

1 Genetic analyses of medication-use and implications for precision medicine

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12 13 **Abstract**

14 It is common that one medication is prescribed for several indications, and conversely that
15 several medications are prescribed for the same indication, suggesting a complex biological
16 network for disease risk and its relationship with pharmacological function. Genome-wide
17 association studies (GWASs) of medication-use may contribute to understanding of
18 disease etiology, generation of new leads relevant for drug discovery and quantify prospects
19 for precision medicine. We conducted GWAS to profile self-reported medication-use from 23
20 categories in approximately 320,000 individuals from the UK Biobank. A total of 505
21 independent genetic loci that met stringent criteria for statistical significance were identified.
22 We investigated the implications of these GWAS findings in relation to biological
23 mechanism, drug target identification and genetic risk stratification of disease. Amongst the
24 medication-associated genes were 16 known therapeutic-effect target genes for medications
25 from 9 categories.

26 27 **Introduction**

28 Susceptibility to most common human diseases is complex and multifactorial, involving both
29 genetic, environmental and stochastic factors¹. During the last decade, large-scale genome-
30 wide association studies (GWASs) have identified thousands of single nucleotide
31 polymorphisms (SNPs) associated with diseases and related traits, consistent with a
32 polygenic genetic architecture of common disease. These results add useful human-relevant
33 information to drug development, drug repurposing and clinical trial pipelines². Here, we
34 have turned the tables, aiming to identify genetic loci associated with medication-taking. In
35 the context of electronic health record data, medication-use may be an easy route to identify
36 disease-case subjects. However, in clinical practice, it is common that one medication is
37 prescribed for several indications, but conversely, several medications can be prescribed for
38 the same indication. It is likely that medication-use reflects not only similarity between
39 different clinical manifestations³ and/or comorbidity⁴ of diseases but also heterogeneity of
40 clinical manifestation (symptoms and signs) and of intervention response (for example, from
41 lifestyle change to the combination of treatments).

42
43 We hypothesise that genetic variants associated with taking medications categorised based on
44 anatomical and therapeutic classifications may add additional relevant information to
45 understanding the underlying biological mechanism of diseases and drug development
46 approaches. Here, we study genetic variation in current medication-use. We report 505 loci
47 independently associated with medication categories. We explore these GWAS findings for
48 biological mechanisms and as drug targets. We estimate the genetic correlation between the
49 23 medication traits, and with other diseases and traits using published GWAS results. We
50 use Mendelian Randomization to investigate putative causal relationships among diseases

51 and traits. We show that genetic predisposition to common disease predicts likelihood of
52 taking relevant medications, a significant finding in relation to future practice of precision
53 medicine for common disease.

54

55 **Results**

56 **Case-control GWAS of medication-use**

57 Medications taken by UKB participants were classified using the Anatomical Therapeutic
58 Chemical Classification System⁵ and provided in **Figure 1** and **S1, Table S1**. **Figure S2**
59 shows the demographics of participants with medication records. The full phenotype
60 extraction pipeline for UKB participants is summarised in **Figure S3**. An overview of
61 analyses is provided in **Figure S4**. The medication-use case-control GWASs identify 910
62 within-trait independent SNPs significantly associated ($P < 5 \times 10^{-8}$) across 23 medication
63 traits (**Figure 2 and S5**). After applying a more stringent multiple testing threshold ($P < 1e-$
64 $8/23$)⁶, a total of 505 SNPs remain (**Table S2 and S3**), with per-trait associations ranging
65 from 0 (C02: hypertensives, N02A:opioids, N06A: antidepressants) to 103 (C09: agents
66 acting on renin-angiotensin system) SNPs. Many of the associated SNPs may simply be a
67 reflection of the primary indication for which the medication is prescribed (**Table S4**). For
68 example, C09 medications have therapeutic effect on hypertension; of the 103 independent
69 SNPs associated with C09 medications ($P < 10^{-8}/23$), we identified SNPs previously linked to
70 hypertension (7 SNPs)⁷, systolic blood pressure (32 SNPs)⁸, diastolic blood pressure (5
71 SNPs)⁹ and pulse pressure (2 SNPs)⁹. Of the 55 independent SNPs associated with C10AA
72 (HMG CoA reductase inhibitors)-associated SNPs ($P < 10^{-8}/23$), 19 SNPs have been reported
73 to be significantly associated with low-density lipoprotein cholesterol (LDLC)¹⁰, supporting
74 the known biological mechanism that statins are effective in lowering LDLC. However, for 3
75 medication-taking traits either small or no GWAS have been conducted for the medication-
76 relevant indications, including A02B (drugs for peptic ulcer and gastro-oesophageal reflux
77 disease), H03A (thyroid preparations) and N02BE (anilides).

78

79 **Genetic predisposition to common disease predicts medication-taking**

80 We undertook polygenic risk prediction analyses using GWAS summary statistics from 8
81 published disease/traits (**Table S5**) as discovery data to predict disease risk in 9 medication-
82 taking phenotypes as target data. Participants in the UK Biobank with a high GRS for
83 different diseases/traits have a higher odds of taking corresponding medications than those
84 with a low GRS (**Figure 3; Table S6**). The top decile of individuals ranked on risk prediction
85 for depression had an odds ratio (OR) of 1.7 in taking anti-depressants compared to the
86 bottom decile. Similarly comparing top and bottom deciles, we find an OR of 3.1 for taking
87 anti-diabetic medication (A10) for individuals ranked on genetic risk for type 2 diabetes and
88 of 3.3 for taking immunosuppressants (L04) for individuals ranked on their genetic risk for
89 rheumatoid arthritis (RA). The OR increased to 5.2 for taking L04 medications specific to
90 RA (**Table S1**).

