the body	0	ukbb	European	0.3717	0.1172	0.0015
Peak expiratory flow (PEF)	0	ukbb	European	-0.1856	0.0585	0.0015
Current employment status: Doing unpaid or voluntary work	0	ukbb	European	-0.4123	0.1303	0.0016
Pain type(s) experienced in last month: Headache	0	ukbb	European	0.2271	0.0718	0.0016
Wears glasses or contact lenses	0	ukbb	European	-0.3256	0.1031	0.0016
Cigarettes per day	30643251	substance use	European	0.267	0.0849	0.0017
Illnesses of father: Chronic bronchitis/emphysema	0	ukbb	European	0.3339	0.1072	0.0018
Impedance of leg (right)	0	ukbb	European	0.1328	0.0424	0.0018
Breastfed as a baby	0	ukbb	European	-0.3292	0.1058	0.0019
Ever had stillbirth_ spontaneous miscarriage or termination	0	ukbb	European	0.3296	0.1077	0.0022
AUDIT	30336701	substance use	European	0.1946	0.0639	0.0023
Types of physical activity in last 4 weeks: None of the above	0	ukbb	European	0.261	0.0855	0.0023
Lung cancer	27488534	cancer	European	0.4359	0.1443	0.0025
Non-cancer illness code_ self-reported: gout	0	ukbb	European	0.232	0.0773	0.0027
Number of days/week walked 10+ minutes	0	ukbb	European	0.1701	0.0571	0.0029
Diagnoses - main ICD10: K62 Other diseases of anus and rectum	0	ukbb	European	0.5499	0.1862	0.0031
Number of operations_ self-reported	0	ukbb	European	0.193	0.0655	0.0032
Diagnoses - main ICD10: K57 Diverticular disease of intestine	0	ukbb	European	0.3173	0.1078	0.0033
Mothers age at death	27015805	aging	European	-0.3488	0.1191	0.0034
Diagnoses - main ICD10: I83 Varicose veins of lower extremities	0	ukbb	European	0.2695	0.0922	0.0035
Illnesses of father: Heart disease	0	ukbb	European	-0.2211	0.0764	0.0038
Neck/shoulder pain for 3+ months	0	ukbb	European	0.5796	0.201	0.0039
Diagnoses - main ICD10: R07 Pain in throat and chest	0	ukbb	European	0.2636	0.0915	0.004
Illness_ injury_ bereavement_ stress in last 2 years: Serious illness_ injury or assault to yourself	0	ukbb	European	0.3417	0.1187	0.004
Loud music exposure frequency	0	ukbb	European	0.3611	0.1259	0.0041
Types of transport used (excluding work): Car/motor vehicle	0	ukbb	European	-0.2589	0.0903	0.0041
Qualifications: CSEs or equivalent	0	ukbb	European	0.2594	0.0907	0.0042
Ever highly irritable/argumentative for 2 days	0	ukbb	European	0.2398	0.0839	0.0043
Diagnoses - main ICD10: K21 Gastro-oesophageal reflux disease	0	ukbb	European	0.4291	0.1513	0.0046
Transport type for commuting to job workplace: Walk	0	ukbb	European	-0.2981	0.1061	0.005
Parents age at death	27015805	aging	European	-0.3796	0.1356	0.0051
Why stopped smoking: Health precaution	0	ukbb	European	0.284	0.1014	0.0051
Bipolar disorder	31043756	psychiatric	European	0.1647	0.059	0.0052
Non-cancer illness code_ self-reported: anxiety/panic attacks	0	ukbb	European	0.4288	0.1552	0.0057
Number of days/week of moderate physical activity 10+ minutes	0	ukbb	European	0.1935	0.0704	0.006
Forced expiratory volume in 1-second (FEV1)_ Best measure	0	ukbb	European	-0.1471	0.0537	0.0062
Time from waking to first cigarette	0	ukbb	European	-0.496	0.181	0.0062

Chest pain or discomfort	0	ukbb	European	0.1965	0.0721	0.0064
Illnesses of siblings: None of the above (group 1)	0	ukbb	European	-0.228	0.0837	0.0065
Financial situation satisfaction -unhappy	0	ukbb	European	0.282	0.1038	0.0066
Age at Menarche	25231870	reproductive	European	0.1417	0.0527	0.0071
Transport type for commuting to job workplace: Cycle	0	ukbb	European	-0.2693	0.1007	0.0075
Pain type(s) experienced in last month: Facial pain	0	ukbb	European	0.3913	0.1466	0.0076
Frequency of stair climbing in last 4 weeks	0	ukbb	European	-0.1933	0.0726	0.0077
Reason for glasses/contact lenses: For short-sightedness_ i.e. only or mainly for distance viewing such as driving_ cinema etc (called myopia)	0	ukbb	European	-0.2033	0.0764	0.0078
Transport type for commuting to job workplace: Public transport	0	ukbb	European	-0.2634	0.0992	0.0079
Difficulty not smoking for 1 day	0	ukbb	European	0.3841	0.146	0.0085
Number of self-reported cancers	0	ukbb	European	0.3639	0.1383	0.0085
Waist-to-hip ratio	25673412	anthropometric	European	0.1413	0.054	0.0089
Loneliness_ isolation	0	ukbb	European	0.1851	0.0711	0.0092
Infant head circumference	22504419	anthropometric	European	-0.3814	0.1469	0.0094
Why stopped smoking: Doctors advice	0	ukbb	European	0.4952	0.1907	0.0094
Family relationship satisfaction -unhappy	0	ukbb	European	0.2444	0.0944	0.0096
Number of depression episodes	0	ukbb	European	0.5403	0.2111	0.0105
Bilateral oophorectomy (both ovaries removed)	0	ukbb	European	0.2863	0.1134	0.0116
Knee pain for 3+ months	0	ukbb	European	0.359	0.1424	0.0117
Fathers age at death	27015805	aging	European	-0.2931	0.1169	0.0121
Shortness of breath walking on level ground	0	ukbb	European	0.2377	0.0958	0.0131
Lifetime cannabis use	30150663	substance use	European	0.1941	0.0786	0.0136
Illnesses of siblings: Diabetes	0	ukbb	European	0.2364	0.0958	0.0136
Nervous feelings	0	ukbb	European	0.1599	0.0648	0.0136
Former alcohol drinker	0	ukbb	European	0.2775	0.114	0.0149
Illness_ injury_ bereavement_ stress in last 2 years: None of the above	0	ukbb	European	-0.197	0.0811	0.0151
Ever manic/hyper for 2 days	0	ukbb	European	0.3528	0.1469	0.0163
Number of full brothers	0	ukbb	European	0.1976	0.0825	0.0166
Diagnoses - main ICD10: K20 Oesophagitis	0	ukbb	European	0.6944	0.2916	0.0172
Automobile speeding	30643258	risk behaviour	European	-0.1301	0.0551	0.0183
Falls in the last year	0	ukbb	European	0.1623	0.0689	0.0185
Non-cancer illness code_ self-reported: osteoarthritis	0	ukbb	European	0.2115	0.0905	0.0194
Tinnitus: Yes_ now most or all of the time	0	ukbb	European	-0.3127	0.1338	0.0195
Mouth/teeth dental problems: Loose teeth	0	ukbb	European	0.2618	0.1133	0.0209
Serumurate overweight	25811787	uric_acid	European	0.2183	0.0947	0.0212
Current employment status: In paid employment or self-employed	0	ukbb	European	-0.2858	0.1244	0.0215
Diagnoses - main ICD10: K51 Ulcerative colitis	0	ukbb	European	0.493	0.2152	0.0219
Diagnoses - main ICD10: R69 Unknown and unspecified causes of morbidity	0	ukbb	European	0.3605	0.1574	0.022
Urate	23263486	other	European	0.1259	0.0557	0.0238
18:2 linoleic acid (LA)	27005778	metabolites	European	-0.3673	0.1665	0.0274
Diagnoses - main ICD10: H26 Other cataract	0	ukbb	European	-0.2505	0.1145	0.0287
