



Early View

Original article

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Shared Genetics of Asthma and Mental Health Disorders: A Large-Scale Genome-Wide Cross-Trait Analysis

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ZZ, XZ, KH, CAC and LL designed the study.

ZZ, HS performed the statistical analysis.

ZZ, XZ, CLL, SS, YY, KH, and CAC wrote the first draft of the manuscript.

All authors helped interpret the data, reviewed and edited the final paper, and approved the submission.

ZZ and LL had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Abstract

Epidemiological studies demonstrate an association between asthma and mental health disorders, although little is known about the shared genetics and causality of this association. Thus, we aim to investigate shared genetic and the causal link between asthma and mental health disorders.

We conducted a large-scale genome-wide cross-trait association study to investigate genetic overlap between asthma from UK Biobank and 8 mental health disorders from Psychiatric Genomics Consortium, including: attention deficit hyperactivity disorder (ADHD), anxiety disorder (ANX), autism spectrum disorder, bipolar disorder, eating disorder, major depressive disorder (MDD), posttraumatic stress disorder, and schizophrenia, with a sample size of 9,537 to 394,283.

In the single trait genome-wide association analysis, we replicated 130 and discovered 31 novel independent loci that are associated with asthma. We identified that ADHD, ANX and MDD have strong genetic correlation with asthma at the genome-wide level. Cross-trait meta-analysis identified 7 loci jointly associated with asthma and ADHD, 1 loci with asthma and ANX and 10 loci with asthma and MDD. Functional analysis revealed that the identified variants regulated gene expression in major tissues belonging to exocrine/endocrine, digestive, respiratory and hemic/immune system. Mendelian randomization analyses suggested that ADHD and MDD (including 6.7% samples overlap with asthma) might increase the risk of asthma.

This large-scale genome-wide cross-trait analysis identified shared genetics and potential causal links between asthma and three mental health disorders (ADHD, ANX, and MDD). Such shared genetics implicate potential new biological functions that are in common among them.

Keywords: asthma; mental health disorder; GWAS; shared genetics; causal relationship.

Take home message:

Our study discovered shared genetic components between asthma and ADHD, anxiety and depression. The shared pathways and potential causal effects from mental disorders to asthma highlight health care focus among patients with these disorders.

INTRODUCTION

Asthma is one of the most common chronic diseases, resulting in a substantial burden of disease worldwide. Accumulating studies have shown significant association between asthma and mental health disorders, such as anxiety, depression and attention deficit hyperactivity disorders (ADHD) [1]. Although consensus has emerged from the clinical, psychiatric, and biological literature that psychosocial factors affect asthma pathobiology in both children and adults [2, 3], their role in the pathobiology, morbidity, and symptomatology of asthma remains controversial [4]. For example, a recent large-scale systematic review and meta-analysis by Cortese et al. supports a significant phenotypic association between asthma and ADHD in both children and adults after controlling for possible confounders [3]. Also Lehto et al. recently have found shared genetic influences between asthma and depression and high neuroticism, but not anxiety, based on genome-wide genetic correlation and polygenic risk score [5]. However, the shared genetics between asthma and ADHD, potential genetic causal effect and direction, specific shared genetic variants and underline mechanisms are still unknown for these traits.

We and colleagues have recently identified shared genetic architecture among respiratory, immune, cardio-metabolic and neurological/mental health disorders [6-9], indicating the potential pleiotropic effect. Asthma and mental health disorders are both highly heritable traits [10, 11]. Parallel epidemic trends in asthma and mental health disorders worldwide suggested shared genetic and environmental components for these both conditions [1]. However, there is limited knowledge about the shared genetic components between asthma and mental health disorders. Furthermore, asthma is highly heterogenous disease. Recent studies showed the genetic background of childhood- and adult-onset asthma can be partly distinct [12, 13].

Therefore, it is unclear if the shared genetics between asthma and mental health disorders can differ in these asthma subtypes.

In the current study, we conducted a large-scale genome-wide association study (GWAS) for cross-trait analysis between asthma from UK Biobank and 8 mental health disorders from Psychiatric Genomics Consortium (PGC), including: ADHD, anxiety disorder (ANX), autism spectrum disorder (ASD), bipolar disorder (BIP), eating disorder (ED), major depressive disorder (MDD), posttraumatic stress disorder (PTSD), and schizophrenia (SCZ). Specifically, we investigated the genome-wide genetic correlation between asthma and these mental health disorders, and used cross-trait meta-analysis to identify shared individual genetic variants between them [14]. We carried out further GWAS functional analysis to delineate the biological impact of such shared genetics. Finally, we investigated the shared genetics between asthma and mental health disorder by childhood- and adult-onset asthma subtypes.

METHOD

Study population, design, data summary and quality control (QC)

The overall study design is shown in Figure 1. In this current study, we have included 2 major data sources, UK Biobank and Psychiatric Genomics Consortium (PGC).

UK Biobank data

The details of UK Biobank cohort were described elsewhere [15] and Supplementary note. All participants provided informed consent to the UK Biobank. We performed a stringent sample QC procedure. We restricted the sample set to European population using the genetic ancestry based on principal components analysis of the genotypes (data field 22006). We excluded individuals with chronic obstructive pulmonary disease, emphysema, or chronic bronchitis (self-reports or

ICD-10 codes) from asthmatic cases and controls. Asthma was treated as primary phenotype of interest. Three asthma subtypes were treated as secondary phenotype and defined in this study: childhood-onset asthma (asthma age of onset [AAO] ≤ 12 years), adult-onset asthma (AAO ≥ 26 years) and young adult-onset asthma ($12 \text{ years} < \text{AAO} < 25 \text{ years}$). The young adult-onset asthma was not included in the genetic analysis due to its higher heterogeneity [12, 13]. Thus 46,802 asthma cases, 9,676 childhood-onset asthma cases, 22,296 adult-onset asthma cases and 347,481 shared controls with high-quality genotyping and complete phenotype/covariate data were included for GWAS analysis. Detailed trait ascertainment, genotyping and QC procedures of UK Biobank were provided in Figure S1 and Supplementary note.

PGC GWAS data for mental health disorders

We retrieved summary statistics from publicly available GWAS studies, ADHD ($n_{\text{case}}/n_{\text{control}}=19,099/34,194$) [16], ANX ($n_{\text{case}}/n_{\text{control}}=5,710/11,600$) [17], ASD ($n_{\text{case}}/n_{\text{control}}=6,179/7,377$) [18], BIP ($n_{\text{case}}/n_{\text{control}}=7,481/9,250$) [19], ED ($n_{\text{case}}/n_{\text{control}}=3,495/10,982$) [20], MDD ($n_{\text{case}}/n_{\text{control}}=59,851/113,154$ after excluding 23andMe) [21], PTSD ($n_{\text{case}}/n_{\text{control}}=2,424/7,113$) [22] and SCZ ($n_{\text{case}}/n_{\text{control}}=34,241/45,604$) [23] from PGC. Details of each of the datasets can be found in Table S1.

We applied standardization of GWAS summary statistics to minimize potential biases due to QC procedures. We converted GWAS summary statistics with hg18 genome built to hg19 using liftOver tool [24]. Indels and rare/low frequency variants with a minor allele frequency (MAF) of $< 1\%$ were not included in this study. Additionally, we restricted our analysis to autosomal chromosomes.

GWAS analysis in UK Biobank

In this study, we focused on common variants for the analysis with minor allele frequency $> 1\%$. We performed stringent GWAS quality control procedure. We included variants that did not deviate from Hardy–Weinberg equilibrium ($P > 1 \times 10^{-6}$), per-variant and per-sample missing rates $< 10\%$, and an imputation quality score (INFO) > 0.8 . Quantile–quantile plots were produced and checked for each asthma phenotype. The LD score regression (LDSC) intercept was used to evaluate genomic inflation due to population stratification. A total of 8,274,727 SNPs passed QC on the whole genome, which were eligible for statistical association analyses.

We performed the 3 GWAS analyses for all asthma, childhood-onset asthma, adult-onset asthma and shared controls adjusting for age, sex, genotyping array, assess center and 30 ancestry principal components. We did not remove any related samples in the UK Biobank since we used linear mixed model (LMM) method for phenotype-genotype association analysis, which proved to be robust to potential confounding due to relatedness [25]. The output of BOLT-LMM linear regression was transformed into log odds ratio for asthma binary phenotypes. We applied PLINK [26] clumping function (parameters: `--clump-p1 5e-8 --clump-p2 1e-5 --clump-r2 0.05 --clump-kb 500`) to determine top loci that are independent to each other, i.e. variants with P -value less than 1×10^{-5} , has r^2 more than 0.05 and less than 500 kb away from the peak will be assigned to that peak's clump. The peak variant was defined as a sentinel variant. We used the NHGRI-EBI GWAS catalog (search date: July 1st, 2019) for checking previous report status of genetic loci associating with asthma and identified novel loci. Novel asthma loci were defined as the clump regions which did not contain any previously reported variants in the NHGRI-EBI GWAS catalog.

LD score regression (LDSC) analysis

We conducted post-GWAS genome-wide genetic correlation analysis between asthma and mental health disorders using all SNPs after merging with HapMap3 SNP excluding the human leukocyte antigen (*HLA*) region. LDSC estimates genetic correlation between the true causal effects of two traits (ranging from -1 to 1) [27]. European-ancestry subjects were used in LDSC analysis for each trait if available. We corrected multiple testing for LDSC *P*-values by Bonferroni method, and a *P*-value of 0.00625 (0.05/8) was considered as significance level for LDSC analysis. Mental health disorders that showed significant genome-wide genetic correlation with asthma were included in the following analyses.

Cross-trait meta-analysis

After investigating the genetic correlations among all traits, we applied association analysis based on SubSETs (ASSET) to combine the association evidence for asthma with ADHD, ANX and MDD respectively at individual variants since it is designed for meta-analysis of binary traits [14, 28]. This method combines effect estimate and standard error of the GWAS summary statistics to test hypothesis of association between the SNP with any subset of studies.

We focused on shared sentinel variants satisfying $P_{meta} < 5 \times 10^{-8}$ and clump specific False Discovery Rate (FDR) < 0.05 to account for multiple testing. We used Variant Effect Predictor (VEP) based on Ensembl/GENCODE basic transcripts database for detailed variant annotation [29].

Fine mapping credible-set analysis

To identify the 99% credible set of variants within each of the 500kb of sentinel variants, we identified a credible set of causal variants at each of the shared loci that met cross-trait meta-analysis criteria using the Bayesian-likelihood fine-mapping algorithm [30]. The Bayesian fine-

mapping algorithm maps the primary signal and uses a flat prior with steepest descent approximation.