91

92 **GWAS results and biological mechanisms**

93 First, we estimated SNP-heritability of the 23 traits using linkage disequilibrium (LD) score
94 regression¹¹ (**Figure S6; Table S7**), all traits showed SNP-heritability (proportion of variance
95 attributed to genome-wide SNPs) significantly different from zero to a maximum of 0.15 (s.e.
96 0.008) for N02A (opioid medications) on the estimated scale. Second, to identify medication-
97 relevant tissue/cell types, we partitioned the SNP-heritability¹² based on annotations of SNPs
98 to genes, and genes to differential gene expression between tissues. Among the 23
99 medication-taking traits, 8 traits showed significantly enriched association with genes
100 expressed in at least one tissue at a false discovery rate (FDR) $< 5\%$ (**Figure S7**). GWAS

101 associations for thyroid preparations (H03A), immunosuppressants (L04), adrenergics
102 inhalants (R03A), glucocorticoid (R06BA) and antihistamines for systemic use (R06A) were
103 enriched in immune cell types. Those of opioid analgesics (N02A) were enriched in central
104 nervous system tissues, such as limbic system, those of antimigraine preparations (N02C)
105 were enriched in cardiovascular tissue, and those of drugs affecting bone structure and
106 mineralization (M05B) were enriched in digestive cell type (**Table S8**).

107
108 Third, we investigated whether associations between SNPs and medication-taking traits were
109 consistent with mediation through gene expression, based on associations between SNPs and
110 gene expression (eQTLs). We identified 177 unique genes for which expression is
111 significantly associated with 19 medication-taking categories (**Table S9**) using summary
112 data-based Mendelian Randomization (SMR) analysis¹³. Gene-based association tests were
113 conducted using MAGMA¹⁴ from the GWAS SNP results for each of the 23 medication-
114 taking traits and a total of 1,841 significantly associated unique genes were identified (**Table**
115 **S10**). To provide biological insights from the GWAS associated loci, we used the gene-based
116 association test summary statistics to test for enrichment in 10,891 gene sets from MSigDB
117 (v5.2)^{15,16}. All 23 medication-taking traits were enriched in at least one gene set at FDR < 5%
118 (**Table S11**). Several of the results showed plausible relevant biological mechanisms. For
119 example, the genetic associations for taking A10 (drugs used in diabetes) were enriched for
120 the glucose homeostasis gene set, those for taking C10AA (statins) were enriched in the
121 cholesterol homeostasis gene set, C09 (agents acting on renin-angiotensin system) for
122 cardiovascular-related gene sets, M05B (drugs affecting bone structure and mineralization)
123 for skeletal system development, chondrocyte differentiation gene sets, N02A for gene sets of
124 behavioural response to cocaine and neurogenesis and lastly H03A, L04, R03A, R03BA
125 medications for immune-related gene sets. Interestingly, genes associated with taking A02B
126 (drugs for peptic ulcer and gastro-oesophageal reflux disease) are enriched in gene sets of
127 central nervous system neuron differentiation and of neurogenesis, highlighting the
128 connection between gut and brain¹⁷.

129 130 **Linking genes associated with medication-taking to drug targets**

131 Secondary analyses of GWAS results not only provide insights into the biological complexity
132 of common diseases, but also offer opportunities relevant to drug development and
133 repurposing^{2,18,19}. To determine whether genes associated with medication-taking could
134 provide clues relevant to drug target identification, we performed analyses using drug-target
135 lists from Santos *et al.*⁵, ChEMBL²⁰ and ClinicalTrials.gov (<https://www.clinicaltrials.gov/>)
136 database as reference. First, for each UKB medication category, we investigated whether
137 there are therapeutic-effect target genes for medications classified in that medication
138 category; a total of 9 genes were identified (**Table S12**). For example, we find *HMGCR*
139 (Entrez ID: 3156) is, as expected²¹, associated with taking C10AA medications (statins) and
140 encodes the HMGCR protein which is targeted by medications from C10AA category.
141 Second, we tested whether there are therapeutic-effect target genes for treating indications
142 relevant to taking medications of each category; a total of 7 genes were identified (**Table**
143 **S12**). *PCSK9* (Entrez ID: 255738) in our analyses is also associated with taking C10AA
144 medications, and encodes the protein mediating lowering-cholesterol effect of evolocumab
145 (ATC code : C10AX13) and alirocumab (ATC code: C10AX14). Third, we looked at
146 whether there are therapeutic-effect target genes (ever or currently in clinical trial and not
147 approved by FDA yet) for treating indications relevant to medications of each category; a
148 total of 8 genes were identified (**Table S13**). For example, *TSLP* (Entrez ID: 85480) is
149 associated with R03A (adrenergics), R03BA (glucocorticoids) and R06A (antihistamines)
150 and also mediates the effect of tezepelumab for the treatment of uncontrolled asthma²².

151 Hence, among our associated genes are 24 genes with some known evidence of therapeutic
152 effect. Therefore, we anticipate that novel genes that are associated with medication may help
153 to prioritise other putative therapies²³. In **Table S14** we provide additional analyses for two
154 genes, *IDE* and *AGT* that we believe merit further study for type 2 diabetes and C07/C09
155 related disorders, respectively.