Diagnoses - main ICD10: N92 Excessive_ frequent and irregular menstruation	0	ukbb	European	0.2615	0.1197	0.0288
Current employment status: Retired	0	ukbb	European	-0.2679	0.1227	0.029
Medication for pain relief_ constipation_ heartburn: Aspirin	0	ukbb	European	0.1763	0.0808	0.029
Duration of moderate activity	0	ukbb	European	0.1725	0.0795	0.03
Leg fat percentage (left)	0	ukbb	European	0.0899	0.0418	0.0316
Other serious medical condition/disability diagnosed by doctor	0	ukbb	European	0.1632	0.076	0.0318
Diagnoses - main ICD10: Z47 Other orthopaedic follow-up care	0	ukbb	European	0.4137	0.1935	0.0325
Headaches for 3+ months	0	ukbb	European	0.2473	0.1161	0.0331
Alcohol drinker status: Previous	0	ukbb	European	0.2245	0.1054	0.0332
Lung adenocarcinoma	27488534	cancer	European	0.3711	0.1747	0.0337
Pulse wave Arterial Stiffness index	0	ukbb	European	0.2506	0.1182	0.0339
Eye problems/disorders: Cataract	0	ukbb	European	-0.2855	0.1347	0.0341
Subjective well being	27089181	psychiatric	European	-0.181	0.0862	0.0357
Current employment status: Looking after home and/or family	0	ukbb	European	-0.2733	0.131	0.037
Diagnoses - main ICD10: M20 Acquired deformities of fingers and toes	0	ukbb	European	0.2211	0.1063	0.0375
PGC cross-disorder analysis	23453885	psychiatric	European	0.1828	0.0882	0.0383

Age when periods started (menarche)	0	ukbb	European	0.1045	0.051	0.0405
Hand grip strength (right)	0	ukbb	European	-0.1	0.0489	0.041
Leg fat percentage (right)	0	ukbb	European	0.0863	0.0423	0.0411
Tinnitus: Yes_ but not now_ but have in the past	0	ukbb	European	0.3005	0.1496	0.0446
Sodium in urine	0	ukbb	European	0.1168	0.0582	0.0449
Had menopause	0	ukbb	European	0.2418	0.1208	0.0453
Blood clot_ DVT_ bronchitis_ emphysema_ asthma_ rhinitis_ eczema_ allergy diagnosed by doctor: Hayfever_ allergic rhinitis or eczema	0	ukbb	European	-0.1155	0.0577	0.0456
Diagnoses - main ICD10: K44 Diaphragmatic hernia	0	ukbb	European	0.399	0.2015	0.0478
Non-cancer illness code_ self-reported: crohns disease	0	ukbb	European	0.3188	0.1614	0.0482
Pulse wave peak to peak time	0	ukbb	European	-0.2273	0.1159	0.0498
Illness_ injury_ bereavement_ stress in last 2 years: Marital separation/divorce	0	ukbb	European	0.3347	0.1708	0.05
Fracture resulting from simple fall	0	ukbb	European	0.3202	0.1642	0.0512
Non-cancer illness code_ self-reported: angina	0	ukbb	European	0.1547	0.0795	0.0517
AUDIT-C	30336701	substance use	European	0.1301	0.067	0.0521
Number of days/week of vigorous physical activity 10+ minutes	0	ukbb	European	0.131	0.0675	0.0522
Fractured bone site(s): Other bones	0	ukbb	European	0.2513	0.1297	0.0527
Why reduced smoking: Illness or ill health	0	ukbb	European	0.3497	0.1809	0.0532
Diagnoses - main ICD10: K50 Crohns disease [regional enteritis]	0	ukbb	European	0.3557	0.1881	0.0586
Non-cancer illness code_ self-reported: chronic obstructive airways disease/copd	0	ukbb	European	0.3033	0.1611	0.0598
Comparative body size at age 10	0	ukbb	European	-0.0809	0.0434	0.0626
Diagnoses - main ICD10: T84 Complications of internal orthopaedic prosthetic devices_ implants and grafts	0	ukbb	European	0.277	0.1496	0.0642
Childhood IQ	23358156	cognitive	European	-0.2125	0.1149	0.0643
Diagnoses - main ICD10: S66 Injury of muscle and tendon at wrist and hand level	0	ukbb	European	0.4653	0.2515	0.0643
Medication for cholesterol_ blood pressure_ diabetes_ or take exogenous hormones: None of the above	0	ukbb	European	-0.1389	0.0751	0.0644
Cancer code_ self-reported: basal cell carcinoma	0	ukbb	European	0.2009	0.1087	0.0645
Illnesses of siblings: Heart disease	0	ukbb	European	0.198	0.1078	0.0662
Blood clot_ DVT_ bronchitis_ emphysema_ asthma_ rhinitis_ eczema_ allergy diagnosed by doctor: Blood clot in the leg (DVT)	0	ukbb	European	0.1983	0.1081	0.0666
Diagnoses - main ICD10: K52 Other non-infective gastro-enteritis and colitis	0	ukbb	European	0.2872	0.1578	0.0687
Non-cancer illness code_ self-reported: diverticular disease/diverticulitis	0	ukbb	European	0.2238	0.124	0.0711
Vascular/heart problems diagnosed by doctor: Angina	0	ukbb	European	0.1423	0.0796	0.0738
Total lipids in very small VLDL	27005778	metabolites	European	-0.2686	0.1503	0.074
Cancer diagnosed by doctor	0	ukbb	European	0.2354	0.1323	0.0752
Duration of strenuous sports	0	ukbb	European	0.3772	0.213	0.0766
Alcohol drinker status: Never	0	ukbb	European	-0.155	0.088	0.078
Illnesses of mother: Breast cancer	0	ukbb	European	-0.2203	0.125	0.078
Cholesterol esters in medium VLDL	27005778	metabolites	European	-0.2253	0.1285	0.0795
Non-cancer illness code_ self-reported: enlarged prostate	0	ukbb	European	-0.2689	0.1543	0.0813
Mouth/teeth dental problems: Painful gums	0	ukbb	European	0.2661	0.1527	0.0815
Leg fat mass (left)	0	ukbb	European	0.0703	0.0404	0.082
Diagnoses - main ICD10: I80 Phlebitis and thrombophlebitis	0	ukbb	European	0.2279	0.1311	0.0821
Diagnoses - main ICD10: M16 Coxarthrosis [arthrosis of hip]	0	ukbb	European	0.2083	0.1202	0.083
Fractured/broken bones in last 5 years	0	ukbb	European	0.1645	0.0956	0.0852
Free cholesterol in large HDL	27005778	metabolites	European	0.2218	0.129	0.0855
Diagnoses - main ICD10: M17 Gonarthrosis [arthrosis of knee]	0	ukbb	European	0.1942	0.114	0.0883
Squamous cell lung cancer	27488534	cancer	European	0.3398	0.1996	0.0886
Types of transport used (excluding work): Cycle	0	ukbb	European	-0.146	0.086	0.0894
Medication for cholesterol_ blood pressure_ diabetes_ or take exogenous hormones: Cholesterol lowering medication	0	ukbb	European	0.1341	0.079	0.0897
Phospholipids in small VLDL	27005778	metabolites	European	-0.2482	0.1477	0.0929
Ever had bowel cancer screening	0	ukbb	European	0.1707	0.102	0.0943
Free cholesterol to esterified cholesterol ratio	27005778	metabolites	European	-0.4049	0.2434	0.0962
Vitamin and mineral supplements: Vitamin B	0	ukbb	European	0.211	0.1271	0.097
Non-cancer illness code_ self-reported: retinal detachment	0	ukbb	European	-0.3748	0.2267	0.0982

Sitting height ratio	25865494	anthropometric	European	-0.1574	0.0952	0.0985
Pain type(s) experienced in last month: Knee pain	0	ukbb	European	0.1151	0.0697	0.0989
Concentration of very small VLDL particles	27005778	metabolites	European	-0.2319	0.1406	0.099
Fasting proinsulin	20081858	glycemic	European	0.2701	0.1642	0.1001