Transcriptome-wide association study (TWAS) analysis

To identify association of asthma with ADHD, ANX and MDD with regard to transcriptome gene expressions in specific tissues, we conducted a TWAS [31] using 3 gene expression data sources: 43 post-mortal GTEx tissues ($n_{\text{average}}=214$) [32], a CommonMind Consortium (CMC) brain ($n=452$) [33] and a Young Finns Study (YFS) blood ($n=1,264$) tissue expressions [34].

Multiple testing correction for each mental health disorder was applied to account for all gene-tissue pairs based on TWAS P -values using FDR Benjamini-Hochberg procedure ($\text{FDR}<0.05$).

Detailed statistical information can be found in the Supplementary note.

GTEx eQTL colocalization analysis

Since the GTEx eQTL signals by themselves are pervasive, we further conducted the colocalization analysis between signals from 3 cross-trait meta-analysis models (asthma with ADHD, ANX and MDD) and 48 single GTEx tissues cis-eQTL (version 7) to find if the same genetic variant related to expression and the diseases. We first extracted summary association data for variants within 500kb of the index SNP at each of the shared loci. Then, we calculated the posterior probability that the two traits (GWAS cross-trait meta-analysis and GTEx eQTL) were associated and shared one common causal variant (PPH4) [35]. Loci were considered to be co-localized with PPH4 greater than 0.7. We conducted the tissue enrichment using permutation test (1,000 permutations) and calculated the permutation P -values for each tissue. We considered significant enrichment based on $P\text{-value}=0.001042$ ($0.05/48$ tissues) after correcting for multiple testing of 48 tissues.

Mendelian randomization (MR) analysis

We applied generalized summary data-based Mendelian randomization (GSMR) [36] under default settings to infer putative causal relationships between asthma and mental health disorders from GWAS summary statistics. GSMR requires a minimum of 10 LD-independent instruments ($r^2 < 0.05$) that are associated with the exposure at GWAS-significant level ($P < 5 \times 10^{-8}$), and removes SNPs displaying horizontal pleiotropy (HEIDI outlier $P < 0.01$). Accordingly, we restricted our analyses to traits that satisfy this criterion. Additionally, we performed outlier sensitivity analysis using a more exclusive HEIDI-outlier threshold of 0.1. Prior to running GSMR, we removed strand-ambiguous SNPs, poorly imputed SNPs (INFO < 0.9), and SNPs in the MHC region (chr6:25-34M).

Sensitivity analysis in childhood- and adult-onset asthma

Recent studies have shown that asthma is a highly heterogeneous disease and its genetics are partially distinct between in childhood- and adult-onset asthma [12, 13]. Thus, we also investigated if the shared genetics between asthma and ADHD/ANX/MDD are different in respect to childhood- and adult-onset asthma, specifically in genetic correlation, cross-trait meta-analysis, TWAS and MR analyses.

RESULTS

Phenotypic association between asthma and mental health disorders in UK Biobank. We conducted the phenotypic association analysis using logistic regression in UK Biobank between asthma and high quality mental disorders based on 2 models: (1) unadjusted; (2) adjusted for age, sex and education. In both models, we found asthma is significantly associated with ANX, BIP, MDD, ED and PTSD (Table S2).

Genome-wide association and SNP-based heritability. There was no evidence of population stratification for 3 asthma GWASs (Figure 2a and Figure S2-3). We identified 161 independent

loci associated with asthma at genome-wide significance level (5×10^{-8}), which contains 130 previously reported loci and 31 novel loci (Figure 2b and Table S3-S4). For the 31 novel loci, we conducted replication analysis in Transnational Asthma Genetics Consortium (TAGC) data (23,948 cases, 118,538 controls)[37]. Twenty-one of these loci were not found in TAGC, likely because TAGC meta-analysis was based on HapMap2 imputation. Thus we used the most significant SNP in the clump region that is available from HapMap2/TAGC as the surrogate SNP and extracted their association results from TAGC for replication purpose. As a result, we found surrogate SNPs for 14 loci, but the remaining 7 loci were not applicable for replication. Thus, a total of 24 loci were sought for replication in TAGC. Among them, we found 14 of them were nominally significant in TAGC multi-ancestry or European population ($P\text{-value} < 0.05$), 10 of the 14 loci had $P\text{-value} < 0.001$ (Table S3). In addition, we found the effect sizes of the 24 loci were highly consistent between UK Biobank and TAGC (Figure S4-S5). Estimates of SNP-based heritability on the observed scale using GWAS summary statistics were 5.02% (SE: 0.62%) for asthma, 3.38% (SE: 0.66%) for childhood-onset asthma and 1.98% (SE: 0.24%) for adult-onset asthma.

Genome-wide genetic correlation. We investigated the genetic correlations of asthma and mental health disorders using LDSC (Table 1). We observed positive genetic correlations between asthma and ADHD ($R_g = 0.197$, $P = 1.21 \times 10^{-5}$), ANX ($R_g = 0.406$, $P = 1.61 \times 10^{-3}$), and MDD ($R_g = 0.215$, $P = 1.09 \times 10^{-8}$). We did not find significant genetic correlation between asthma and other mental health disorders.

Cross-trait meta-analysis between asthma and mental health disorders. We applied ASSET for genome-wide cross-trait meta-analysis to identify genetic loci associated with asthma and ADHD, ANX and MDD ($P_{meta} < 5 \times 10^{-8}$; single trait $FDR < 0.05$). After pruning, we found 7 loci

significantly associated with asthma and ADHD. The most significant SNP was rs2025758 ($P_{meta}=4.52\times10^{-18}$, $FDR_{asthma}=1.29\times10^{-14}$, $FDR_{ADHD}=1.09\times10^{-3}$), located at an intergenic region. We also found the HLA locus (sentinel SNP: rs3117006, $P_{meta}=2.81\times10^{-8}$, $FDR_{asthma}=6.61\times10^{-7}$, $FDR_{ADHD}=3.13\times10^{-2}$) shared by asthma and ADHD. Further, we found 1 locus significantly associated with both asthma and ANX (sentinel SNP: rs1709393, $P_{meta}=4.29\times10^{-8}$, $FDR_{asthma}=2.30\times10^{-4}$, $FDR_{ANX}=2.06\times10^{-6}$). In addition, we identified 10 loci significantly associated with asthma and MDD. The top sentinel SNP was rs2855812 ($P_{meta}=2.1\times10^{-16}$, $FDR_{asthma}=7.64\times10^{-13}$, $FDR_{MDD}=1.07\times10^{-5}$), where its clump covers many genes in the region, mainly including *HLA* genes. Notably, we found 2 regions shared by multiple traits; 5q21.2 and HLA region shared by asthma, ADHD and MDD (Table 2 and S5).

Identification of causal exonic missense variants. We identified a credible set of causal SNPs using Bayesian fine-mapping at each shared locus meeting significance criteria in the asthma–mental health disorders meta-analysis. The credible set of variants at each locus were 99% likely to contain the causal variant. A list of credible sets of SNPs for each locus is provided in Tables S6–S8.

We found 1 locus (in *BX927320.1*) for asthma and MDD (Table S9), in which the credible set included exonic missense polymorphisms. However, we did not find any exonic missense polymorphisms in the credible set of SNPs for asthma/ADHD and asthma/ANX (Table S10-11), since most variants were either intronic or intergenic, aligning with the theory that most variants identified by GWAS involve gene regulatory effects rather than protein structure changes [38].

TWAS and GTEx eQTL colocalization. To investigate specific tissue-gene pairs that are shared by asthma and mental health disorders, we further performed TWAS analysis on asthma, ADHD, MDD and ANX using 3 gene expression data sources. We investigated the overlap of

significant tissue-gene pairs in asthma, ADHD, MDD and ANX. There was an overlap in 18 significant tissue-gene pairs in GTEx and 3 pairs in CMC brain for asthma and ADHD. There was an overlap in one significant tissue-gene pair in YFS blood for asthma and MDD (Table 3). No overlapped tissue-gene pair was found for asthma and ANX. Since CMC brain and YFS blood gene expression datasets have larger sample size than GTEx, for tissues of brain and blood, we considered CMC and YFS as discovery datasets and GTEx as replication dataset. We additionally extracted the association statistics of 4 significant gene-tissue pairs between asthma and mental health disorder (*CISD2*, *KATNA1* and *MANBA* from CMC brain; *POLI* from YFS blood) from GTEx results. We replicated all of them in GTEx dataset accounting multiple testing for available genes ($P < 0.05/3$ genes) except for *KATNA1*, which is not available in GTEx brain tissues (Table S12).

We further conducted colocalization analysis for the shared genetic variants from cross-trait meta-analysis between asthma and ADHD, ANX, and MDD with GTEx eQTLs across 48 tissues. For asthma and ADHD, we found shared variants at the 10p14 region (e.g. *GATA3*), 4q24 (e.g. *MANBA*) and *HLA* region was the potential causal eQTL variant in many tissues (Table S13). Notably, in asthma and MDD, *HLA* was also the major causal eQTL colocalized region (Table S14). Through the permutation analysis, we observed significant amount of colocalized signals between asthma and ADHD/MDD in some specific tissues, belonging mainly to exocrine/endocrine, digestive, respiratory and hemic/immune system (Figure S6-S7).

MR results. We observed small but significant positive causal effect of ADHD on asthma ($\beta_{\text{ADHD} \rightarrow \text{Asthma}} = 0.054$, $P = 0.036$), but not vice versa (Table 4), corroborating the putative model that ADHD causally increases the risk of asthma. We also observed strongly significant positive causal effect of MDD on asthma ($\beta_{\text{MDD} \rightarrow \text{Asthma}} = 0.21$, $P = 1.80 \times 10^{-5}$). However, since there is a

small fraction of overlapping samples between MDD and asthma GWAS data (~6.7%) and potential unobserved confounders, our MR conclusion should be interpreted with caution. Due to limited power of the GWAS, we could not identify causal relationships between asthma and ANX.

Sensitivity analysis in childhood- and adult-onset asthma. We found ADHD, ANX and MDD have a positive genetic correlation with adult-onset asthma (ADHD: $R_g=0.28$, $P=9.91\times10^{-6}$; ANX: $R_g=0.50$, $P=3.29\times10^{-3}$; MDD: $R_g=0.34$, $P=1.52\times10^{-10}$). We did not observe any genetic correlation between childhood-onset asthma and mental health disorders (Table S15). In terms of the 18 shared genetic sentinel variants, we found some of them have stronger association with childhood-onset asthma, but the others have stronger association with adult-onset asthma (Table S16). For shared genes in TWAS, we found most of them have approximately even association between childhood- and adult-onset asthma except for POLI, which have much stronger association with childhood-onset asthma (Table S17). Finally, we identified a modest but non-significant causal effect between ADHD and childhood-/adult-onset asthma. We also observed a strong positive causal effect of MDD on adult-onset asthma ($\beta_{\text{MDD}\rightarrow\text{Adult-onset asthma}}=0.26$, $P=3.00\times10^{-4}$) (Table S18).