156

157 **Shared genetic architecture between medication-taking traits and relevant complex** 158 **traits**

159 The genetic correlation (r_g) between the 23 medication-taking traits and 21 traits/diseases
160 (**Table S5**) related to them were calculated using bivariate LD score regression²⁴. Many r_g
161 estimated were significantly different from zero. For example, body mass index, educational
162 attainment (EA), former/current smoker and coronary artery disease were significantly
163 correlated with most of the medication categories in expected directions. Major depression
164 and neuroticism showed positive r_g with A02B (gastro-oesophageal reflux drugs), suggesting
165 a link between the brain and the digestive system. Type 2 diabetes showed correlations with
166 taking medications C02, C03, C07~C09 and C10AA, implying a shared genetic architecture
167 of type 2 diabetes, hypertension and hypercholesterolemia. The r_g between B01A and
168 N02BA show similar patterns of r_g with other diseases/traits are similar to those for N02BA
169 medications with other diseases/traits because the original medication aspirin (code number:
170 1140868226, 59150 individuals in our analysis) has multiple ATC codes (A01AD05,
171 B01AC06 and N02BA01). Full results are presented in **Figure 4** and **Table S15**.

172

173 **Putative causal relationship of diseases for using medication**

174 It is reasonable to assume that having a disease is causal for taking the associated medication
175 (rather than reverse causation). Therefore, we used Mendelian Randomisation (MR) in a
176 proof-of-principle analysis to quantify causality. Independent SNPs (P -value $< 5E-8$)
177 associated with 15 selected diseases/traits (**Table S5**) were used as instruments to evaluate
178 putative causal relationships²⁵ among these 15 diseases/traits and the 23 medication-taking
179 traits (**Table S16 and Figure 5**). Increasing BMI increases the likelihood of taking A10,
180 B01A, C01D, C02, C03, C07, C08, C09, C10AA, R03A medications, consistent with the role
181 of BMI across diseases related to these medications²⁵. The effect of obesity on bone health is
182 controversial²⁶. However, results from our analysis clearly show that increasing BMI
183 decreases the likelihood of taking M05B (bone-associated) medications (OR 0.68 per SD of
184 BMI). Major depression (MD) increases the likelihood of taking A02B medication (drugs for
185 peptic ulcer and gastro-oesophageal reflux disease; 1.23-fold increase per SD in liability to
186 MD), capturing a link between the brain and the digestive system. In addition to this, MD
187 increases the likelihood of taking N02BE (1.23-fold increase per SD in liability to MD)
188 medication, which is consistent with comorbidity of pain in some MD patients²⁷.

189

190 **Discussion**

191 To our knowledge, this is the first paper profiling genetic contributions to medication-use.
192 Traditional GWAS identify DNA variants associated with disease, with a goal that these
193 discoveries ultimately may open the door to new drug treatments. Here, we have taken the
194 reverse approach, aiming to identify DNA variants associated with medication-taking, in
195 recognition that underlying biology may contribute to the same medication being prescribed
196 for several indications, and conversely that only some of those with a given diagnosis may
197 take a particular medication. As expected, some of our results for medication-taking
198 recapitulate GWAS results of the disease traits for which the medication is prescribed.
199 However, we have also identified some novel associations that may be worthy of follow-up.

200 We identified 505 linkage disequilibrium independent SNPs associated ($P < 1e-8/23$) with
201 different medication-taking traits. For some of our traits, large GWAS for the medication
202 relevant indications have not been conducted, such as A02B (drugs for peptic ulcer and
203 gastro-oesophageal reflux disease, 2 SNPs) and N02BE (anilides, 4 SNPs). Notably, 76 SNPs
204 were associated with H03A (thyroid preparations – the main indication is hypothyroidism),
205 only 11 of these loci have been previously reported to be associated with hypothyroidism.
206 Conditional (mtCOJO) analysis suggested that these 76 SNPs associated with taking H03A
207 medication are indeed associated with hypothyroidism. We showed that individuals with
208 higher genetic risk of disease have higher likelihood to take relevant medications, for
209 example, individuals with higher GRS for RA have an OR of 3.3 to take immunosuppressants
210 compared with lower GRS individuals (**Figure 3**), thereby providing a proof-of-principle
211 validation of precision medicine based upon risk prediction of common diseases, since
212 individuals with high genetic risk of disease can be identified well before the onset of
213 symptoms and the time of medication prescription.

214
215 To provide biological insight to the SNP associations for medication-taking²⁸, we linked
216 GWAS findings to relevant biological gene sets and drug target efficacy. These analyses
217 generated a series of expected or plausible results, such as genes associated with taking A10
218 (drugs used in diabetes) enriched in gene sets for glucose homeostasis. Our analyses also
219 generate new hypotheses; genes associated with taking N06A (antidepressants) showed
220 enrichment in the gene set for the synthesis and secretion and diacylation of ghrelin, a gut-
221 derived hormone²⁹. Previous studies have described an antidepressant-like role of ghrelin^{30,31}.
222 This line of evidence suggests that testing a pharmacological effect of ghrelin on depression
223 may be worthwhile. Although medication-associated genes overlapped with only a small
224 proportion of current drug target genes, the framework of genetic association studies provides
225 a potentially valuable resource for new drug target identification and prediction of
226 unfavourable side effects¹⁸.

227
228 Comorbidity is commonly observed in clinical practice, which means the presence of
229 additional diseases in relation to an index disease³². Results from genetic correlation and
230 disease-medication (exposure-outcome) MR highlight potential shared aetiology, and may
231 help explain medication use in clinical practice. Our analysis showed that major depression
232 increased the likelihood of taking A02B (drugs for peptic ulcer and gastro-oesophageal reflux
233 disease) and N02BE (anilides), the latter consistent with reports that antidepressant
234 prescriptions are not only indicated for depression, but also for pain³³.