Handedness (chirality/laterality): Left-handed	0	ukbb	European	0.1876	0.1142	0.1004
Non-cancer illness code_ self-reported: deep venous thrombosis (dvt)	0	ukbb	European	0.1776	0.1085	0.1016
Doctor diagnosed hayfever or allergic rhinitis	0	ukbb	European	-0.1419	0.0868	0.102
Total lipids in small VLDL	27005778	metabolites	European	-0.2207	0.1358	0.1043
Diagnoses - main ICD10: I30 Acute pericarditis	0	ukbb	European	-0.4716	0.2908	0.1048
Systemic lupus erythematosus	26502338	autoimmune	European	0.1594	0.0986	0.1062
Ever taken oral contraceptive pill	0	ukbb	European	0.1803	0.1131	0.111
Total lipids in large HDL	27005778	metabolites	European	0.1878	0.1181	0.1118
Concentration of small VLDL particles	27005778	metabolites	European	-0.2052	0.1304	0.1156
Reason for reducing amount of alcohol drunk: Health precaution	0	ukbb	European	0.1412	0.0902	0.1174
Leg fat mass (right)	0	ukbb	European	0.0635	0.0407	0.1187
Phospholipids in very small VLDL	27005778	metabolites	European	-0.2675	0.1721	0.1201
Diagnoses - main ICD10: I84 Haemorrhoids	0	ukbb	European	0.1809	0.1167	0.1209
Forced vital capacity (FVC)_ Best measure	0	ukbb	European	-0.0801	0.0519	0.1225
Phospholipids in large HDL	27005778	metabolites	European	0.1864	0.1208	0.1228
Free cholesterol	27005778	metabolites	European	-0.392	0.2547	0.1238
Cough on most days	0	ukbb	European	0.1683	0.1107	0.1283
Mineral and other dietary supplements: Glucosamine	0	ukbb	European	-0.1218	0.0801	0.1283
Cholesterol esters in large VLDL	27005778	metabolites	European	-0.1773	0.1168	0.1289
Diagnoses - main ICD10: K43 Ventral hernia	0	ukbb	European	0.2079	0.137	0.129
Diagnoses - main ICD10: J22 Unspecified acute lower respiratory infection	0	ukbb	European	0.3181	0.2098	0.1296
Getting up in morning	0	ukbb	European	-0.0813	0.0538	0.131
Illnesses of siblings: None of the above (group 2)	0	ukbb	European	-0.1909	0.1265	0.1312
Non-cancer illness code_ self-reported: pulmonary embolism +/- dvt	0	ukbb	European	0.2267	0.1505	0.1318
Diagnoses - main ICD10: K30 Dyspepsia	0	ukbb	European	0.3716	0.2473	0.133
Types of transport used (excluding work): Public transport	0	ukbb	European	-0.131	0.0873	0.1336
Diagnoses - main ICD10: I20 Angina pectoris	0	ukbb	European	0.172	0.1148	0.134
Amyotrophic lateral sclerosis	27455348	neurological	European	0.2386	0.1602	0.1362
Total cholesterol in small VLDL	27005778	metabolites	European	-0.267	0.1796	0.1372
Description of average fatty acid chain length; not actual carbon number	27005778	metabolites	European	0.2694	0.1815	0.1377
Crohns disease	26192919	autoimmune	European	0.1057	0.0713	0.1381
Inflammatory Bowel Disease (Euro)	26192919	autoimmune	European	0.0908	0.0617	0.1413
Total cholesterol in large VLDL	27005778	metabolites	European	-0.1867	0.1277	0.1439
Cholesterol esters in large HDL	27005778	metabolites	European	0.1777	0.1221	0.1456
Diagnoses - main ICD10: K40 Inguinal hernia	0	ukbb	European	-0.1327	0.0913	0.1459
Number of children ever born	27798627	reproductive	European	0.1196	0.0824	0.1467
Transport type for commuting to job workplace: Car/motor vehicle	0	ukbb	European	0.1643	0.1134	0.1475
Non-cancer illness code_ self-reported: hiatus hernia	0	ukbb	European	0.1985	0.1373	0.1483
Concentration of large HDL particles	27005778	metabolites	European	0.1691	0.1172	0.1491
Triglycerides in IDL	27005778	metabolites	European	-0.2028	0.1409	0.15
Medication for pain relief_ constipation_ heartburn: Ibuprofen (e.g. Nurofen)	0	ukbb	European	0.121	0.0842	0.1507
Diagnoses - main ICD10: C61 Malignant neoplasm of prostate	0	ukbb	European	0.2417	0.1693	0.1535
Total cholesterol in large HDL	27005778	metabolites	European	0.1818	0.1279	0.155
Number of pregnancy terminations	0	ukbb	European	0.1688	0.1189	0.1555
Citrate	27005778	metabolites	European	-0.2841	0.2006	0.1566
Triglycerides in very small VLDL	27005778	metabolites	European	-0.1805	0.1281	0.1588
Omega-9 and saturated fatty acids	27005778	metabolites	European	-0.2483	0.1765	0.1596
Diagnoses - main ICD10: N81 Female genital prolapse	0	ukbb	European	0.2132	0.152	0.1607
Concentration of IDL particles	27005778	metabolites	European	-0.2637	0.189	0.1629
Age at Menopause	26414677	reproductive	European	-0.1146	0.0824	0.1645
Leptin_adjBMI	26833098	hormone	European	-0.16	0.1153	0.1651
Mineral and other dietary supplements: Selenium	0	ukbb	European	0.2039	0.1471	0.1657
Mouth/teeth dental problems: Toothache	0	ukbb	European	0.1623	0.1176	0.1673
Impedance of whole body	0	ukbb	European	0.0559	0.0406	0.1679
Bring up phlegm/sputum/mucus on most days	0	ukbb	European	0.2104	0.1527	0.1681

Systolic blood pressure_ automated reading	0	ukbb	European	-0.0708	0.0514	0.1684
Triglycerides in small HDL	27005778	metabolites	European	-0.2554	0.1861	0.1701
Total lipids in IDL	27005778	metabolites	European	-0.2717	0.1983	0.1706
Mean diameter for HDL particles	27005778	metabolites	European	0.1672	0.1223	0.1716
Illnesses of father: Diabetes	0	ukbb	European	-0.1263	0.0931	0.1747
Non-cancer illness code_ self-reported: asthma	0	ukbb	European	0.0782	0.0576	0.175
Rheumatoid Arthritis	24390342	autoimmune	European	0.1303	0.0966	0.1777
Free cholesterol in small VLDL	27005778	metabolites	European	-0.2074	0.1544	0.1793
Diagnoses - main ICD10: J33 Nasal polyp	0	ukbb	European	0.2181	0.1625	0.1796
Vitamin and mineral supplements: Multivitamins +/- minerals	0	ukbb	European	0.1076	0.0804	0.1812
Triglycerides in small VLDL	27005778	metabolites	European	-0.181	0.1358	0.1826
Serum total cholesterol	27005778	metabolites	European	-0.2854	0.2146	0.1836
Diagnoses - main ICD10: F31 Bipolar affective disorder	0	ukbb	European	0.2244	0.1689	0.184
Non-cancer illness code_ self-reported: hypertension	0	ukbb	European	0.0671	0.0506	0.185
Glycoprotein acetyls; mainly a1-acid glycoprotein	27005778	metabolites	European	-0.2025	0.1539	0.1883
Urinary albumin-to-creatinine ratio (non-diabetes)	26631737	kidney	European	0.1453	0.1109	0.1904
Femoral Neck bone mineral density	26367794	bone	European	0.1232	0.0943	0.1914
Illnesses of mother: Alzheimers disease/dementia	0	ukbb	European	-0.4058	0.3125	0.1941
Illnesses of mother: None of the above (group 2)	0	ukbb	European	-0.1809	0.1395	0.1947
Diagnoses - main ICD10: R55 Syncope and collapse	0	ukbb	European	0.1688	0.1305	0.1958