DISCUSSION

To our knowledge, this study is the largest genome-wide analysis that has investigated the genetic overlap between asthma and mental health disorders. In this study, we identified 161 independent loci associated with asthma at genome-wide significance level, which contains 130 previously reported loci and 31 novel loci. More than half of the novel loci were replicated in

TAGC cohort. We also showed a strong positive genetic correlation between asthma and 3 mental health disorders – ADHD, ANX and MDD.

We also identified the genetic overlap between asthma and ADHD, ANX or MDD at individual variants level, including 7 loci shared by asthma and ADHD, 1 loci shared by asthma and ANX and 10 loci shared by asthma and MDD from cross-trait meta-analysis. We highlighted *HLA* region (several sentinel SNPs) for its significant role in between asthma and mental health disorders. *HLA* region harbors more than 200 genes located close to each other on chromosome 6. It is a gene complex that contains abundant pleiotropy for many complex diseases, especially involved in immune related process [39]. Wang et al. also identified *HLA* region showed the strongest role contributing to pleiotropic effect between psychiatric and immune disorders, although asthma was not assessed in their study [40]. For example, with the inclusion of *HLA* region, the pleiotropy significance between SCZ and rheumatoid arthritis was around 280 magnitude stronger than with the exclusion of *HLA* region [40].

Furthermore, we investigated whether shared genes between asthma and mental health disorders have potential functional connection with the human tissues. In the TWAS analysis, we found multiple shared tissue-gene pairs between asthma and ADHD, including exocrine/endocrine, digestive, respiratory and nervous system. Of them, *CISD2* were found to be shared between asthma and ADHD in most of tissues and potentially have significant biological function.

CDGSH iron sulfur domain 2 (*CISD2*) deficiency causes mitochondrial breakdown and dysfunction, and drive premature aging [41]. A transmission electron microscopy (TEM) study revealed that mitochondrial degeneration occurs in the brain cells and skeletal muscle cells in the *Cisd2*^{-/-} mice [41]. Mitochondrial dysfunction was associated with allergic asthma [42] and affected digestive system. Mitochondrial defects are also detected in ADHD cybrids created

from patients' platelets, implying mitochondrial dysfunction could be a contributory factor for ADHD pathology [43]. In addition, we found *POLI* gene in YFS whole blood tissue was shared by asthma and MDD. One possible mechanism for such connection is through DNA polymerase iota (η) enzyme, which is encoded by *POLI* gene. DNA polymerase η is the sole contributor of A/T modifications during immunoglobulin gene hypermutation in the mouse [44].

Immunoglobulin E (IgE) is a key component in the pathology of asthma. Recognition of allergen by IgE depends on a combination of choice of human immunoglobulin heavy-chain-variable genes, utilization of certain mutational hotspots, and improvement of affinity via additional mutations in complementarity-determining regions (CDR) [45]. DNA polymerase η also modulates DNA damage response and DNA damage is the key to treat many of the genetically inherited central nervous system disorders including depression [46].

In this study, we also investigated causal relationships between asthma and mental health disorders using MR. Our results suggested that ADHD and MDD might increase the risk of asthma, providing insights into the pathological mechanisms of asthma. Due to limited power, we were not able to perform bidirectional MR for ANX and asthma. In addition, our MR analyses using a more exclusive outlier *P*-value threshold of 0.1 showed most of the MR analysis results remain unchanged (Table S19). We emphasize that our inferred causal relationships are putative as all MR analyses in this study are based on GWAS summary statistics – unobserved confounders and overlapping samples may lead to false conclusion. Further analysis, such as gene function biological experiments, longitudinal studies, would confirm the inferred causal relationships.

In the asthma subtype sensitivity analysis, we found the shared genetics between asthma and mental health disorders are distinct for childhood- and adult-onset asthma. In terms of the

genome-wide genetic correlation, childhood-onset asthma did not show genetic correlation with any mental health disorders, where several studies observed robust phenotypic correlation between asthma and ADHD in children and adults [3, 47]. Such finding suggests the phenotypic correlation between asthma and ADHD in children maybe more attributed by environmental factors but no substantial from genetic origins [47]. Furthermore, our genetic correlation results suggest the genetic predisposition on ADHD (majority are children) might have more impact on genetic predisposition of adult-onset asthma. However, there is limited research demonstrate the phenotypic correlation between childhood-onset ADHD and adult-onset asthma, which could be investigated by longitudinal studies in the future. On the other hand, for the top genes identified in cross-trait meta-analysis and TWAS, we found the genetic effects are similar in both childhood- and adult-onset asthma, which suggested the shared genetics among complex diseases may be different at genome-wide polygenic level and top association level. Also Lehto et al. recently reported on the shared genetics between asthma and depression and high neuroticism in adults, based on their analysis of genome-wide genetic correlation and polygenic risk score [5]. In complement with the Lehto study, we further examined the shared genetics at variant, gene and tissue function level for both childhood- and adult-onset asthma. And we fully utilized the genetic effect to infer the potential genetic causality of the observed associations.

We acknowledge several potential limitations in this study. First, as the statistical power of our GWAS analysis was restricted to the sample sizes of each of mental health disorders; the genetic correlation between asthma and additional mental health disorders may be discovered with larger sample sizes. Second, the asthma information in UK Biobank is about lifetime asthma diagnosis without information about current asthma or asthma duration. Thus, we were not able to align occurrence of asthma and mental health disorders. Third, in the asthma subtype analysis, it

would be ideal to find corresponding well-powered childhood- and adult-onset mental health disorders for matched analysis with childhood- and adult-onset asthma. However, such mental health disorder GWAS data are currently unavailable. Also, other asthma endotypes, such as by IgE (allergic status) and eosinophil level (type 2 inflammation) [48], may provide additional insights of pathophysiological connection between asthma and mental health disorders. Finally, it is important to evaluate the common non-genetic risks for morbidity and mortality in asthma and mental health disorders, such as environmental and social factors. For example, inhaled corticosteroid, the most common medication for asthma, which is not available in UK Biobank, may have the potential adverse effects on mental health, such as depression and anxiety [49]. The current study was limited to assessing shared genetic factors between asthma and mental health disorders, and future studies on shared environmental factors between them are needed.

CONCLUSION

Understanding the genetic overlap between asthma and mental health disorders may be beneficial to the management of both conditions. Our study shows evidence of significant positive genetic correlations between asthma and 3 mental health disorders. Shared genetic variants were fine-mapped to improve resolution and identify potential shared causal variants with exonic missense polymorphisms. We also found multiple potential common biological mechanisms, which can advance our understanding of the connection between asthma and some mental health disorders and offer new avenues for future functional validation, disease prevention and clinical treatment.

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DECLARATION OF INTERESTS

All authors declare no competing interest.

DATA AVAILABILITY

UK Biobank GWAS summary statistics will be available at the NHGRI-EBI GWAS Catalog website (<https://www.ebi.ac.uk/gwas/>) or please contact Dr. Zhaozhong Zhu for inquiries about the GWAS data.

FIGURE LEGENDS

Figure 1. Overall study design.

Figure 2. Results of genome-wide association analysis of UK Biobank cohort for asthma. a. Association test quantile-quantile plot showing departure from null hypothesis of no association. b. Manhattan plot for association test of 46,802 asthma cases and 347,481 controls. X-axis denotes the genomic position (chromosomes 1-22), Y-axis denotes the $-\log_{10}(P\text{-value})$ of association test. Total of 31 novel independent loci. The most significant novel SNP in each locus is highlighted in yellow orange diamond shape. Genome-wide significance level after accounting for multiple testing ($P=5\times 10^{-8}$) is denoted by red line.

Figure S1. Sample QC procedure in UK Biobank for 3 asthma phenotypes.

Figure S2. Quantile-quantile plot of childhood-onset asthma. LDSC intercept=1.04 showed no evidence of population stratification bias.

Figure S3. Quantile-quantile plot of adult-onset asthma. LDSC intercept=1.03 showed no evidence of population stratification bias.

Figure S4. Correlation of effect size of 24 novel loci between UK Biobank and TAGC multiancestry population. R denotes Pearson correlation coefficient; P denotes *P*-value for Pearson correlation coefficient. Red line denotes diagonal line.

Figure S5. Correlation of effect size of 24 novel loci between UK Biobank and TAGC European population. R denotes Pearson correlation coefficient; P denotes *P*-value for Pearson correlation coefficient. Red line denotes diagonal line.

Figure S6. Colocalization of asthma and ADHD meta-analysis loci and GTEx eQTL. Tissues are categorized into organ/body system. X-axis denotes number of genes with posterior probability $H_4 > 0.7$ (GWAS cross-trait meta-analysis and GTEx eQTL were associated and shared one common causal variant). Enrichment test based on 1000 permutations was performed. We assigned the 1 red asterisk to the tissue if it's nominally significant enriched, 2 red asterisks if it's significantly enriched after multiple testing correction for 48 tissues.

Figure S7. Colocalization of asthma and MDD meta-analysis loci and GTEx eQTL. Tissues are categorized into organ/body system. X-axis denotes number of genes with posterior probability $H_4 > 0.7$ (GWAS cross-trait meta-analysis and GTEx eQTL were associated and shared one common causal variant). Enrichment test based on 1000 permutations was performed. We assigned the 1 red asterisk to the tissue if it's nominally significant enriched, 2 red asterisks if it's significantly enriched after multiple testing correction for 48 tissues.