235
236 There are a number of limitations in our study. First, although the medication-use data were
237 obtained by trained nurses during interviews, the self-reported nature may limit the accuracy
238 of information. Second, the ambiguous names of medications may limit the accurate
239 classification of medications. The reasons (e.g. disease diagnosis) for taking medication were
240 not recorded and hence not available for further analysis, nor were duration and dosage of
241 medications. Third, our findings are specific to the UK biobank participants, which are
242 recognized to be a non-random sample of the UK population. Fourth, the medication-taking
243 in UK biobank participants may be more representative of medication-taking in the UK and
244 may not translate to other populations and different health systems.

245
246 In summary, we identified 505 independent loci associated with different medication-use in
247 318,177 individuals from UKB, with implications for biological mechanisms, drug target
248 identification and precision medicine for common disease.

249

250 **Methods**

251 **Medication data**

252 We used self-report data of regular medication (prescription and over-the-counter) and health
253 supplements taken weekly, monthly or three-monthly from participants in the United
254 Kingdom Biobank (UKB) study (<http://www.ukbiobank.ac.uk>)³⁴, mainly aged 37-73 years
255 when recruited between 2006 and 2010. Medication and health supplements data were coded
256 and manually mapped to their corresponding active ingredients and then to their Anatomical
257 Therapeutic Chemical (ATC) Classification System⁵ codes (**Table S1**). In total, medications
258 were classified into 1,752 categories, collapsing to 184 subgroups according to the first three
259 ATC levels (**Figure 1, S1**). 23 of these medication subgroups (based on participant numbers)
260 were selected for analysis. Detailed methods are provided in the **Supplementary Appendix**.

261

262 **Genome-wide association study design and statistical analysis**

263 Analyses used genome-wide genotypes for 318,177 participants of white European descent
264 (**Figure S2**). 23 medication-taking case groups and their corresponding control groups were
265 generated. Case groups were defined as those taking medications classified at the same ATC
266 level. Control groups comprised participants taking neither the case medication nor similar
267 medications. Similar medications were defined as those sharing the first two ATC levels as
268 the case medication or medications containing the case medication active ingredients.
269 Following standard quality control and genotype imputation methods (see **Supplementary**
270 **Appendix**), 7,288,503 SNPs with minor allele frequency (MAF) > 0.01 were used in
271 analyses. Case-control genome-wide association analyses were conducted using BOLT-
272 LMM³⁵ with age, sex, assessment centre and 20 genetic principal components fitted as
273 covariates. Conditional analyses tested if SNPs associated with taking medications have been
274 previously linked to their corresponding medication-specific related indications/traits^{36,37}.
275 Multi-trait-based conditional and joint (mtCOJO) analyses tested if medication-taking
276 associated SNPs are also associated with their relevant main indications in UKB²⁵.

277 Genetic risk score (GRS) for UKB individuals were generated for 8 diseases using SNP
278 effect size estimates from published GWAS summary statistics (discovery sample data)
279 (**Table S2**). These GRS were used to predict the medication use traits related to these
280 diseases (asthma mapped to two medication use traits). Selection of the discovery samples
281 data was based on relationship to the medication-taking traits, availability of GWAS
282 summary statistics, cohort ancestry and no sample overlap with UKB. GRS were generated
283 for a range of discovery data association *P* value thresholds (5×10^{-8} , 1×10^{-5} , 1×10^{-4} , 0.001,
284 0.01, 0.05, 0.1, 0.5). The GRS were evaluated as medication-taking odds ratio for each GRS
285 decile (relative to the 1st decile).

286 LD score regression^{11,24} was used to estimate the proportion of variance attributable to
287 genome-wide SNPs (h_{SNP}^2) and to quantify genetic sharing at common variants across the 23
288 medication-taking traits and other traits. LD score regression for cell type specific analysis¹²
289 was applied to test the h_{SNP}^2 enrichment in different tissues for each of the 23 medication-
290 taking traits. Gene expression data of 205 tissues (53 from GTEx³⁸ and 152 from other
291 sources^{39,40}) were used for analyses. Summary-data-based Mendelian Randomization
292 (SMR)¹³ was used to integrate our trait association with blood expression quantitative trait
293 loci (eQTL, i.e., SNP-gene expression association) data⁴¹. Gene-based association analyses
294 were conducted using MAGMA (v1.06)¹⁴ to identify genes associated with different
295 medication-taking traits. Gene sets association analyses were conducted using MAGMA
296 (v1.06)¹⁴ with curated gene sets (c2.all) and gene ontology sets (c5.bp, c5.cc, c5.mf) from
297 MSigDB (v5.2)^{15,16}.

298 Mendelian Randomization (MR) was used to investigate a putative causal relationship
299 between the 23 medication-taking traits and 15 significantly correlated traits (selected from

300 **Table S2**), using Generalized Summary-data-based MR (GSMR)²⁵. We required that all
301 analyses had at least 7 genome-wide significant loci to use as MR instruments; the median
302 number of SNP instruments was 65.

303

304 **Analyses linking GWAS results to drugs and disease**

305 To check whether associated genes from MAGMA and SMR encode effect-mediating
306 targets for FDA-approved medications or corresponding indications, we used information
307 from Santos *et al.*⁵, based on medication approved by the FDA before June 2015. For those
308 approved later, we used the ChEMBL database²⁰. To check whether associated genes encode
309 trait-relevant effect-mediating targets for drugs in clinical trial, we used ClinicalTrial.gov
310 (<https://www.clinicaltrials.gov/>). The CLUE Touchstone tool (<https://clue.io/>)⁴² was used to
311 check the correlation between signatures of drugs and knocking down a gene.

312

313 **URLs**

314 UK Biobank: <http://www.ukbiobank.ac.uk>; ClinicalTrial.gov: <https://www.clinicaltrials.gov/>;
315 CLUE Touchstone tool: <https://clue.io/>.