Eye problems/disorders: Diabetes related eye disease	0	ukbb	European	0.1864	0.1445	0.197
Free cholesterol in large VLDL	27005778	metabolites	European	-0.1586	0.1231	0.1976
Diagnoses - main ICD10: C50 Malignant neoplasm of breast	0	ukbb	European	0.1454	0.1129	0.1977
Serum creatinine	26831199	kidney	European & African	0.0871	0.0678	0.1989
Ever stopped smoking for 6+ months	0	ukbb	European	0.2204	0.172	0.2002
Non-cancer illness code_ self-reported: mania/bipolar disorder/manic depression	0	ukbb	European	0.2303	0.1805	0.2021
Type of tobacco previously smoked: Cigars or pipes	0	ukbb	European	-0.2808	0.2205	0.2028
Illness_ injury_ bereavement_ stress in last 2 years: Serious illness_ injury or assault of a close relative	0	ukbb	European	-0.1584	0.1245	0.2033
Leg pain on walking	0	ukbb	European	0.1114	0.0877	0.204
Total cholesterol in medium VLDL	27005778	metabolites	European	-0.1725	0.1362	0.2052
Diagnoses - main ICD10: I25 Chronic ischaemic heart disease	0	ukbb	European	0.1088	0.0859	0.2053
Home area population density - urban or rural: Scotland - Large Urban Area	0	ukbb	European	-0.1831	0.1446	0.2053
Cholesterol esters in medium LDL	27005778	metabolites	European	-0.2717	0.2159	0.2081
Diastolic blood pressure_ automated reading	0	ukbb	European	-0.062	0.0493	0.2086
Diagnoses - main ICD10: K22 Other diseases of oesophagus	0	ukbb	European	0.2536	0.2019	0.2091
Total cholesterol in IDL	27005778	metabolites	European	-0.2666	0.2124	0.2093
Total lipids in very large HDL	27005778	metabolites	European	0.2348	0.1877	0.211
Diagnoses - main ICD10: N32 Other disorders of bladder	0	ukbb	European	0.1945	0.1556	0.2112
Alcohol intake versus 10 years previously - less nowadays	0	ukbb	European	0.0904	0.0725	0.2129
Difference in height between childhood and adulthood; age 8	23449627	anthropometric	European	-0.1355	0.1094	0.2153
Waist circumference	25673412	anthropometric	European	0.0619	0.0503	0.2183
Total cholesterol in HDL	27005778	metabolites	European	0.1689	0.1379	0.2206
Diagnoses - main ICD10: R04 Haemorrhage from respiratory passages	0	ukbb	European	0.2876	0.2352	0.2213
Illnesses of mother: Heart disease	0	ukbb	European	0.1261	0.1035	0.2228
Mono-unsaturated fatty acids	27005778	metabolites	European	-0.1745	0.144	0.2257
Types of physical activity in last 4 weeks: Strenuous sports	0	ukbb	European	-0.1112	0.0922	0.2274
Blood clot_ DVT_ bronchitis_ emphysema_ asthma_ rhinitis_ eczema_ allergy diagnosed by doctor: Asthma	0	ukbb	European	0.0676	0.0564	0.2308
Father still alive	0	ukbb	European	-0.1773	0.148	0.231
Forced expiratory volume in 1 second (FEV1)	28166213	lung_function	European	-0.077	0.0644	0.2319
Serum total triglycerides	27005778	metabolites	European	-0.1539	0.1288	0.2322
ICV	25607358	brain_volume	European	-0.1688	0.1414	0.2324
Mineral and other dietary supplements: Calcium	0	ukbb	European	-0.136	0.1139	0.2324
Duration of heavy DIY	0	ukbb	European	-0.1158	0.0973	0.2339
Cholesterol esters in large LDL	27005778	metabolites	European	-0.2651	0.2248	0.2382
Phenylalanine	27005778	metabolites	European	-0.232	0.1969	0.2387
Blood clot_ DVT_ bronchitis_ emphysema_ asthma_ rhinitis_ eczema_ allergy diagnosed by doctor: Blood clot in the lung	0	ukbb	European	0.1707	0.1449	0.239
Frequency of travelling from home to job workplace	0	ukbb	European	0.1427	0.1214	0.2397
Non-cancer illness code_ self-reported: hypothyroidism/myxoedema	0	ukbb	European	0.08	0.068	0.2397

Mouth/teeth dental problems: Bleeding gums	0	ukbb	European	0.1029	0.0877	0.2404
Duration of fitness test	0	ukbb	European	-0.2319	0.1976	0.2405
Leptin_not_adjBMI	26833098	hormone	European	-0.1328	0.1133	0.2415
Reproduciblity of spirometry measurement using ERS/ATS criteria	0	ukbb	European	-0.1338	0.1144	0.2422
Phospholipids in very large HDL	27005778	metabolites	European	0.158	0.139	0.2559
Forearm Bone mineral density	26367794	bone	European	0.2385	0.2104	0.257
Mean diameter for VLDL particles	27005778	metabolites	European	-0.1361	0.121	0.2607
Phospholipids in IDL	27005778	metabolites	European	-0.2369	0.211	0.2617
Non-cancer illness code_ self-reported: high cholesterol	0	ukbb	European	0.0884	0.0788	0.2619
Forced Vital capacity(FVC)	28166213	lung_function	European	-0.0732	0.0663	0.27
Tinnitus: Yes_ now some of the time	0	ukbb	European	0.2808	0.2546	0.2701
Diagnoses - main ICD10: M67 Other disorders of synovium and tendon	0	ukbb	European	0.2634	0.2408	0.274
Obesity class 2	23563607	anthropometric	European	0.0701	0.0643	0.2755
Concentration of large LDL particles	27005778	metabolites	European	-0.2269	0.2085	0.2765
Total lipids in large LDL	27005778	metabolites	European	-0.2337	0.2148	0.2765
Alzheimers disease	30617256	neurological	European	0.1516	0.1397	0.2777
Diagnoses - main ICD10: I48 Atrial fibrillation and flutter	0	ukbb	European	0.1206	0.1111	0.2778
Non-cancer illness code_ self-reported: muscle or soft tissue injuries	0	ukbb	European	0.2335	0.2168	0.2815
Serum creatinine (non-diabetes)	26831199	kidney	European & African	0.0731	0.0681	0.283
Chronic Kidney Disease	26831199	kidney	European & African	-0.1861	0.1752	0.2884
Diagnoses - main ICD10: S09 Other and unspecified injuries of head	0	ukbb	European	0.2237	0.2111	0.2892
Duration of vigorous activity	0	ukbb	European	0.0986	0.0934	0.2912
Reason for glasses/contact lenses: For astigmatism	0	ukbb	European	-0.1304	0.1238	0.2925
Free cholesterol in very large HDL	27005778	metabolites	European	0.1954	0.1865	0.2947
Diagnoses - main ICD10: Z09 Follow-up examination after treatment for conditions other than malignant neoplasms	0	ukbb	European	0.2053	0.1962	0.2955
Triglycerides	20686565	lipids	European	0.0685	0.0658	0.2979
Free cholesterol in IDL	27005778	metabolites	European	-0.1953	0.1878	0.2983
Platelet count	22139419	haemotological	European	0.0704	0.0681	0.3009
Total cholesterol in large LDL	27005778	metabolites	European	-0.2207	0.2147	0.3038
Coronary artery disease	26343387	cardiometabolic	European, South Asian, East Asian, Hispanic & African American	0.0632	0.0615	0.304
Apolipoprotein B	27005778	metabolites	European	-0.1887	0.1843	0.306
Omega-3 fatty acids	27005778	metabolites	European	-0.1503	0.1469	0.3062
Total lipids in medium LDL	27005778	metabolites	European	-0.2081	0.2045	0.3089