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Table 1. Genome-wide genetic correlation between asthma and mental health disorders

Phenotype 1	Phenotype 2	Rg	Rg_SE	Z	P
Asthma	ADHD	0.1968	0.045	4.3763	1.21×10 ⁻⁰⁵
	ANX	0.4056	0.1286	3.1548	1.61×10 ⁻⁰³
	ASD	0.0167	0.0515	0.3237	7.46×10 ⁻⁰¹
	BIP	0.0845	0.0542	1.5603	1.19×10 ⁻⁰¹
	ED	0.0025	0.0547	0.0453	9.64×10 ⁻⁰¹
	MDD	0.2152	0.0376	5.7169	1.09×10 ⁻⁰⁸
	PTSD	0.4579	0.4712	0.9718	3.31×10 ⁻⁰¹
	SCZ	0.0123	0.0262	0.4706	6.38×10 ⁻⁰¹

Abbreviations: Rg: genetic correlation estimate

Table 2. Genome-wide significant loci by cross-trait meta-analysis associated with asthma and ADHD, MDD or anxiety ($P < 5 \times 10^{-8}$; single trait FDR < 0.05)

Traits	Sentinel SNP	Genome position	A1	A2	FDR1	FDR2	P	Genes within clumping region
Asthma and ADHD	rs2025758	chr10:8777640-8855244	T	C	1.29×10^{-14}	1.09×10^{-03}	4.52×10^{-18}	Intergenic region
	rs7094182	chr10:8452766-8543732	G	C	1.09×10^{-09}	4.89×10^{-03}	5.15×10^{-12}	Intergenic region
	rs325485	chr5:103769738-104048590	A	G	2.64×10^{-05}	5.31×10^{-05}	1.94×10^{-08}	Intergenic region
	rs227283	chr4:103550006-103885568	C	G	8.60×10^{-05}	5.58×10^{-06}	2.67×10^{-08}	CISD2,MANBA,SLC9B1,UBE2D3
	rs3117006	chr6:33096426-33124972	G	A	6.61×10^{-07}	3.13×10^{-02}	2.81×10^{-08}	HLA-DPB2
	rs6736411	chr2:63508703-63906628	G	A	1.71×10^{-06}	3.45×10^{-02}	2.91×10^{-08}	MDH1,WDPCP
Asthma and ANX	rs71565398	chr6:33581633-33775446	C	G	9.68×10^{-07}	2.18×10^{-02}	3.70×10^{-08}	IP6K3,ITPR3,LEMD2,MLN,UQCC2
	rs1709393	chr3:101684480-101713472	C	T	2.30×10^{-04}	2.06×10^{-06}	4.29×10^{-08}	LOC152225
								ABHD16A,AIF1,APOM,ATP6V1G2,ATP6V1G2-DDX39B,BAG6,C6orf15,C6orf25,C6orf47,C6orf48,CHCR1,CDSN,CLIC1,CSNK2B,DDAH2,DDX39B,GPANK1,HCG26,HCG27,HCP5,HLA-B,HLA-C,HSPA1A,HSPA1B,HSPA1L,LSM2,LST1,LTA,LTB,LY6G5B,LY6G5C,LY6G6C,LY6G6D,LY6G6E,LY6G6F,MCCD1,MICA,MICB,MIR4646,MIR6832,MIR6891,MSH5,MSH5-SAPCD1,NCR3,NEU1,NFKBIL1,POU5F1,PRRC2A,PSORS1C1,PSORS1C2,PSORS1C3,SAPCD1,SLC44A4,SNORA38,SNORD48,SNORD52,SNORD84,SNO RD117,TCF19,TNF,VARS,VWA7
	rs2855812	chr6:31078809-31835164	G	T	7.64×10^{-13}	1.07×10^{-05}	2.09×10^{-16}	HLA-DOB,HLA-DQA1,HLA-DQA2,HLA-DQB1,HLA-DQB2,TAP2
	rs2854275	chr6:32606970-32808299	C	A	1.18×10^{-13}	1.31×10^{-02}	3.47×10^{-13}	
Asthma and MDD	rs396755	chr5:103791044-104088117	C	G	3.80×10^{-05}	9.59×10^{-08}	1.55×10^{-11}	Intergenic region
	rs150814685	chr6:28207991-29196418	T	G	9.84×10^{-09}	1.78×10^{-04}	1.91×10^{-11}	C6orf100,GPX5,GPX6,HCG14,LOC401242,LOC100129636,NKAPL,OR2B3,OR2J2,OR2J3,OR2W1,PGBD1,TRIM27,ZBED9,ZKSCAN3,ZKSCAN4,ZNF311,Z

rs149702363	chr6:29218513-29448128	T	G	1.33×10^{-08}	2.50×10^{-03}	3.55×10^{-10}	SCAN12,ZSCAN23,ZSCAN26,ZSCAN31 OR2H1,OR5V1,OR10C1,OR11A1,OR12D2,OR12D3, OR14J1 HIST1H1B,HIST1H2AI,HIST1H2AJ,HIST1H2AK,HIS T1H2AL,HIST1H2AM,HIST1H2BL,HIST1H2BM,HIST 1H2BN,HIST1H2BO,HIST1H3H,HIST1H3I,HIST1H3J ,HIST1H4J,HIST1H4K,HIST1H4L,LINC01012,LOC10 0131289,NKAPL,OR2B2,OR2B6,PGBD1,TOB2P1,Z KSCAN4,ZKSCAN8,ZNF165,ZNF184,ZNF192P1,ZN F391,ZSCAN9,ZSCAN12P1,ZSCAN16,ZSCAN16- AS1,ZSCAN26,ZSCAN31
rs493161	chr6:27357414-28304384	A	T	9.84×10^{-05}	9.38×10^{-07}	9.69×10^{-10}	RERE
rs301817	chr1:8415235-8847380	C	A	1.59×10^{-09}	4.59×10^{-02}	2.94×10^{-09}	Intergenic region
rs148696809	chr6:28934352-28934352	T	C	1.53×10^{-03}	1.96×10^{-07}	4.78×10^{-09}	LINC01012,LOC100131289,POM121L2,PRSS16,VN 1R10P,ZNF184,ZNF204P,ZNF391
rs147121091	chr6:27174557-27765899	A	G	1.87×10^{-04}	4.58×10^{-05}	2.63×10^{-08}	NEGR1
rs10789340	chr1:72565800-72945128	A	G	1.44×10^{-03}	3.36×10^{-06}	2.68×10^{-08}	

Table 3. Significant overlap transcriptome-wide association analysis results between asthma and ADHD or MDD (FDR<0.05)

Tissue	Gene	CHR	NSNP	Asthma		Mental health disorder		
				BEST.GWAS.ID	FDR	BEST.GWAS.ID	FDR	Trait
GTEX.Adrenal_Gland	CISD2	4	326	rs227375	0.046	rs227369	0.008	ADHD
GTEX.Artery_Aorta	CISD2	4	326	rs227375	0.038	rs227369	0.035	ADHD
GTEX.Cells_Transformed_fibroblasts	MANBA	4	389	rs227375	0.009	rs227369	0.001	ADHD
GTEX.Cells_Transformed_fibroblasts	UBE2D3	4	343	rs227375	0.045	rs227369	0.036	ADHD
GTEX.Colon_Sigmoid	CISD2	4	326	rs227375	0.046	rs227369	0.025	ADHD
GTEX.Colon_Transverse	CISD2	4	326	rs227375	0.027	rs227369	0.006	ADHD
GTEX.Esophagus_Gastroesophageal_Junction	CISD2	4	326	rs227375	0.049	rs227369	0.036	ADHD
GTEX.Esophagus_Muscularis	CISD2	4	326	rs227375	0.022	rs227369	0.025	ADHD
GTEX.Lung	CISD2	4	326	rs227375	0.038	rs227369	0.025	ADHD
GTEX.Muscle_Skeletal	CISD2	4	326	rs227375	0.004	rs227369	0.004	ADHD
GTEX.Ovary	CISD2	4	326	rs227375	0.032	rs227369	0.032	ADHD
GTEX.Pancreas	MANBA	4	389	rs227375	0.013	rs227369	0.039	ADHD
GTEX.Pancreas	UBE2D3	4	343	rs227375	0.007	rs227369	0.021	ADHD
GTEX.Skin_Not_Sun_Exposed_Suprapubic	CISD2	4	326	rs227375	0.045	rs227369	0.042	ADHD
GTEX.Skin_Sun_Exposed_Lower_leg	CISD2	4	326	rs227375	0.034	rs227369	0.028	ADHD
GTEX.Small_Intestine_Terminal_Ileum	CISD2	4	326	rs227375	0.025	rs227369	0.022	ADHD
GTEX.Spleen	MANBA	4	389	rs227375	0.038	rs227369	0.005	ADHD
GTEX.Uterus	CISD2	4	326	rs227375	0.038	rs227369	0.007	ADHD
CMC.Brain	CISD2	4	322	rs227375	0.003	rs227369	0.010	ADHD
CMC.Brain	KATNA1	6	469	rs112225	0.010	rs2342764	0.048	ADHD
CMC.Brain	MANBA	4	390	rs228617	0.009	rs227369	0.009	ADHD
YFS.Blood	POLI	18	347	rs3730783	0.016	rs4801003	0.046	MDD

Abbreviations: CMC: CommonMind Consortium; YFS: Young Finns Study

Table 4. Estimates of causal effect size between asthma and mental health disorders.

Phenotype 1	Phenotype 2	Direction	Causal Effect Size (S.E.)	P	No. Instruments
ADHD	Asthma	→	0.054 (0.026)	0.036	10
		←	-0.034 (0.025)	0.16	126
ANX	Asthma	→*	N/A	N/A	N/A
		←	-0.014 (0.055)	0.8	159
MDD	Asthma	→ [#]	0.21 (0.049)	1.80×10^{-05}	20
		←	0.012 (0.015)	0.45	124

“→” refers to the Phenotype 1 → Phenotype 2 causal direction, and “←” refers to Phenotype 2 → Phenotype 1 causal direction.