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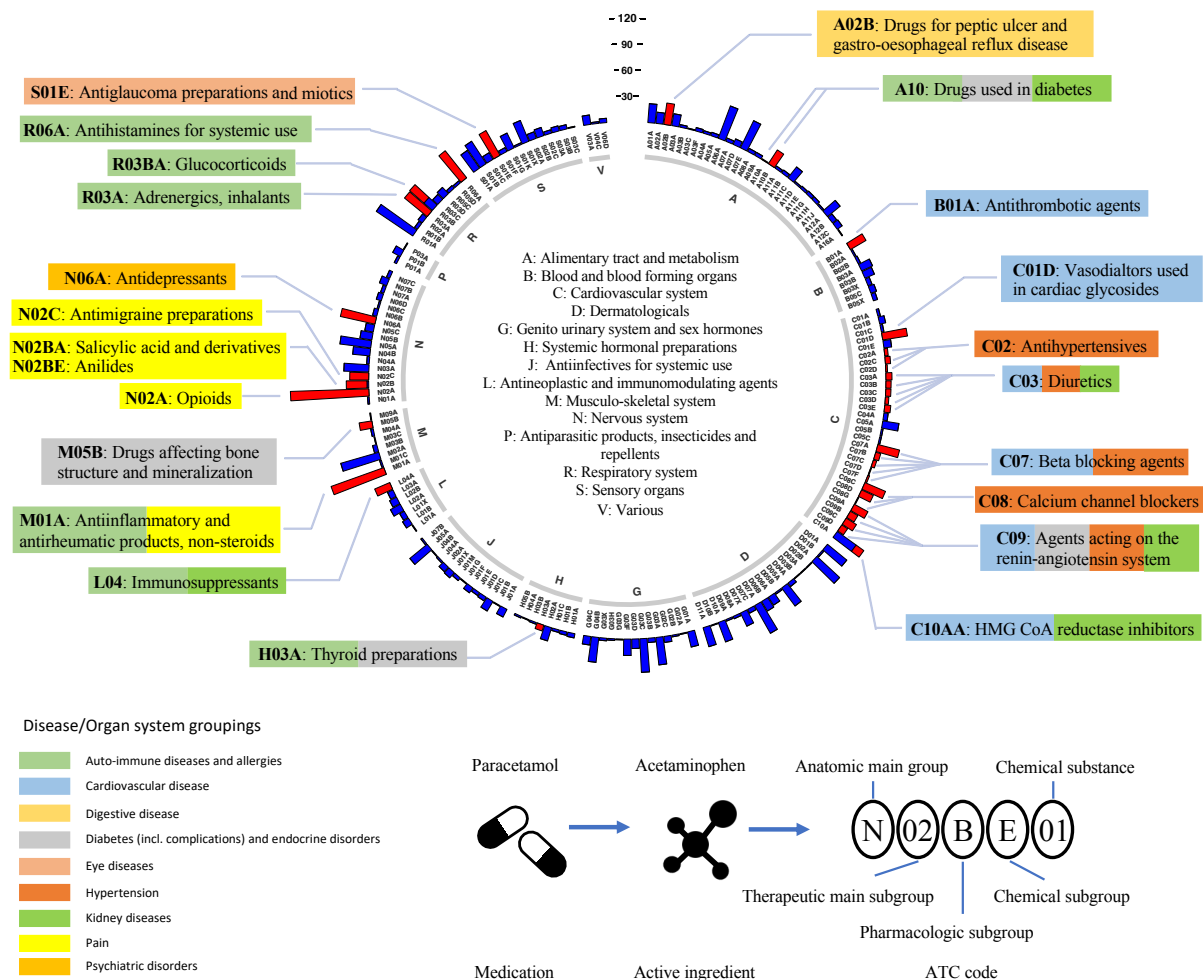
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