Vascular/heart problems diagnosed by doctor: None of the above	0	ukbb	European	-0.0511	0.0504	0.3099
Pulse rate_ automated reading	0	ukbb	European	0.0555	0.0547	0.31
Concentration of medium LDL particles	27005778	metabolites	European	-0.2047	0.202	0.3109
Vascular/heart problems diagnosed by doctor: Heart attack	0	ukbb	European	0.0831	0.0821	0.3117
Non-cancer illness code_ self-reported: heart attack/myocardial infarction	0	ukbb	European	0.0812	0.0805	0.313
Diagnoses - main ICD10: B37 Candidiasis	0	ukbb	European	0.5244	0.5237	0.3167
Daytime dozing / sleeping (narcolepsy)	0	ukbb	European	0.0681	0.0686	0.3208
Happiness -unhappy	0	ukbb	European	0.092	0.0929	0.322
Relative age voice broke	0	ukbb	European	-0.0672	0.068	0.3236
Neo-conscientiousness	21173776	personality	European	-0.173	0.1766	0.3272
Isoleucine	27005778	metabolites	European	-0.1745	0.1792	0.3302
Vascular/heart problems diagnosed by doctor: High blood pressure	0	ukbb	European	0.0492	0.051	0.3343
Mean Hippocampus	25607358	brain_volume	European	0.1743	0.1808	0.335
Qualifications: NVQ or HND or HNC or equivalent	0	ukbb	European	0.089	0.0924	0.3354
Triglycerides in very large VLDL	27005778	metabolites	European	-0.1232	0.1282	0.3364
Total lipids in very large VLDL	27005778	metabolites	European	-0.1158	0.1207	0.3372
Eczema	26482879	autoimmune	European,	0.1106	0.1165	0.3423

			African, East Asian & Hispanic			
Total lipids in medium VLDL	27005778	metabolites	European	-0.1206	0.1275	0.3442
Primary biliary cirrhosis	26394269	autoimmune	European	0.0886	0.0939	0.3453
Illnesses of father: None of the above (group 1)	0	ukbb	European	0.1077	0.1141	0.3454
Length of working week for main job	0	ukbb	European	0.1075	0.114	0.3454
Mean platelet volume	22139419	haemotological	European	-0.0791	0.0847	0.3501
Back pain for 3+ months	0	ukbb	European	0.1	0.1071	0.3502
Apolipoprotein A-I	27005778	metabolites	European	0.1559	0.1669	0.3503
Home area population density - urban or rural: England/Wales - Village - less sparse	0	ukbb	European	-0.2535	0.2728	0.3526
Frequency of light DIY in last 4 weeks	0	ukbb	European	-0.1116	0.1201	0.3529
Vitamin and mineral supplements: Vitamin A	0	ukbb	European	0.1764	0.1901	0.3532
Total cholesterol in small LDL	27005778	metabolites	European	-0.2042	0.2205	0.3546
Concentration of medium VLDL particles	27005778	metabolites	European	-0.1107	0.1196	0.3548
Pulse rate	0	ukbb	European	-0.067	0.0725	0.3556
Mean Pallidum	25607358	brain_volume	European	0.1114	0.1208	0.3563
Ever had prostate specific antigen (PSA) test	0	ukbb	European	-0.0956	0.1037	0.3564
Phospholipids in medium VLDL	27005778	metabolites	European	-0.1256	0.1366	0.3579
Free cholesterol in medium HDL	27005778	metabolites	European	0.1425	0.1554	0.3591
Lumbar Spine bone mineral density	26367794	bone	European	0.0847	0.0933	0.364
Ulcerative colitis	26192919	autoimmune	European	0.0711	0.0784	0.3643
Cancer code_ self-reported: squamous cell carcinoma	0	ukbb	European	0.2673	0.2965	0.3674
Mean diameter for LDL particles	27005778	metabolites	European	-0.1952	0.2167	0.3678
Tyrosine	27005778	metabolites	European	0.1331	0.1479	0.3683
Child birth weight	23202124	anthropometric	European	-0.1037	0.1158	0.3706
Primary sclerosing cholangitis	27992413	autoimmune	European & non-European	-0.092	0.1029	0.3713
Non-cancer illness code_ self-reported: joint disorder	0	ukbb	European	0.2414	0.2703	0.3718
Frequency of other exercises in last 4 weeks	0	ukbb	European	0.1024	0.1147	0.3721
Time spent driving	0	ukbb	European	-0.0644	0.0724	0.3741
Leg predicted mass (right)	0	ukbb	European	-0.04	0.045	0.3749
Leg fat-free mass (right)	0	ukbb	European	-0.0395	0.045	0.3796
Distance between home and job workplace	0	ukbb	European	-0.1397	0.159	0.3798
Arm predicted mass (left)	0	ukbb	European	0.0381	0.0436	0.3817
Phospholipids in large LDL	27005778	metabolites	European	-0.1777	0.2032	0.3818
Forced expiratory volume in 1 second (FEV1)/Forced Vital capacity(FVC)	28166213	lung_function	European	-0.0566	0.0656	0.3881
Concentration of small LDL particles	27005778	metabolites	European	-0.1453	0.1701	0.3931
HbA1C	20858683	glycemic	European	-0.1027	0.1205	0.394
Alcohol intake frequency - lower frequency	0	ukbb	European	-0.0441	0.052	0.3955
Phospholipids in very large VLDL	27005778	metabolites	European	-0.112	0.1318	0.3956
Diagnoses - main ICD10: R31 Unspecified haematuria	0	ukbb	European	0.1687	0.1995	0.3977
Underlying (primary) cause of death: ICD10: J84.1 Other interstitial pulmonary diseases with fibrosis	0	ukbb	European	-0.1818	0.216	0.4
Duration of light DIY	0	ukbb	European	-0.078	0.0928	0.4006
Illnesses of father: High blood pressure	0	ukbb	European	-0.0847	0.1016	0.4045
Diagnoses - main ICD10: K35 Acute appendicitis	0	ukbb	European	-0.1592	0.1923	0.4079
Non-cancer illness code_ self-reported: hyperthyroidism/thyrotoxicosis	0	ukbb	European	0.1004	0.1217	0.4093
Whole body fat mass	0	ukbb	European	0.0331	0.0401	0.4093
Transferrin	25352340	metal	European	0.0808	0.0981	0.4101
Weight change compared with 1 year ago	0	ukbb	European	0.0959	0.117	0.4123
Hand grip strength (left)	0	ukbb	European	-0.0393	0.0485	0.4175
Creatinine (enzymatic) in urine	0	ukbb	European	0.0458	0.057	0.4213
Hair/balding pattern: Pattern 2	0	ukbb	European	0.0651	0.0812	0.423
Fractured bone site(s): Ankle	0	ukbb	European	0.1363	0.1716	0.4269
Heel bone mineral density (BMD) T-score_ automated (left)	0	ukbb	European	-0.0438	0.0552	0.4273
Free cholesterol in medium VLDL	27005778	metabolites	European	-0.1067	0.1353	0.4305
Had other major operations	0	ukbb	European	0.0763	0.0978	0.4352
Neo-openness to experience	21173776	personality	European	-0.1153	0.1483	0.4369
Albumin	27005778	metabolites	European	-0.1694	0.2186	0.4383
Illnesses of siblings: High blood pressure	0	ukbb	European	0.0615	0.0795	0.4391
Diagnoses - main ICD10: M10 Gout	0	ukbb	European	0.2266	0.293	0.4393
Diagnoses - main ICD10: I10 Essential (primary)	0	ukbb	European	0.2014	0.2605	0.4394

hypertension						
Mean Thalamus	25607358	brain_volume	European	-0.1191	0.1541	0.4395
Trunk fat percentage	0	ukbb	European	0.0317	0.0411	0.4411
Total lipids in chylomicrons and largest VLDL particles	27005778	metabolites	European	-0.0935	0.122	0.4437
Total lipids in small LDL	27005778	metabolites	European	-0.1387	0.1816	0.445