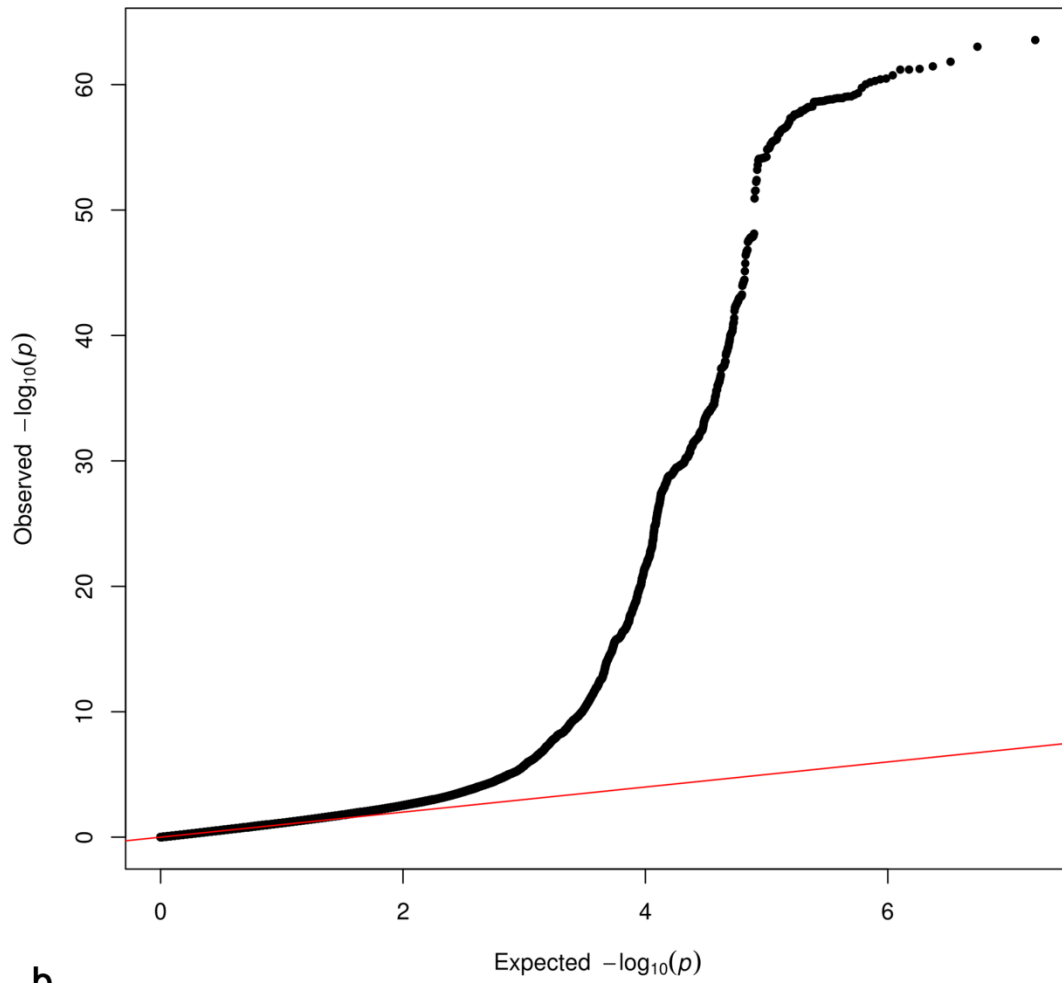
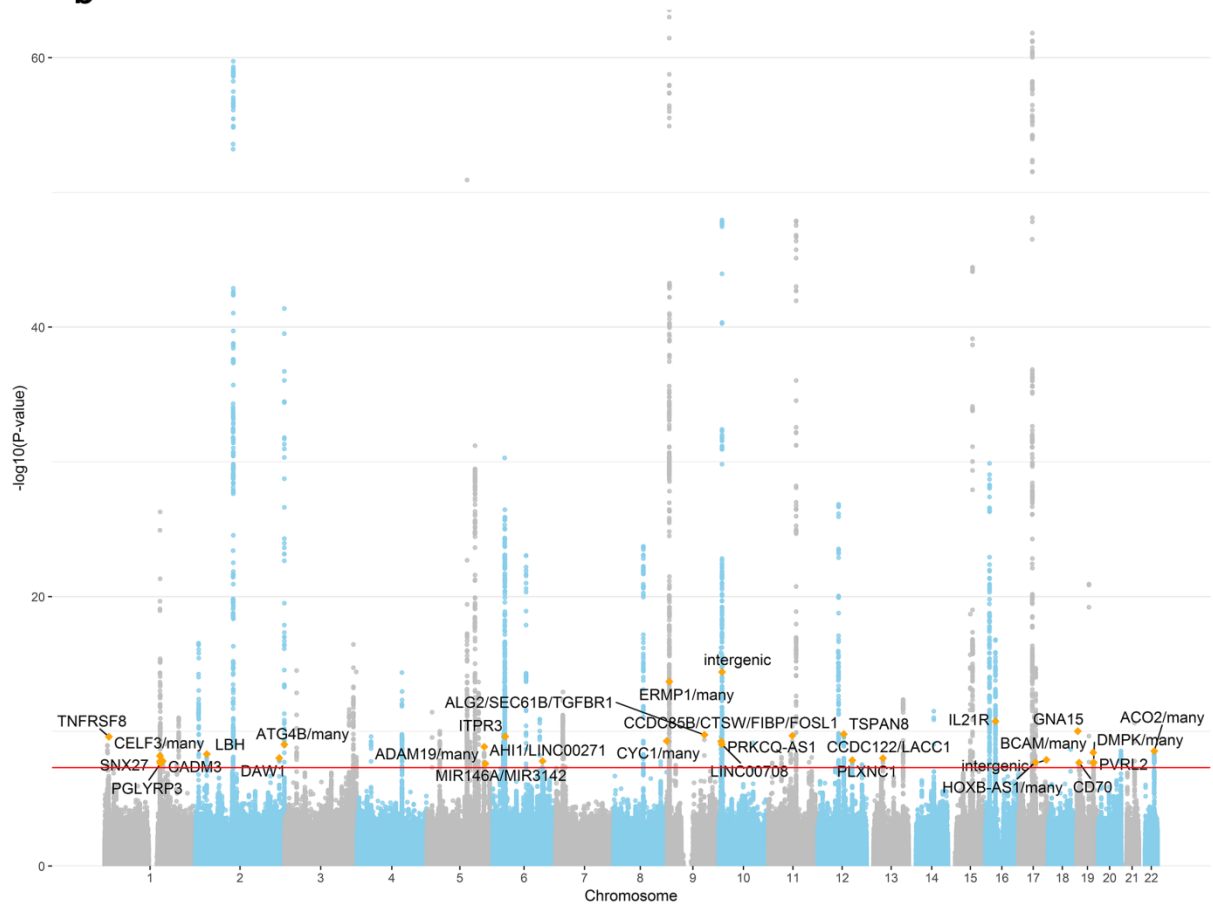
*ANX GWASs does not have enough SNPs at genome-wide significance level for constructing instrument variable and is marked with “N/A” .

[#]MDD GWAS data include 23andme



a

Quantile-Quantile plot
LDSC intercept=1.0615, s.e.=0.0114

**b**

Shared Genetics of Asthma and Mental Health Disorders: A Large-Scale Genome-Wide Cross-Trait Analysis

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Online supplementary note

UK Biobank dataset

The UK Biobank study is a prospective study of >500,000 participants living in the UK. In total, 503,325 participants who registered in the National Health Service with ages ranging 40–69 years were recruited out of 9.2 million mailed invitations. Baseline data were collected using questionnaires, and anthropometric assessments were performed. All detailed genotyping, quality control, and imputation procedures are described at the UK Biobank website

(<http://biobank.ctsu.ox.ac.uk>). Currently ~500,000 individuals in UK Biobank have been genotyped for ~800,000 SNPs using Affymetrix facilities. Population structure was captured by principal component analysis on ~500,000 UK Biobank samples using ~100,000 SNPs. Quality control filters were applied before phasing. Data were prephased using SHAPEIT3 [1].

Haplotype Reference Consortium (HRC) panel data was used as a reference panel for imputation. This reference panel has many more haplotypes (64,976) than the 1000G reference panel, and so is expected to produce better imputation performance [2].

We used 4 data fields to determine asthmatic cases: 6152, 20002, 41202 and 41204. Data field 6152 is from the participant questionnaire to determine the doctor-diagnosed asthma phenotypes. This data field contains the question: “Has a doctor ever told you that you have had any of the following conditions?” Participants could select more than one answer from the following: Blood clot in the leg (DVT); blood clot in the lung; emphysema/chronic bronchitis; asthma; hayfever,

allergic rhinitis or eczema; none of the above; prefer not to answer. If participants chose either “none of the above” or “prefer not to answer”, they could not select other answers. Data field 20002 denotes self-reported non-cancer illness code. Data field 41202 and 41204 denote ICD10 main and secondary diagnoses from hospital.

We used data fields 3786 (age of first asthma was diagnosed based on touchscreen questionnaire) and 22147 (age of first asthma was diagnosed by doctor based on an online follow-up questionnaire finished only by subset of participants) to determine the asthma age of onset. Three asthma subtypes were used in this study: childhood-onset asthma (defined as asthma age of onset $[AAO] \leq 12$ years old), adult-onset asthma ($AAO \geq 26$) and young adult-onset asthma ($12 < AAO < 25$). The young adult-onset asthma was not included in the genetic analysis due to its higher heterogeneity. Since we used both data fields 3786 and 22147 to determine AAO, we performed additional quality control to handle inconsistencies between these 2 data fields. Specifically, we first excluded 8,307 subjects with missing AAO for both data fields; then we excluded 426 subjects with data fields 3786 and 22147 for AAO inconsistency > 10 years; finally we excluded 441 subjects with AAO inconsistency ≤ 10 years but have inconsistent age group from these 2 data fields.

To assess phenotypic correlation between asthma and mental health disorders in UK Biobank, we additionally extracted phenotypes from UK Biobank, including depression (MDD) (data fields 20002, 20126, 20544), anxiety (ANX) (20002, 20544, 20544, 41202, 41204), posttraumatic stress disorder (PTSD) (20002, 41202, 41204), bipolar disorder (BIP) (20002, 20126, 20544, 41202, 41204), eating disorder (ED) (20002, 20544, 41202, 41204) and schizophrenia (SCZ) (20002, 20544, 41202, 41204).

All participants from this study provided UK Biobank-acquired informed consent and provided data according to the UK Biobank protocol. We have complied with all ethical regulations according to UK Biobank policy. This research was approved and conducted using the UK Biobank under application number 16549 and 45052.

Attention Deficit Hyperactivity Disorder (ADHD) dataset

An international collaborative team including the Psychiatric Genomics Consortium (PGC) conducted a meta-analysis of GWAS of individuals with ADHD. Participants included both children and adults. A European subset of GWAS data was used in current study. Key summary information can be found in Table S1.

ANX dataset

The Anxiety NeuroGenetics STudy (ANGST) Consortium conducted a meta-analysis of GWAS of individuals with ANX and controls. All participants were adults and European ancestry. Key summary information can be found in Table S1.

ASD dataset

The ASD working group of the PGC conducted a meta-analysis of GWAS of individuals with ASD and controls. Participants included both children and adults. A European subset of GWAS data was used in current study. Key summary information can be found in Table S1.

BIP dataset

The BIP working group of the PGC conducted a meta-analysis of GWAS of individuals with bipolar disorder and controls. Participants included both children and adults. All subjects from this study are European ancestry. Key summary information can be found in Table S1.

ED dataset

This study is based on a meta-analysis of GWAS of individuals with ED and controls.

Participants included both children and adults. All subjects from this study are European ancestry.

Key summary information can be found in Table S1.

MDD dataset

The MDD working group of the PGC conducted a meta-analysis of GWAS of individuals with MDD and controls. Participants included both children and adults, but majority are adults. A European subset of GWAS data excluding 23andme was used in current study. However, for Mendelian randomization analysis, 10K top significant SNPs including 23andme samples were used. Key summary information can be found in Table S1.

PTSD dataset

The PTSD working group of PGC conducted a meta-analysis of GWAS of individuals with PTSD and controls. All participants were adults. A European subset of GWAS data was used in current study. Key summary information can be found in Table S1.

SCZ dataset

The SCZ working group of the PGC conducted a meta-analysis of GWAS of individuals with SCZ and controls. Although the meta-analysis of 49 cohorts contains 2 ancestries, majority of them are from European ancestry (46 of European and three of east Asian ancestry, 34,241 cases and 45,604 controls). These comprise the primary PGC GWAS data set. Participants included both children and adults. Key summary information can be found in Table S1.