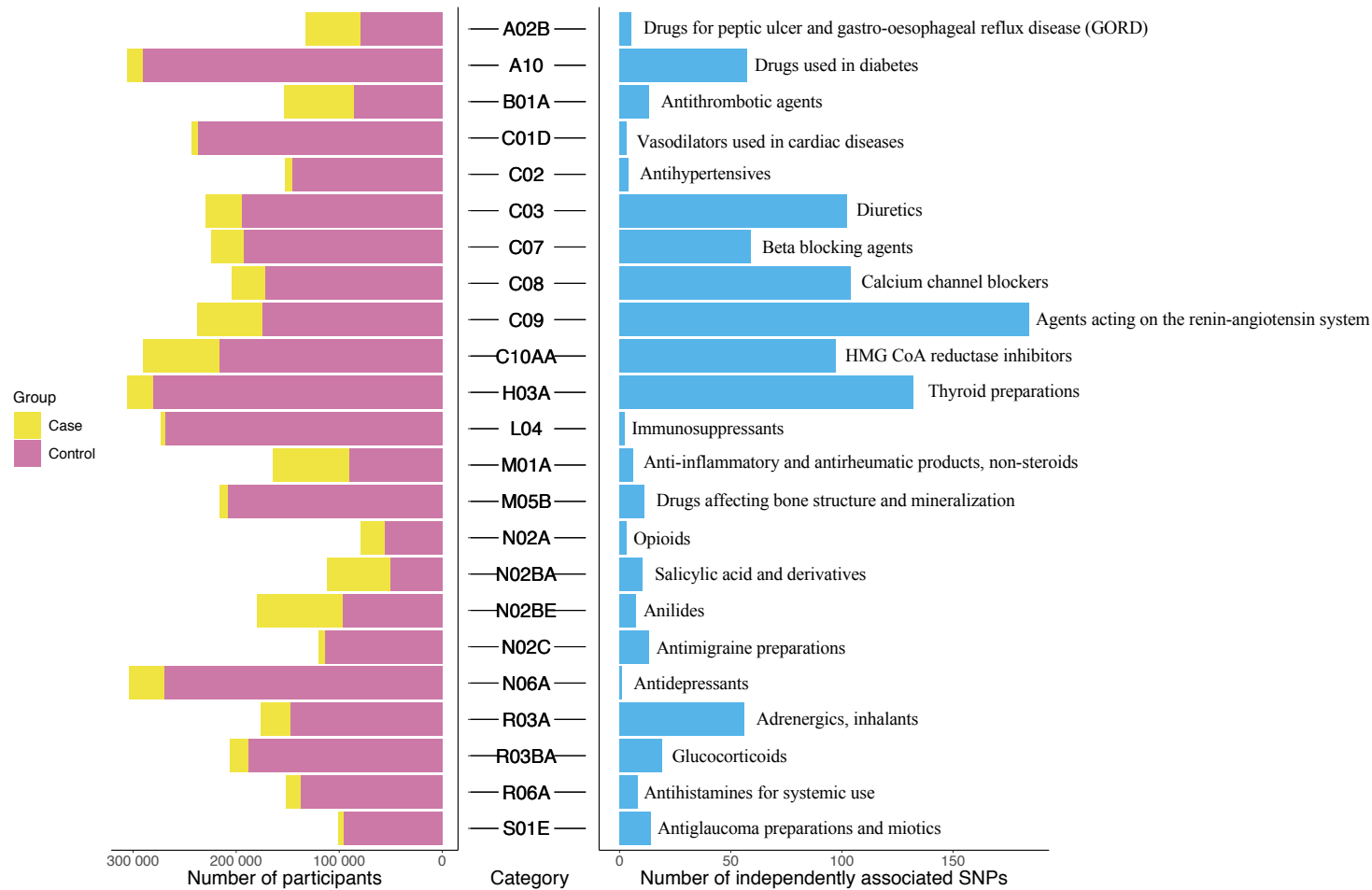
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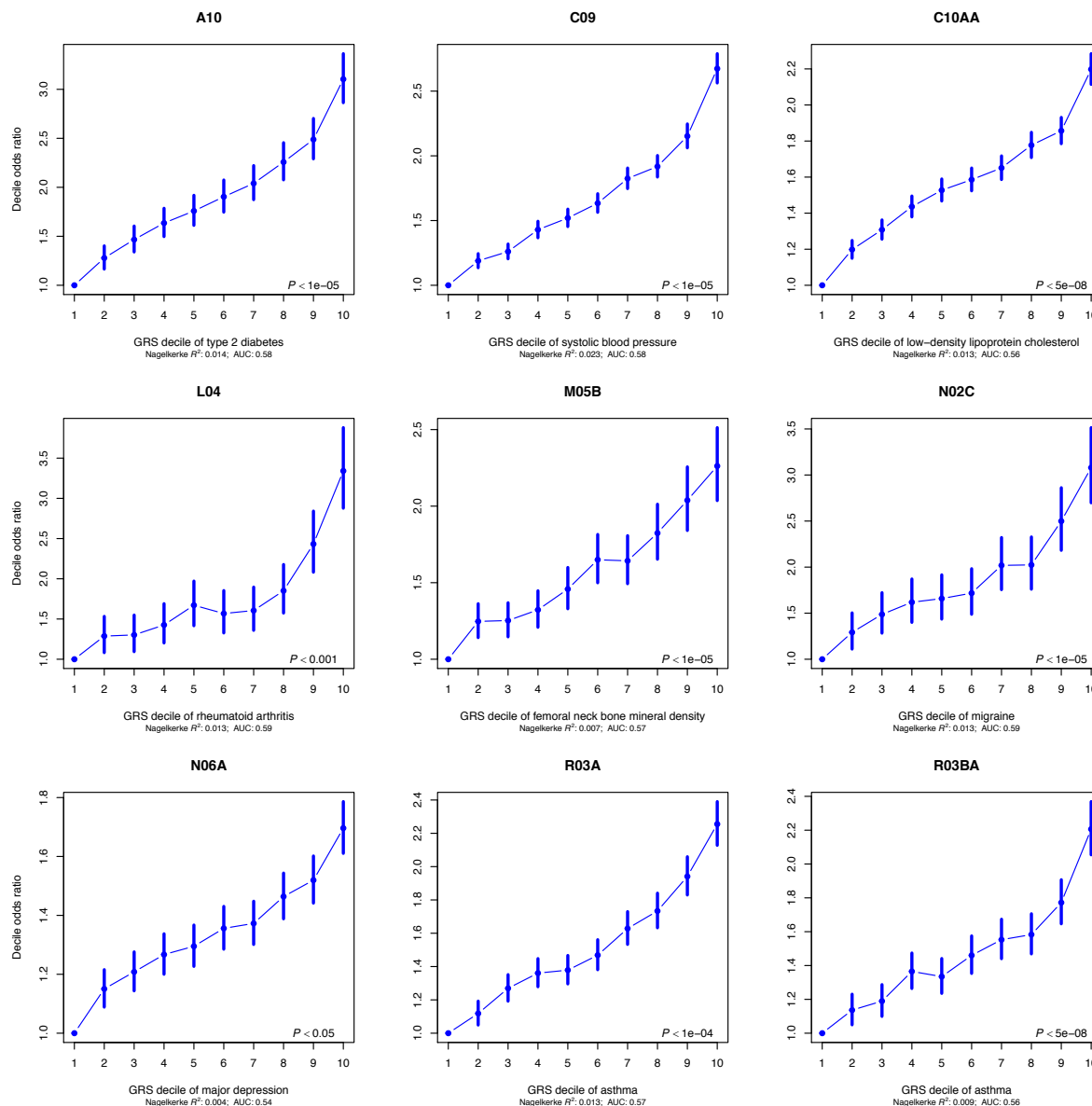