Hearing difficulty/problems: Yes	0	ukbb	European	0.0472	0.0619	0.446
Duration of walks	0	ukbb	European	0.0518	0.068	0.4461
Trunk fat mass	0	ukbb	European	0.0312	0.041	0.4464
Target heart rate achieved	0	ukbb	European	0.1307	0.1722	0.4477
Cholesterol esters in medium HDL	27005778	metabolites	European	0.1417	0.1868	0.4482
Arm predicted mass (right)	0	ukbb	European	0.0343	0.0452	0.4486
Non-cancer illness code_ self-reported: type 2 diabetes	0	ukbb	European	-0.1054	0.1398	0.4512
Arm fat-free mass (left)	0	ukbb	European	0.0331	0.0442	0.4541
Cancer code_ self-reported: malignant melanoma	0	ukbb	European	0.1307	0.1756	0.4568
Free cholesterol in large LDL	27005778	metabolites	European	-0.1508	0.2027	0.4569
Non-cancer illness code_ self-reported: ulcerative colitis	0	ukbb	European	0.1061	0.1443	0.4622
Pulse wave reflection index	0	ukbb	European	0.0738	0.1005	0.4626
No-wear time bias adjusted acceleration standard deviation	0	ukbb	European	-0.0702	0.0959	0.4641
Concentration of very large HDL particles	27005778	metabolites	European	0.1096	0.1503	0.466
Total cholesterol in very large HDL	27005778	metabolites	European	0.159	0.2187	0.4673
Leg predicted mass (left)	0	ukbb	European	-0.0321	0.0445	0.4702
Non-cancer illness code_ self-reported: iron deficiency anaemia	0	ukbb	European	0.1264	0.1756	0.4715
Leg fat-free mass (left)	0	ukbb	European	-0.032	0.0444	0.4716
Fractured bone site(s): Arm	0	ukbb	European	0.1274	0.1782	0.4745
Diagnoses - main ICD10: R14 Flatulence and related conditions	0	ukbb	European	-0.1364	0.191	0.4751
Phospholipids in large VLDL	27005778	metabolites	European	-0.0927	0.1301	0.4763
Diagnoses - main ICD10: E04 Other non-toxic goitre	0	ukbb	European	0.1289	0.181	0.4766
Arm fat-free mass (right)	0	ukbb	European	0.032	0.045	0.4772
Birth weight of first child	0	ukbb	European	-0.0444	0.0632	0.4821
Serum cystatin c	26831199	kidney	European & African	0.0712	0.1015	0.4827
Reason for glasses/contact lenses: For just reading/near work as you are getting older (called presbyopia)	0	ukbb	European	0.1276	0.1837	0.4874
Total lipids in medium HDL	27005778	metabolites	European	0.1233	0.1776	0.4875
Non-cancer illness code_ self-reported: nasal polyps	0	ukbb	European	0.1034	0.1494	0.4888
Non-cancer illness code_ self-reported: bone disorder	0	ukbb	European	0.2431	0.3568	0.4957
Celiac disease	20190752	autoimmune	European	-0.0876	0.129	0.4974
Diagnoses - main ICD10: Z80 Family history of malignant neoplasm	0	ukbb	European	-0.204	0.3012	0.4983
Total cholesterol in LDL	27005778	metabolites	European	-0.141	0.2084	0.4986
Non-cancer illness code_ self-reported: psoriasis	0	ukbb	European	-0.0871	0.1288	0.4988
Diagnoses - main ICD10: D25 Leiomyoma of uterus	0	ukbb	European	0.1018	0.1507	0.4991
Concentration of chylomicrons and largest VLDL particles	27005778	metabolites	European	-0.0939	0.1394	0.5005
Parkinsons disease	19915575	neurological	European	-0.0705	0.1052	0.5027
Glutamine	27005778	metabolites	European	0.1021	0.1526	0.5036
Anorexia Nervosa	28494655	psychiatric	European	0.0783	0.1174	0.5047
Diagnoses - main ICD10: R35 Polyuria	0	ukbb	European	-0.1669	0.2526	0.5087
Diagnoses - main ICD10: K76 Other diseases of liver	0	ukbb	European	0.1477	0.2253	0.5121
Difference in height between adolescence and adulthood; age 14	23449627	anthropometric	European	0.0877	0.1341	0.513
Diagnoses - main ICD10: L03 Cellulitis	0	ukbb	European	0.129	0.198	0.5147
Asthma	17611496	autoimmune	European	0.0906	0.1395	0.5157
Average weekly spirits intake	0	ukbb	European	-0.0576	0.0889	0.5174
Phospholipids in medium HDL	27005778	metabolites	European	0.1003	0.155	0.5177
Phospholipids in chylomicrons and largest VLDL particles	27005778	metabolites	European	-0.0852	0.1333	0.523
Most recent bowel cancer screening	0	ukbb	European	0.1277	0.2008	0.5248
Total lipids in large VLDL	27005778	metabolites	European	-0.0763	0.1209	0.5279
Mean Accumbens	25607358	brain_volume	European	0.1448	0.23	0.5292
Concentration of medium HDL particles	27005778	metabolites	European	0.1095	0.1742	0.5296
Non-cancer illness code_ self-reported: varicose veins	0	ukbb	European	-0.1051	0.1675	0.5306
Total cholesterol in medium LDL	27005778	metabolites	European	-0.1246	0.1998	0.5329
Total cholesterol in medium HDL	27005778	metabolites	European	0.1063	0.1709	0.5337
Extreme bmi	23563607	anthropometric	European	0.049	0.0788	0.5343
Non-cancer illness code_ self-reported: migraine	0	ukbb	European	-0.0524	0.0845	0.5356
Non-cancer illness code_ self-reported: sleep apnoea	0	ukbb	European	0.1314	0.2124	0.5361

Diagnoses - main ICD10: D12 Benign neoplasm of colon_ rectum_ anus and anal canal	0	ukbb	European	-0.0729	0.1181	0.537
Diagnoses - main ICD10: K80 Cholelithiasis	0	ukbb	European	0.0723	0.1187	0.5425
HDL cholesterol	20686565	lipids	European	-0.0425	0.0698	0.5428
Illness_ injury_ bereavement_ stress in last 2 years: Death of a close relative	0	ukbb	European	0.0882	0.146	0.5458
Other eye problems	0	ukbb	European	0.0778	0.1295	0.5478
Mineral and other dietary supplements: None of the above	0	ukbb	European	0.0493	0.0825	0.5496
Heart rate	23583979	haemotological	European & Indian Asian	-0.0541	0.0911	0.5528
Work/job satisfaction - unhappy	0	ukbb	European	0.0723	0.1223	0.5545
Diagnoses - main ICD10: C44 Other malignant neoplasms of skin	0	ukbb	European	0.0654	0.1109	0.5556
Diagnoses - main ICD10: M72 Fibroblastic disorders	0	ukbb	European	-0.0658	0.112	0.557
Heel bone mineral density (BMD) T-score_ automated (right)	0	ukbb	European	-0.0324	0.0553	0.5575
Non-cancer illness code_ self-reported: pneumothorax	0	ukbb	European	0.105	0.1793	0.558
Medication for cholesterol_ blood pressure or diabetes: Cholesterol lowering medication	0	ukbb	European	0.0457	0.0782	0.5591
Triglycerides in chylomicrons and largest VLDL particles	27005778	metabolites	European	-0.0803	0.1395	0.5646
Impedance of arm (left)	0	ukbb	European	-0.0244	0.0425	0.5661
Used an inhaler for chest within last hour	0	ukbb	European	0.1036	0.1816	0.5685
Friendships satisfaction -unhappy	0	ukbb	European	-0.0484	0.0855	0.5715
Eye problems/disorders: Glaucoma	0	ukbb	European	-0.067	0.1187	0.5723
Fasting insulin main effect	22581228	glycemic	European	0.0526	0.0933	0.5732
Medication for cholesterol_ blood pressure or diabetes: Insulin	0	ukbb	European	0.1217	0.2171	0.5751