GWAS analysis of UK Biobank data

To account for relatedness, the association between cardiac traits in UK Biobank data and imputed SNPs was carried out using BOLT-linear mixed model (LMM) [3]. The output of BOLT-LMM linear regression was transformed into log odds ratio (logOR) for HBP binary phenotype using the following equation:

$$\log OR = \frac{Beta_{BOLT-LMM}}{\frac{N_{case}}{N_{control}} * \left(1 - \frac{N_{case}}{N_{control}}\right)}$$

Association analysis based on subsets (ASSET)

ASSET is a generalized fixed-effects meta-analysis model that combines effect estimate and standard error of GWAS of related but distinct traits to identify promising directions to discover loci with small but common pleiotropic effects. The ASSET method explores subsets of studies for the presence of true association signals that are either in the same direction or opposite directions [4]. When S represents a set of study traits selected from K studies, meta-analysis statistics of the one-sided test ASSET is defined as:

$$Z_{\max-ASSET} = \max_{S \in \mathcal{S}} |Z(S)| = \max_{S \in \mathcal{S}} \left| \sum_{k \in S} \sqrt{\pi_k(S)} Z_k \right|$$

where S is all possible $2^K - 1$ subsets of K studies, and $\pi_k(T) = n_k / \sum_{k \in T} n_k$ represents sample size of the study K relative to total sample size of the given subset S .

An advantage of using ASSET is that it can account for correlation among studies/subjects that might arise due to shared subjects across distinct studies or due to correlation among related traits in the same study by using case-control overlap matrices. If $Z(A)$ and $Z(B)$ denote Z statistics for the association test for a SNP from case-control studies A and B with an arbitrary

amount of overlap between subjects, then—under the null hypothesis of no association and the assumption that there is no covariate adjustment—the correlation between statistics is given by

$$Corr\{Z(A), Z(B)\} = \sqrt{\frac{n_A^{(1)} n_A^{(0)}}{N_A}} \sqrt{\frac{n_B^{(1)} n_B^{(0)}}{N_B}} \left[\frac{n_{AB}^{(11)}}{n_A^{(1)} n_B^{(1)}} - \frac{n_{AB}^{(10)}}{n_A^{(1)} n_B^{(0)}} - \frac{n_{AB}^{(01)}}{n_A^{(0)} n_B^{(1)}} + \frac{n_{AB}^{(00)}}{n_A^{(0)} n_B^{(0)}} \right]$$

where $n_A^{(1)}$, $n_A^{(0)}$, and N_A are the number of cases, controls, and subjects, respectively, in study A; $n_B^{(1)}$, $n_B^{(0)}$, and N_B are the number of cases, controls, and subjects, respectively, in study B; and $n_{AB}^{(ij)}$ represents the number of subjects with different phenotype categories $(i,j) \in (0,1)$ that overlap between studies A and B. For example, $n_{AB}^{(11)}$ denotes the number of shared cases between studies A and B; $n_{AB}^{(10)}$ denotes the number of individuals who are treated as cases in study A but as controls in study B; $n_{AB}^{(01)}$ denotes the number of individuals who are treated as controls in study A but as cases in study B; and $n_{AB}^{(00)}$ denotes the number of shared controls between studies A and B [4].

Reference

1. O'Connell J, Sharp K, Shrine N, Wain L, Hall I, Tobin M, Zagury JF, Delaneau O, Marchini J. Haplotype estimation for biobank-scale data sets. *Nat Genet* 2016: 48(7): 817-820.
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4. Bhattacharjee S, Rajaraman P, Jacobs KB, Wheeler WA, Melin BS, Hartge P, Yeager M, Chung CC, Chanock SJ, Chatterjee NJ. A subset-based approach improves power and interpretation for the combined analysis of genetic association studies of heterogeneous traits. 2012: 90(5): 821-835.

Figures

Figure S1. Sample QC procedure in UK Biobank for 3 asthma phenotypes.

Figure S2. Quantile-quantile plot of childhood-onset asthma. LDSC intercept=1.04 showed no evidence of population stratification bias.

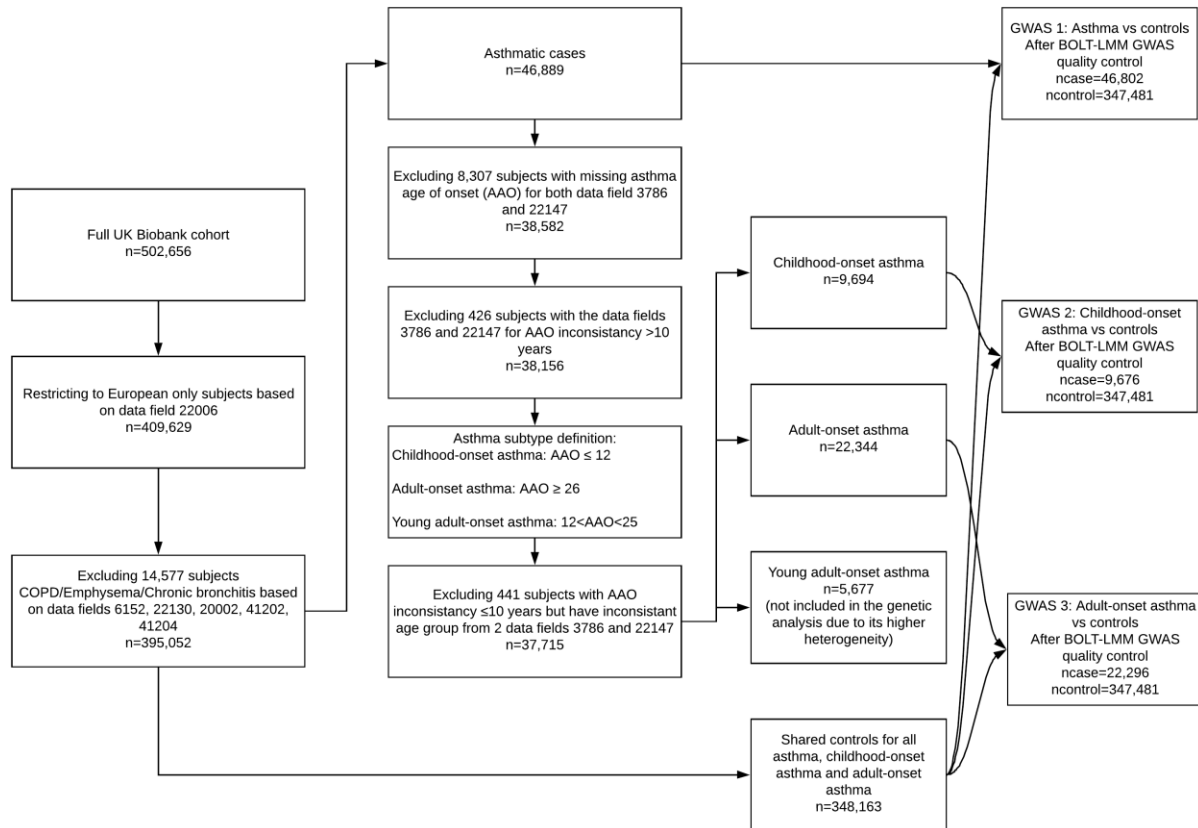
Figure S3. Quantile-quantile plot of adult-onset asthma. LDSC intercept=1.03 showed no evidence of population stratification bias.

Figure S4. Correlation of effect size of 24 novel loci between UK Biobank and TAGC multiancestry population. R denotes Pearson correlation coefficient; P denotes P-value for Pearson correlation coefficient. Red line denotes diagonal line.

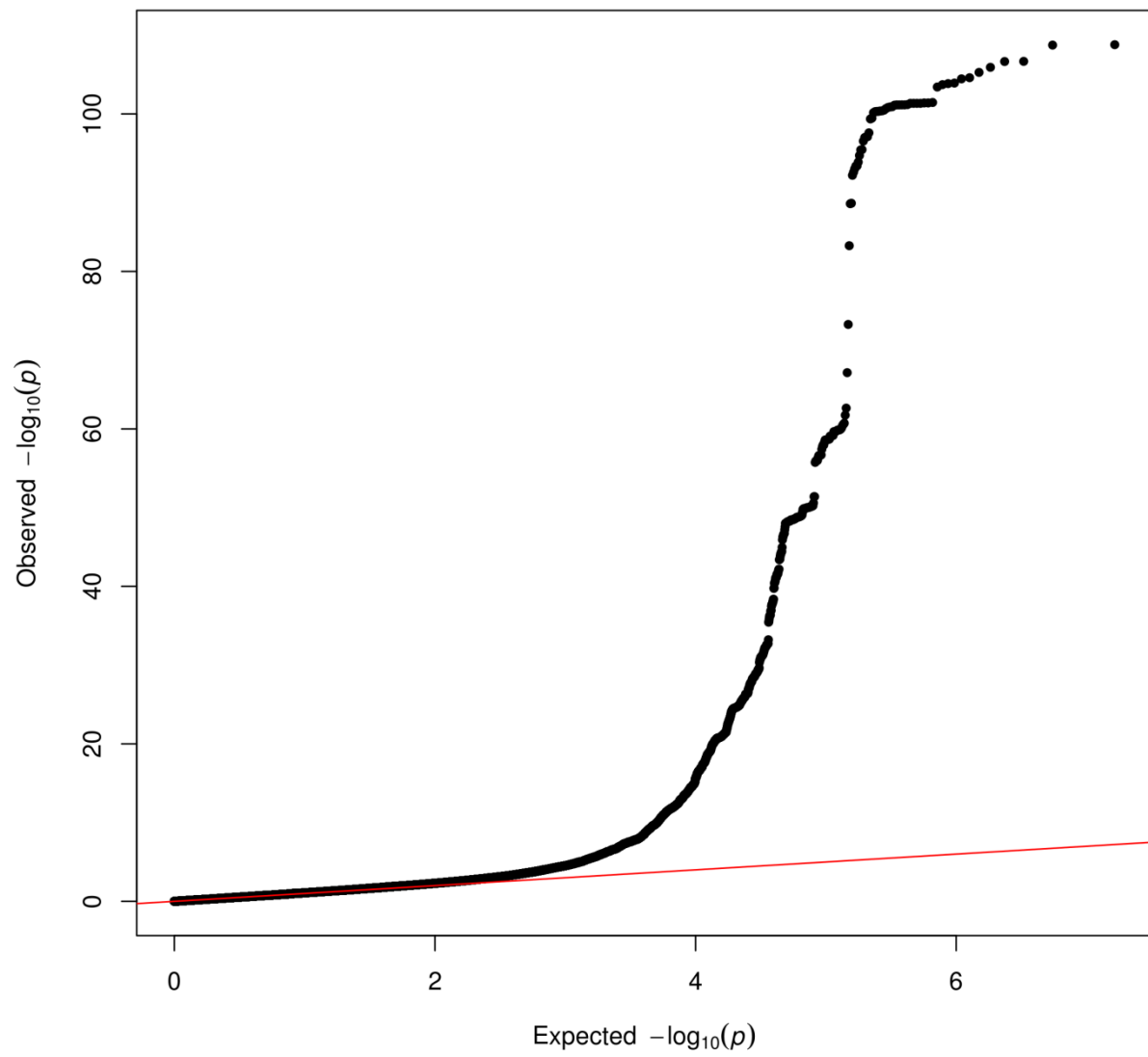
Figure S5. Correlation of effect size of 24 novel loci between UK Biobank and TAGC European population. R denotes Pearson correlation coefficient; P denotes P-value for Pearson correlation coefficient. Red line denotes diagonal line.