489 **Figure 1.** Distribution of 1,752 UKB medications at the first three ATC level.
 490 The inner ring corresponds to the 1st level of the ATC code. The outer ring represents the first
 491 3 level of the ATC code (184 subgroups). The length of the bar represents the number of
 492 classified UKB medications assigned to that subgroup (numbers of participants are shown in
 493 Figure 2). Red bars are the 23 medication-taking traits used in analyses (selected based on
 494 participant numbers). The 23 medication-taking traits are grouped into 9 diseases and organ
 495 system categories according to the main indications, which is highlighted using different
 496 colours (legend bottom left). The legend at the bottom right shows how ATC codes are
 497 assigned to each UKB medication.

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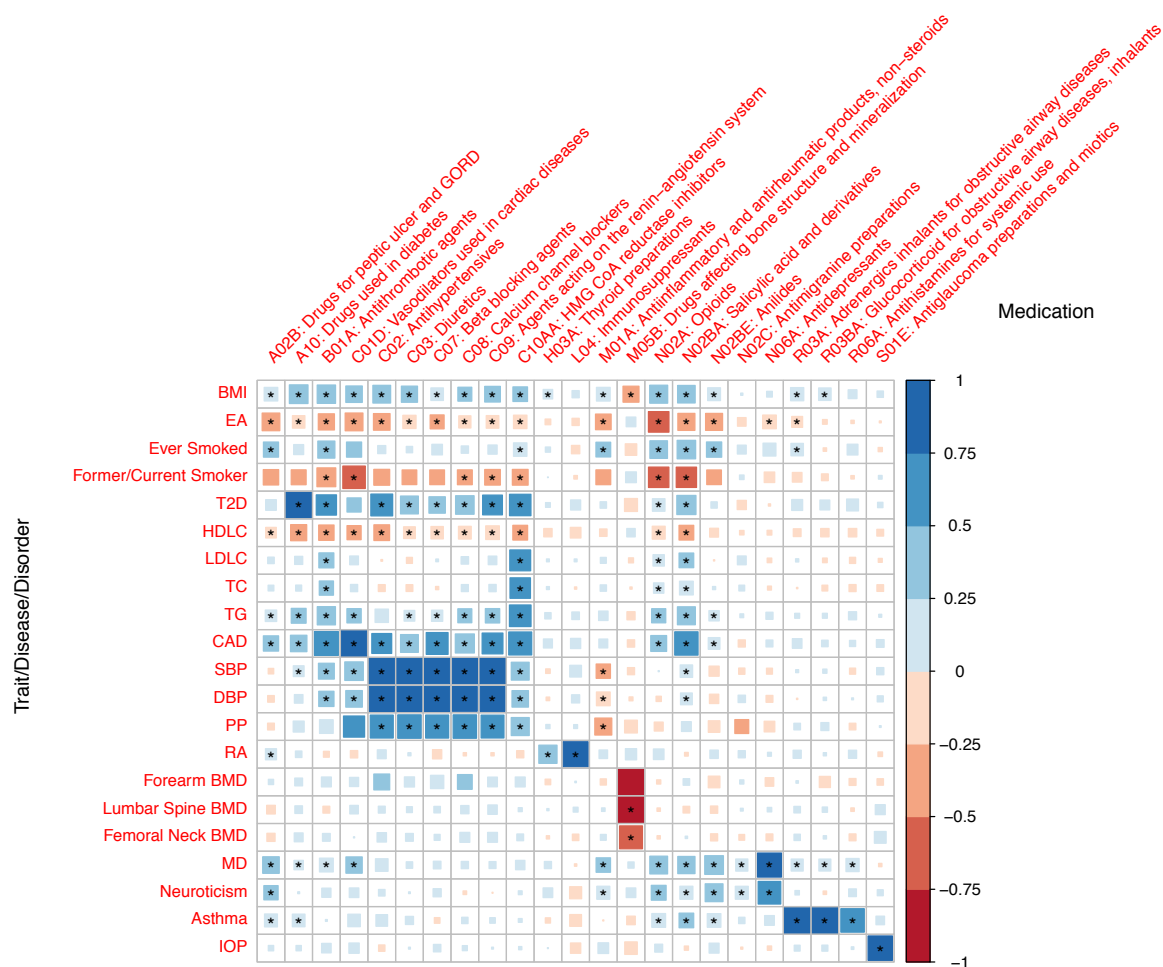


504 **Figure 2.** Summary of UKB medication-taking GWAS analyses.
 505 Text on the right side of each bar represents the meaning of each medication-taking ATC coded trait.
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508 **Figure 3.** Odds ratio (OR) by genetic risk score (GRS) profile decile (1 = lowest, 10 =
509 highest GRS), with OR reported relative to decile 1 as the reference.
510 OR and 95% confidence intervals (blue bars) were estimated using logistic regression. The P
511 value in the bottom right hand corner of each plot refers to the P -value threshold in the
512 discovery sample used to generate the GRS. Note: An increased GRS of femoral neck bone
513 mineral density implies a lower density.

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523 **Figure 4.** Genetic correlation of the 23 medication-taking traits and 21 diseases/traits related
 524 to them.