Autism spectrum disorder	28540026	psychiatric	European	-0.0598	0.1075	0.578
Birth weight	27680694	anthropometric	European	0.036	0.065	0.5796
Ferritin	25352340	metal	European	-0.0755	0.1363	0.5796
Reason for glasses/contact lenses: For long-sightedness_ i.e. for distance and near_ but particularly for near tasks like reading (called hypermetropia)	0	ukbb	European	-0.0732	0.1333	0.5828
Fasting glucose main effect	22581228	glycemic	European	0.0445	0.0816	0.5857
Doctor diagnosed asthma	0	ukbb	European	-0.0461	0.0846	0.5857
Valine	27005778	metabolites	European	-0.0923	0.1697	0.5866
Vitamin and mineral supplements: None of the above	0	ukbb	European	-0.0401	0.074	0.5877
Medication for cholesterol_ blood pressure or diabetes: Blood pressure medication	0	ukbb	European	0.0352	0.0651	0.5888
Cancer code_ self-reported: breast cancer	0	ukbb	European	0.0616	0.114	0.5889
Illnesses of mother: None of the above (group 1)	0	ukbb	European	-0.0543	0.101	0.5905
Average weekly intake of other alcoholic drinks	0	ukbb	European	0.1176	0.2205	0.594
Multiple sclerosis	21833088	autoimmune	European	0.0951	0.1826	0.6027
Diagnoses - main ICD10: S76 Injury of muscle and tendon at hip and thigh level	0	ukbb	European	-0.1527	0.2963	0.6064
Non-cancer illness code_ self-reported: diabetes	0	ukbb	European	-0.04	0.0779	0.607
Ratio of bisallylic groups to total fatty acids	27005778	metabolites	European	0.0506	0.0986	0.6076
Hearing difficulty/problems with background noise	0	ukbb	European	0.033	0.0649	0.6112
Heel bone mineral density (BMD) T-score_ automated	0	ukbb	European	-0.0229	0.0451	0.6114
Extreme waist-to-hip ratio	23563607	anthropometric	European	0.0648	0.1301	0.6187
Diagnoses - main ICD10: K60 Fissure and fistula of anal and rectal regions	0	ukbb	European	-0.0729	0.1471	0.6201
Mean time to correctly identify matches	0	ukbb	European	0.0284	0.0581	0.6251
Non-cancer illness code_ self-reported: vitiligo	0	ukbb	European	0.1898	0.3938	0.6297
Concentration of large VLDL particles	27005778	metabolites	European	-0.0591	0.1237	0.6327
Diagnoses - main ICD10: N40 Hyperplasia of prostate	0	ukbb	European	-0.0665	0.1395	0.6335
Diagnoses - main ICD10: J44 Other chronic obstructive pulmonary disease	0	ukbb	European	0.0884	0.1854	0.6336
Fractured bone site(s): Wrist	0	ukbb	European	0.0746	0.1578	0.6364
Number of older siblings	0	ukbb	European	0.5854	1.2456	0.6384
Diagnoses - main ICD10: N19 Unspecified renal failure	0	ukbb	European	-0.109	0.2321	0.6387
Triglycerides in medium VLDL	27005778	metabolites	European	-0.0672	0.1441	0.641
Mouth/teeth dental problems: Mouth ulcers	0	ukbb	European	0.0421	0.0907	0.6424
Illnesses of father: Prostate cancer	0	ukbb	European	0.0622	0.1351	0.6451
Height_2010	20881960	anthropometric	European	0.0211	0.0461	0.647
Concentration of very large VLDL particles	27005778	metabolites	European	-0.0592	0.1302	0.6492
Vitamin and mineral supplements: Vitamin D	0	ukbb	European	-0.0629	0.1403	0.6541

Average weekly champagne plus white wine intake	0	ukbb	European	-0.0363	0.0824	0.6596
Diagnoses - main ICD10: M21 Other acquired deformities of limbs	0	ukbb	European	0.2297	0.5233	0.6607
Child birth length	25281659	anthropometric	European	-0.0427	0.0981	0.6631
Ratio of bisallylic groups to double bonds	27005778	metabolites	European	0.0405	0.0936	0.6651
Non-cancer illness code_ self-reported: uterine fibroids	0	ukbb	European	0.0565	0.1314	0.6671
Triglycerides in large VLDL	27005778	metabolites	European	-0.0559	0.1309	0.6694
Illnesses of mother: High blood pressure	0	ukbb	European	0.0349	0.0818	0.67
Medication for cholesterol_ blood pressure or diabetes: None of the above	0	ukbb	European	-0.0306	0.0725	0.6733
Diagnoses - main ICD10: N20 Calculus of kidney and ureter	0	ukbb	European	0.047	0.1135	0.6788
Hip circumference	25673412	anthropometric	European	-0.0198	0.0481	0.6799
Total Cholesterol	20686565	lipids	European	0.0303	0.074	0.6824
Urinary albumin-to-creatinine ratio	26631737	kidney	European	0.0464	0.1141	0.684
Diagnoses - main ICD10: G47 Sleep disorders	0	ukbb	European	0.0671	0.1649	0.684
Comparative height size at age 10	0	ukbb	European	0.0183	0.0456	0.6883
Phospholipids in medium LDL	27005778	metabolites	European	-0.0723	0.181	0.6897
Mineral and other dietary supplements: Fish oil (including cod liver oil)	0	ukbb	European	-0.0322	0.0819	0.6941
Leucine	27005778	metabolites	European	-0.0833	0.2122	0.6946
Diagnoses - main ICD10: M70 Soft tissue disorders related to use_ overuse and pressure	0	ukbb	European	0.0768	0.1983	0.6984
Maximum heart rate during fitness test	0	ukbb	European	-0.0515	0.1344	0.7018
Extreme height	23563607	anthropometric	European	0.0267	0.07	0.7029
Non-cancer illness code_ self-reported: kidney stone/ureter stone/bladder stone	0	ukbb	European	-0.0426	0.1123	0.7044
Non-cancer illness code_ self-reported: malabsorption/coeliac disease	0	ukbb	European	0.0479	0.1269	0.7057
Average number of double bonds in a fatty acid chain	27005778	metabolites	European	0.041	0.1108	0.7118
Diagnoses - main ICD10: M25 Other joint disorders_ not elsewhere classified	0	ukbb	European	0.2542	0.6958	0.7148
Potassium in urine	0	ukbb	European	0.024	0.0662	0.7165
Mean Caudate	25607358	brain_volume	European	0.0403	0.1132	0.7215
Started insulin within one year diagnosis of diabetes	0	ukbb	European	0.0449	0.1266	0.7227
HOMA-B	20081858	glycemic	European	-0.0373	0.1057	0.7242
Forced expiratory volume in 1-second (FEV1)_ predicted	0	ukbb	European	-0.0201	0.0577	0.7276
2hr glucose adjusted for BMI	20081857	glycemic	European	-0.0615	0.1782	0.73
Diabetes diagnosed by doctor	0	ukbb	European	-0.0247	0.0728	0.7348
Non-accidental death in close genetic family	0	ukbb	European	-0.0431	0.1304	0.7413
Overweight	23563607	anthropometric	European	0.0183	0.0556	0.7415
Diagnoses - main ICD10: H25 Senile cataract	0	ukbb	European	-0.0692	0.2177	0.7505
Non-cancer illness code_ self-reported: arthritis (nos)	0	ukbb	European	0.0838	0.2695	0.756
Non-cancer illness code_ self-reported: allergy or anaphylactic reaction to drug	0	ukbb	European	-0.1376	0.4458	0.7576
22:6 docosahexaenoic acid	27005778	metabolites	European	-0.0442	0.1457	0.7617
Non-cancer illness code_ self-reported: pernicious anaemia	0	ukbb	European	0.0619	0.2043	0.7619