Figure S6. Colocalization of asthma and ADHD meta-analysis loci and GTEx eQTL. Tissues are categorized into organ/body system. X-axis denotes number of genes with posterior probability $H_4 > 0.7$ (GWAS cross-trait meta-analysis and GTEx eQTL were associated and shared one common causal variant). Enrichment test based on 1000 permutations was performed. We assigned the 1 red asterisk to the tissue if it's nominally significant enriched, 2 red asterisks if it's significantly enriched after multiple testing correction for 48 tissues.

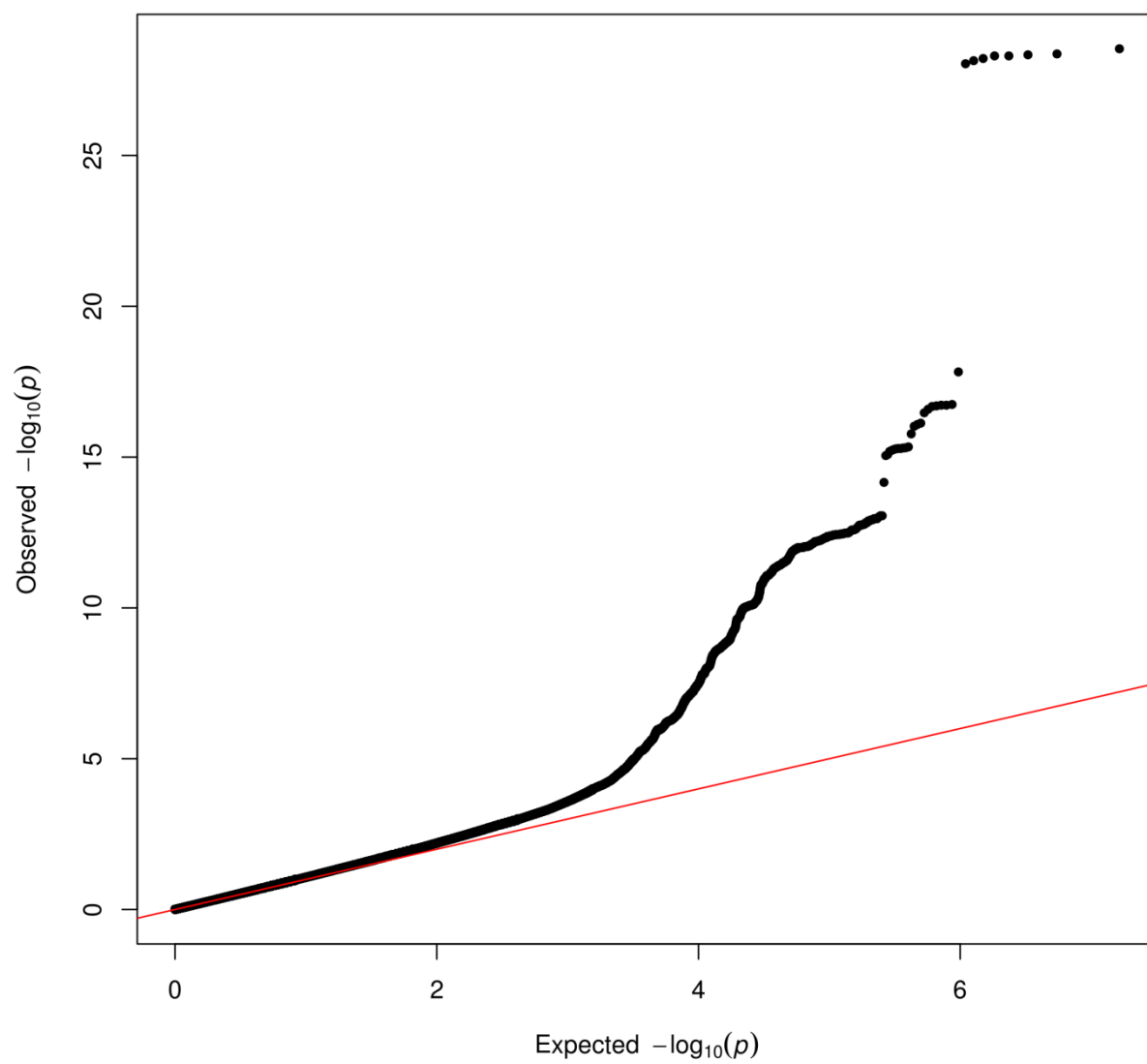
Figure S7. Colocalization of asthma and MDD meta-analysis loci and GTEx eQTL. Tissues are categorized into organ/body system. X-axis denotes number of genes with posterior probability $H_4 > 0.7$ (GWAS cross-trait meta-analysis and GTEx eQTL were associated and shared one common causal variant). Enrichment test based on 1000 permutations was performed. We assigned the 1 red asterisk to the tissue if it's nominally significant enriched, 2 red asterisks if it's significantly enriched after multiple testing correction for 48 tissues.



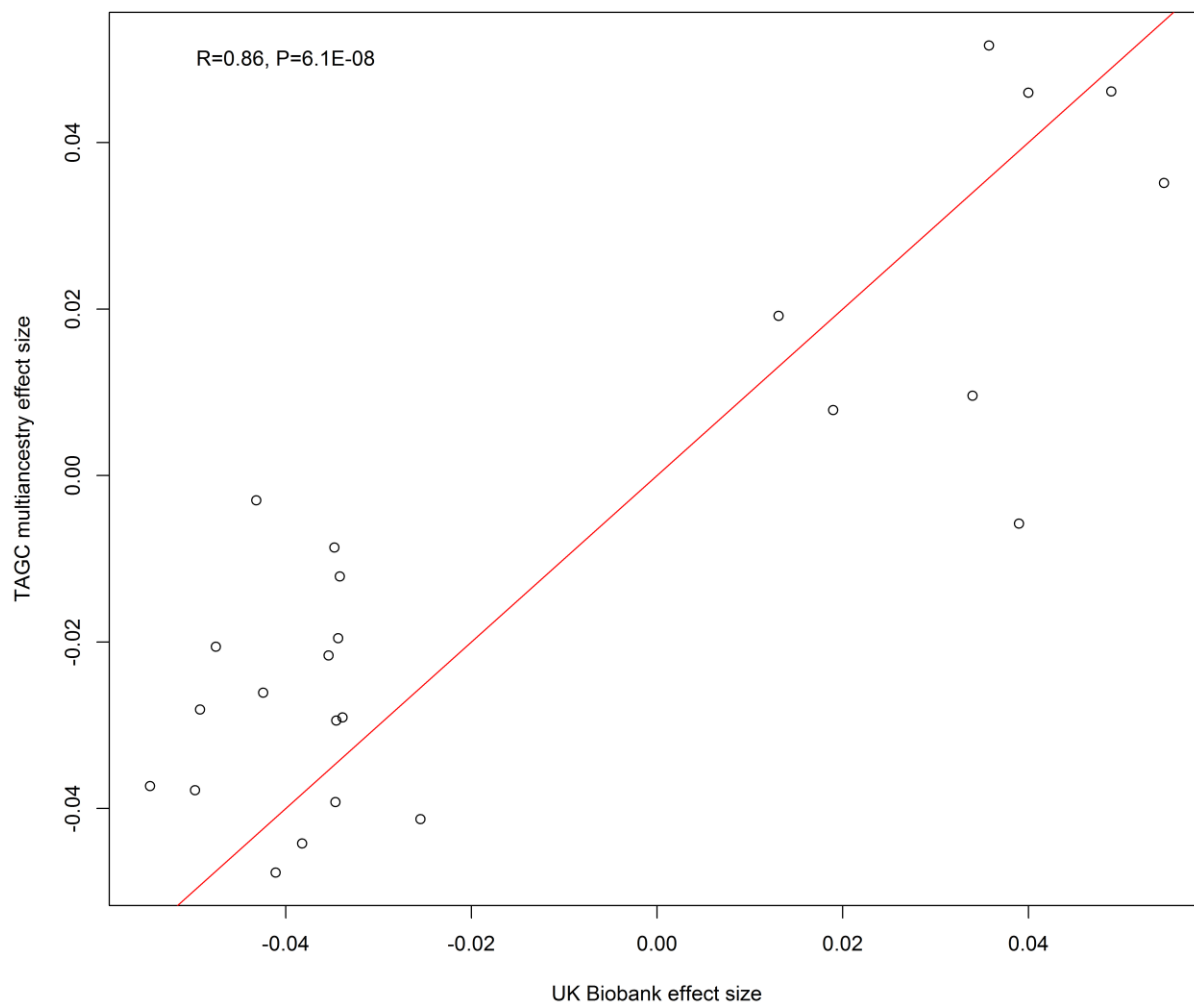
Childhood-onset asthma Quantile-Quantile plot
LDSC intercept=1.0373, s.e.=0.0194