525 Abbreviations: Body mass index (BMI), Education attainment (EA), Type 2 diabetes (T2D),
 526 High-density lipoprotein cholesterol (HDLC), Low-density lipoprotein cholesterol (LDLC),
 527 Total cholesterol (TC), Triglyceride (TG), Coronary artery disease (CAD), Systolic blood
 528 pressure (SBP), Diastolic blood pressure (DBP), Pulse pressure (PP), Rheumatoid arthritis
 529 (RA), Bone mineral density (BMD), Major depression (MD), Intraocular pressure (IOP).

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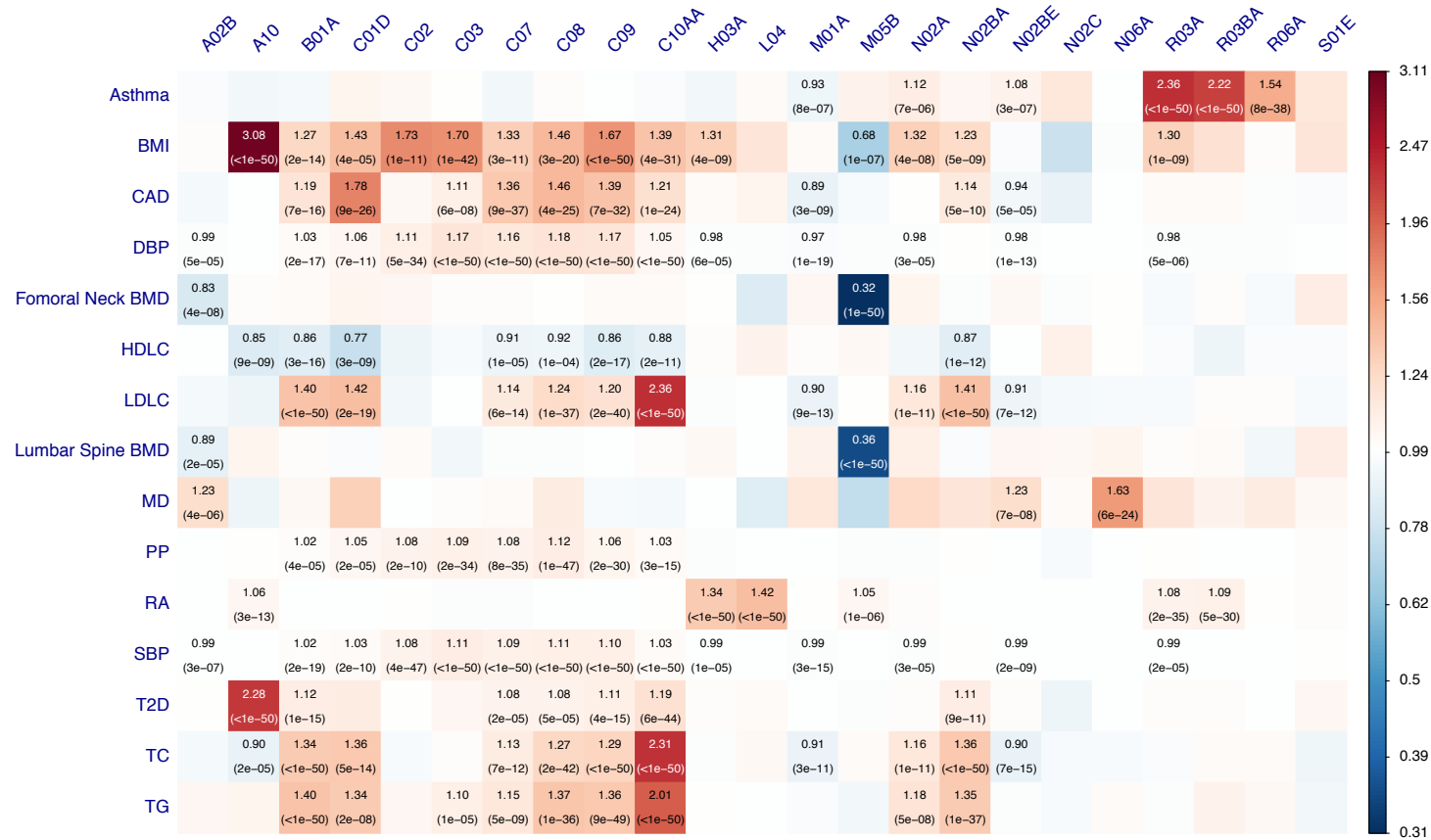


Figure 5. Mendelian Randomisation results using published SNPs associated with 15 diseases/traits as instrument. Rows are the exposure traits and columns are the outcome medication traits. Rows represent exposure and columns represent outcome. The significant effects after correcting for 345 tests (P value $\leq 1.4 \times 10^{-4}$) are labelled with OR (P value). The OR is per SD in liability when the exposure is disease. Abbreviation: Body mass index (BMI), Coronary artery disease (CAD), Diastolic blood pressure (DBP), Bone mineral density (BMD), High-density lipoprotein cholesterol (HDLC), Low-density lipoprotein cholesterol (LDLC), Major depression (MD), Pulse pressure (PP), Rheumatoid arthritis (RA), Systolic blood pressure (SBP), Type 2 diabetes (T2D), Total cholesterol (TC), Triglyceride (TG).

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580 **Author contributions**

581 P.M.V. , N.R.W. and Y.W conceived and designed the experiment. Y.W. performed the
582 analysis with assistance and guidance from E.M.B., Z.Z., K.E.K., J.Y., Z.Z., K.E.K. and L.Y.
583 contributed to data quality of UKB data. Y.W., P.M.V. and N.R.W. wrote the manuscript
584 with the participation of all authors.

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586 **Declaration of interests**

587 We declare that all authors have no competing interests.