Snoring	0	ukbb	European	0.0182	0.0624	0.77
Impedance of arm (right)	0	ukbb	European	-0.0121	0.0422	0.7737
Obsessive–compulsive disorder	28761083	psychiatric	European	0.0284	0.0996	0.7753
Diagnoses - main ICD10: G56 Mononeuropathies of upper limb	0	ukbb	European	0.0301	0.1079	0.7807
Cancer code_ self-reported: prostate cancer	0	ukbb	European	0.0408	0.148	0.7828
Worry too long after embarrassment	0	ukbb	European	-0.0173	0.0632	0.7837
Height; Females at age 10 and males at age 12	23449627	anthropometric	European	0.022	0.0846	0.7947
Weight	0	ukbb	European	0.0106	0.041	0.7954
Mean Putamen	25607358	brain_volume	European	0.0263	0.1035	0.7993
Frequency of heavy DIY in last 4 weeks	0	ukbb	European	0.0316	0.1295	0.8072
Acetate	27005778	metabolites	European	0.045	0.1902	0.8131
Non-cancer illness code_ self-reported: hypopituitarism	0	ukbb	European	0.0825	0.3497	0.8136
Handedness (chirality/laterality): Use both right and left hands equally	0	ukbb	European	-0.0457	0.1945	0.8141
Obesity class 3	23563607	anthropometric	European	0.0214	0.092	0.8163
Maximum workload during fitness test	0	ukbb	European	-0.032	0.1424	0.8221
Arm fat mass (left)	0	ukbb	European	0.0088	0.0395	0.8245
Alanine	27005778	metabolites	European	0.0296	0.1356	0.8274
Vitamin and mineral supplements: Vitamin C	0	ukbb	European	0.0209	0.1008	0.8354
Non-cancer illness code_ self-reported: cholelithiasis/gall	0	ukbb	European	0.0276	0.1366	0.8401

stones						
Total lipids in small HDL	27005778	metabolites	European	0.037	0.1834	0.8403
Blood clot_ DVT_ bronchitis_ emphysema_ asthma_ rhinitis_ eczema_ allergy diagnosed by doctor: None of the above	0	ukbb	European	-0.0107	0.0532	0.8412
Mineral and other dietary supplements: Zinc	0	ukbb	European	0.0231	0.116	0.8423
Non-cancer illness code_ self-reported: hayfever/allergic rhinitis	0	ukbb	European	-0.0171	0.0874	0.845
Diagnoses - main ICD10: S52 Fracture of forearm	0	ukbb	European	0.0254	0.1342	0.8499
Sleep duration	27494321	sleeping	European	-0.0142	0.0756	0.8509
Non-cancer illness code_ self-reported: glaucoma	0	ukbb	European	0.0221	0.1181	0.8515
Arm fat mass (right)	0	ukbb	European	0.0072	0.039	0.8543
Arm fat percentage (left)	0	ukbb	European	-0.0071	0.0394	0.8568
Trunk predicted mass	0	ukbb	European	0.0081	0.0448	0.8569
Had major operations	0	ukbb	European	0.0205	0.1157	0.8592
Sitting height	0	ukbb	European	-0.0077	0.0437	0.8599
Childhood obesity	22484627	anthropometric	European	0.014	0.0798	0.8612
Glucose	27005778	metabolites	European	0.0233	0.1398	0.8676
Vitamin and mineral supplements: Vitamin E	0	ukbb	European	0.0222	0.139	0.8729
Relative age of first facial hair	0	ukbb	European	-0.0086	0.0576	0.8818
Body fat	26833246	anthropometric	European, South Asian, East Asian & African American	0.0108	0.0739	0.8835
LDL cholesterol	20686565	lipids	European	-0.0123	0.0844	0.8843
Average number of methylene groups per a double bond	27005778	metabolites	European	-0.0155	0.1074	0.8851
Medication for cholesterol_ blood pressure_ diabetes_ or take exogenous hormones: Blood pressure medication	0	ukbb	European	0.0087	0.0624	0.8884
Diagnoses - main ICD10: M23 Internal derangement of knee	0	ukbb	European	-0.0178	0.1318	0.8925
Non-cancer illness code_ self-reported: osteoporosis	0	ukbb	European	0.0122	0.1018	0.9045
Non-cancer illness code_ self-reported: back problem	0	ukbb	European	-0.0183	0.1565	0.9069
Trunk fat-free mass	0	ukbb	European	0.005	0.0446	0.9106
Non-cancer illness code_ self-reported: bladder problem (not cancer)	0	ukbb	European	0.0247	0.2232	0.9118
Excessive daytime sleepiness	27992416	sleeping	European	-0.0097	0.0906	0.9144
Diagnoses - main ICD10: M24 Other specific joint derangements	0	ukbb	European	0.0198	0.1923	0.9178
Number of trend entries	0	ukbb	European	-0.0164	0.1646	0.9205
Non-cancer illness code_ self-reported: ankylosing spondylitis	0	ukbb	European	0.0208	0.2106	0.9214
Diagnoses - main ICD10: J34 Other disorders of nose and nasal sinuses	0	ukbb	European	0.0195	0.2044	0.9242
Whole body fat-free mass	0	ukbb	European	-0.0041	0.0444	0.9257
Adiponectin	22479202	cardiometabolic	European, African American & Asian	-0.0102	0.1121	0.9273
Triglycerides in very large HDL	27005778	metabolites	European	0.012	0.135	0.9291
Illnesses of siblings: Severe depression	0	ukbb	European	0.0093	0.1112	0.9335
HOMA-IR	20081858	glycemic	European	0.0097	0.1214	0.9362
Arm fat percentage (right)	0	ukbb	European	-0.003	0.0393	0.9399
Length of menstrual cycle	0	ukbb	European	-0.0092	0.1248	0.9413
Acetoacetate	27005778	metabolites	European	-0.0112	0.1528	0.9414
Whole body water mass	0	ukbb	European	-0.0032	0.0441	0.942
Illnesses of mother: Diabetes	0	ukbb	European	0.0064	0.0907	0.9434
Body mass index	20935630	anthropometric	European	-0.0033	0.0499	0.9474
Diagnoses - main ICD10: I21 Acute myocardial infarction	0	ukbb	European	0.0073	0.1192	0.9513
Non-cancer illness code_ self-reported: polio / poliomyelitis	0	ukbb	European	0.0109	0.1912	0.9547
Duration of other exercises	0	ukbb	European	0.0064	0.1193	0.9574
Chronotype	27494321	sleeping	European	0.0028	0.0628	0.964
Diagnoses - main ICD10: O75 Other complications of labour and delivery_ not elsewhere classified	0	ukbb	European	0.0108	0.2388	0.9641
Non-cancer illness code_ self-reported: rheumatoid arthritis	0	ukbb	European	-0.0062	0.1389	0.9643
Hair/balding pattern: Pattern 4	0	ukbb	European	0.0026	0.0588	0.9648
Creatinine	27005778	metabolites	European	-0.0045	0.1084	0.967
Hair/balding pattern: Pattern 3	0	ukbb	European	-0.0031	0.0838	0.9708

Illnesses of siblings: Stroke	0	ukbb	European	-0.0065	0.1915	0.973
Non-cancer illness code_ self-reported: vaginal prolapse/uterine prolapse	0	ukbb	European	0.0052	0.1663	0.9749
Hearing aid user	0	ukbb	European	-0.0026	0.1221	0.983
Non-cancer illness code_ self-reported: eczema/dermatitis	0	ukbb	European	0.0025	0.1266	0.9841
Basal metabolic rate	0	ukbb	European	-0.0008	0.0436	0.9849
Type 2 Diabetes	22885922	glycemic	European	-0.0014	0.082	0.9865
Idiopathic pulmonary fibrosis	29066090	lung_function	European	0.0032	0.2891	0.991
Obesity class 1	23563607	anthropometric	European	0.0005	0.0492	0.9911
Non-cancer illness code_ self-reported: hypertrophic cardiomyopathy (hcm / hocm)	0	ukbb	European	0.0022	0.3409	0.9949

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