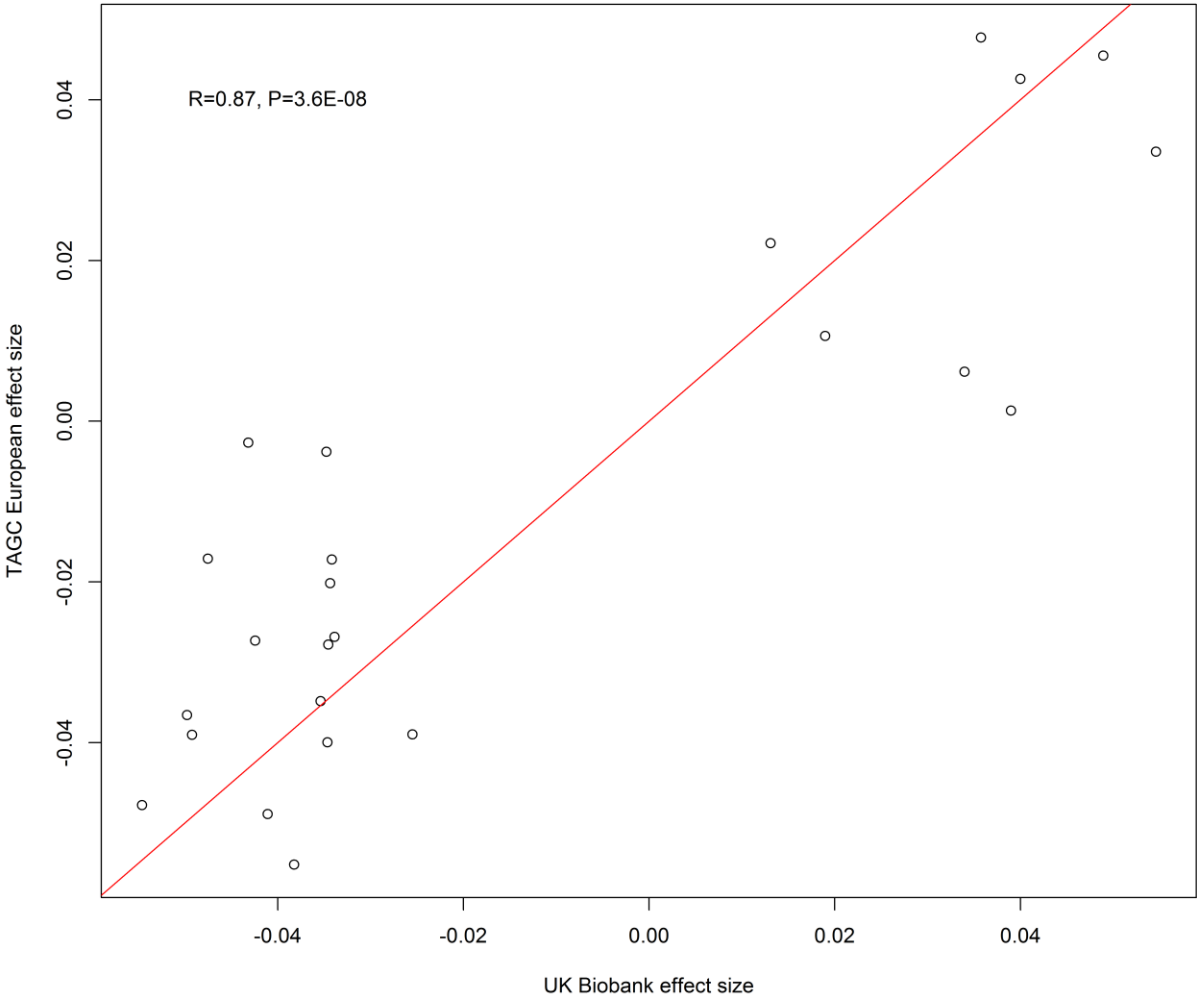
Adult-onset asthma Quantile-Quantile plot
LDSC intercept=1.0347, s.e.=0.0122



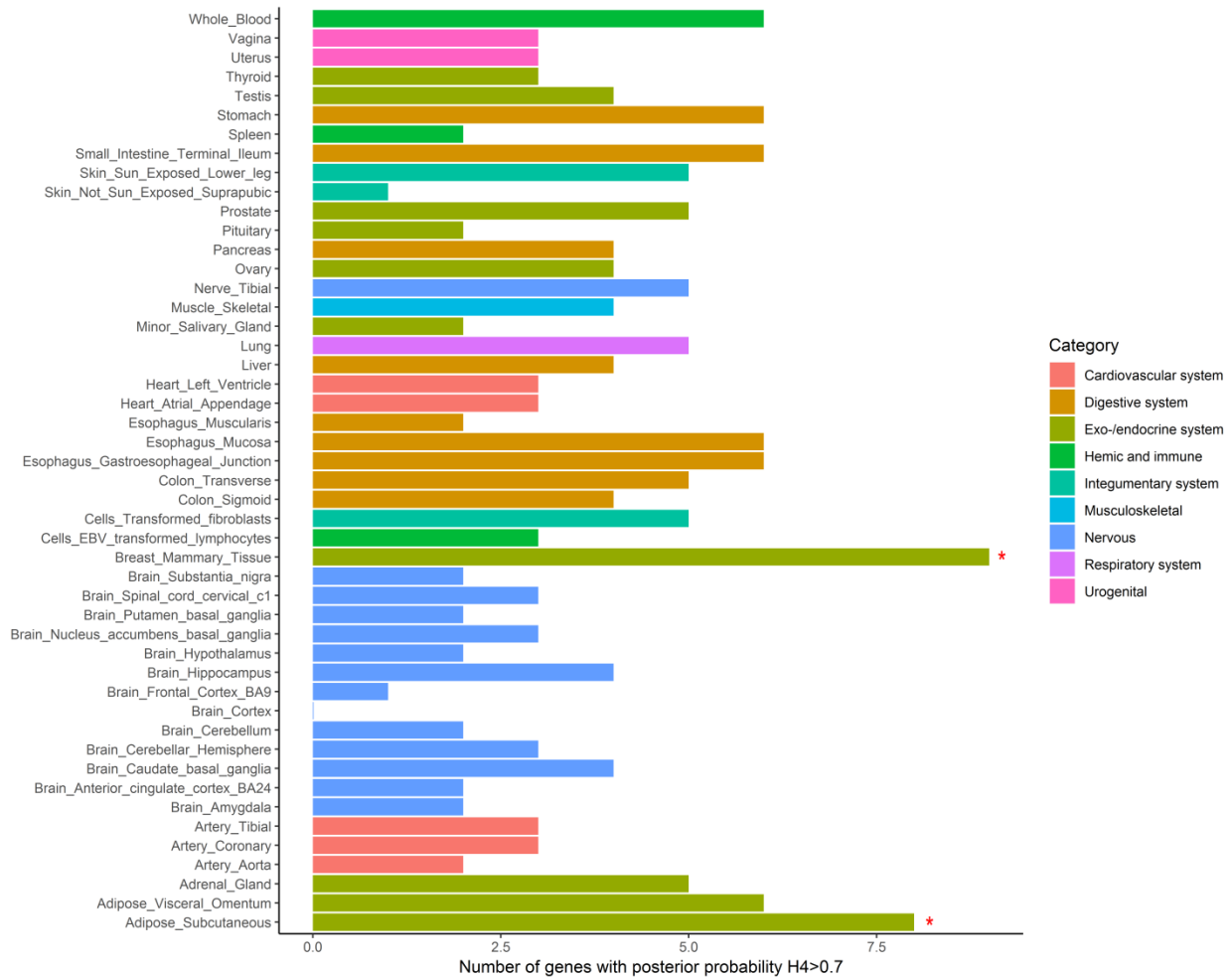
Correlation of effect size of 10 novel loci between UK Biobank and TAGC multiancestry population



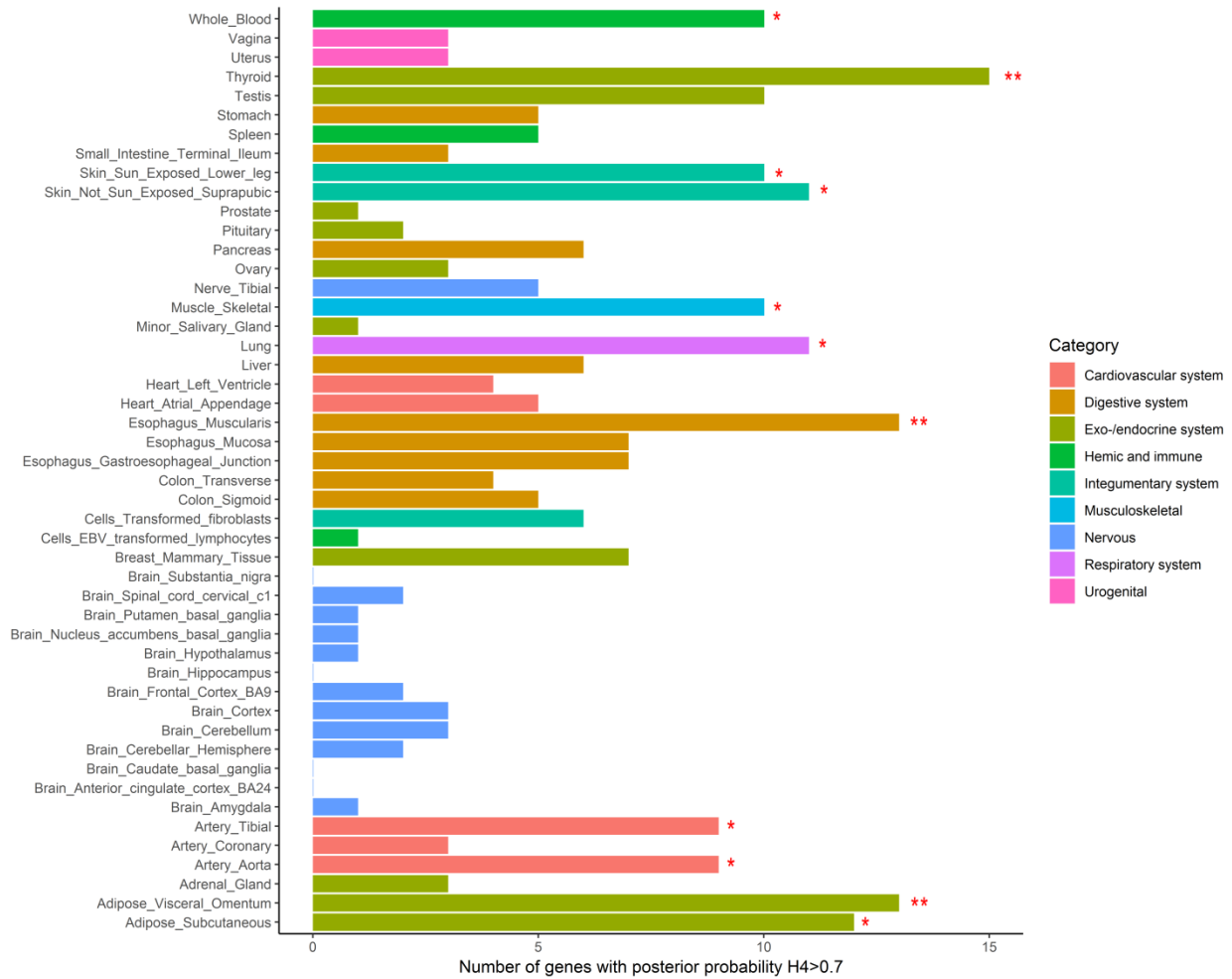
Correlation of effect size of 10 novel loci between UK Biobank and TAGC European population



Colocalization of asthma and ADHD cross-trait meta-analysis loci and GTEx eQTL



Colocalization of asthma and MDD cross-trait meta-analysis loci and GTEx eQTL



Online supplementary tables

Dear Editor/Reviewers

This paper contains 19 supplementary tables in Microsoft Excel file format, please use this link to get access to the supplementary table file. Thank you.

https://www.dropbox.com/s/bz0slk38h0zqrm5/Supplementary%20tables_ERJ_revision.xlsx?dl=0