Shared genetics of asthma and mental health disorders: a large-scale genome-wide cross-trait analysis

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This 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 a healthcare focus among patients with these disorders. http://bit.ly/2MsALoa

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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 aimed to investigate shared genetics 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 the UK Biobank and eight mental health disorders from the Psychiatric Genomics Consortium: attention deficit hyperactivity disorder (ADHD), anxiety disorder (ANX), autism spectrum disorder, bipolar disorder, eating disorder, major depressive disorder (MDD), post-traumatic stress disorder and schizophrenia (sample size 9537–394 283).

In the single-trait genome-wide association analysis, we replicated 130 previously reported loci and discovered 31 novel independent loci that are associated with asthma. We identified that ADHD, ANX and MDD have a strong genetic correlation with asthma at the genome-wide level. Cross-trait meta-analysis identified seven loci jointly associated with asthma and ADHD, one locus 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 the exocrine/endocrine, digestive, respiratory and haemic/immune systems. Mendelian randomisation analyses suggested that ADHD and MDD (including 6.7% sample 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.

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Data availability: UK Biobank GWAS summary statistics will be available at the NHGRI-EBI GWAS Catalog website (www.ebi.ac.uk/gwas) or contact Zhaozhong Zhu for inquires about the GWAS data.

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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 disorder (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.* [3] supports a significant phenotypic association between asthma and ADHD in both children and adults after controlling for possible confounders. Lehto *et al.* [5] also recently found shared genetic influences between asthma and depression and high neuroticism, but not anxiety, based on genome-wide genetic correlation and polygenic risk scores. However, the shared genetics between asthma and ADHD, potential genetic causal effect and direction, specific shared genetic variants, and underlying 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 both these conditions [1]. However, there is limited knowledge about the shared genetic components between asthma and mental health disorders. Furthermore, asthma is a highly heterogeneous 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 the UK Biobank and eight mental health disorders from the Psychiatric Genomics Consortium (PGC): ADHD, anxiety disorder (ANX), autism spectrum disorder (ASD), bipolar disorder (BIP), eating disorder (ED), major depressive disorder (MDD), post-traumatic 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 disorders by childhood- and adult-onset asthma subtypes.

Methods

Study population, design, data summary and quality control

The overall study design is shown in figure 1. In this current study, we included two major data sources: the UK Biobank and the PGC.

UK Biobank data

The details of the UK Biobank cohort are described elsewhere [15] and in the supplementary material. All participants provided informed consent to the UK Biobank. We performed a stringent sample quality control procedure. We restricted the sample set to a European population using 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 International Statistical Classification of Diseases and Related Health Problems, 10th Revision codes) from asthmatic cases and controls. Asthma was treated as the primary phenotype of interest. Three asthma subtypes were treated as secondary phenotypes and were defined in this study as: childhood-onset asthma (age of onset $\leqslant$12 years), adult-onset asthma (age of onset $\geqslant$26 years) and young adult-onset asthma (age of onset >12–25 years). Young adult-onset asthma was not included in the genetic analysis due to its higher heterogeneity [12, 13]. Thus, 46 802 asthma cases, 9676 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 quality control procedures of the UK Biobank are provided in supplementary figure S1 and the supplementary material.

PGC GWAS data for mental health disorders

We retrieved summary statistics from publicly available GWAS studies from the PGC: ADHD (n_{case}/$n_{control}$=19 099/34 194) [16], ANX (n_{case}/$n_{control}$=5710/11 600) [17], ASD (n_{case}/$n_{control}$=6179/7377) [18], BIP (n_{case}/$n_{control}$=7481/9250) [19], ED (n_{case}/$n_{control}$=3495/10 982) [20], MDD (n_{case}/$n_{control}$=59 851/113 154 after excluding 23andMe) [21], PTSD (n_{case}/$n_{control}$=2424/7113) [22] and SCZ (n_{case}/$n_{control}$=34 241/45 604) [23]. Details of each of the datasets can be found in supplementary table S1.

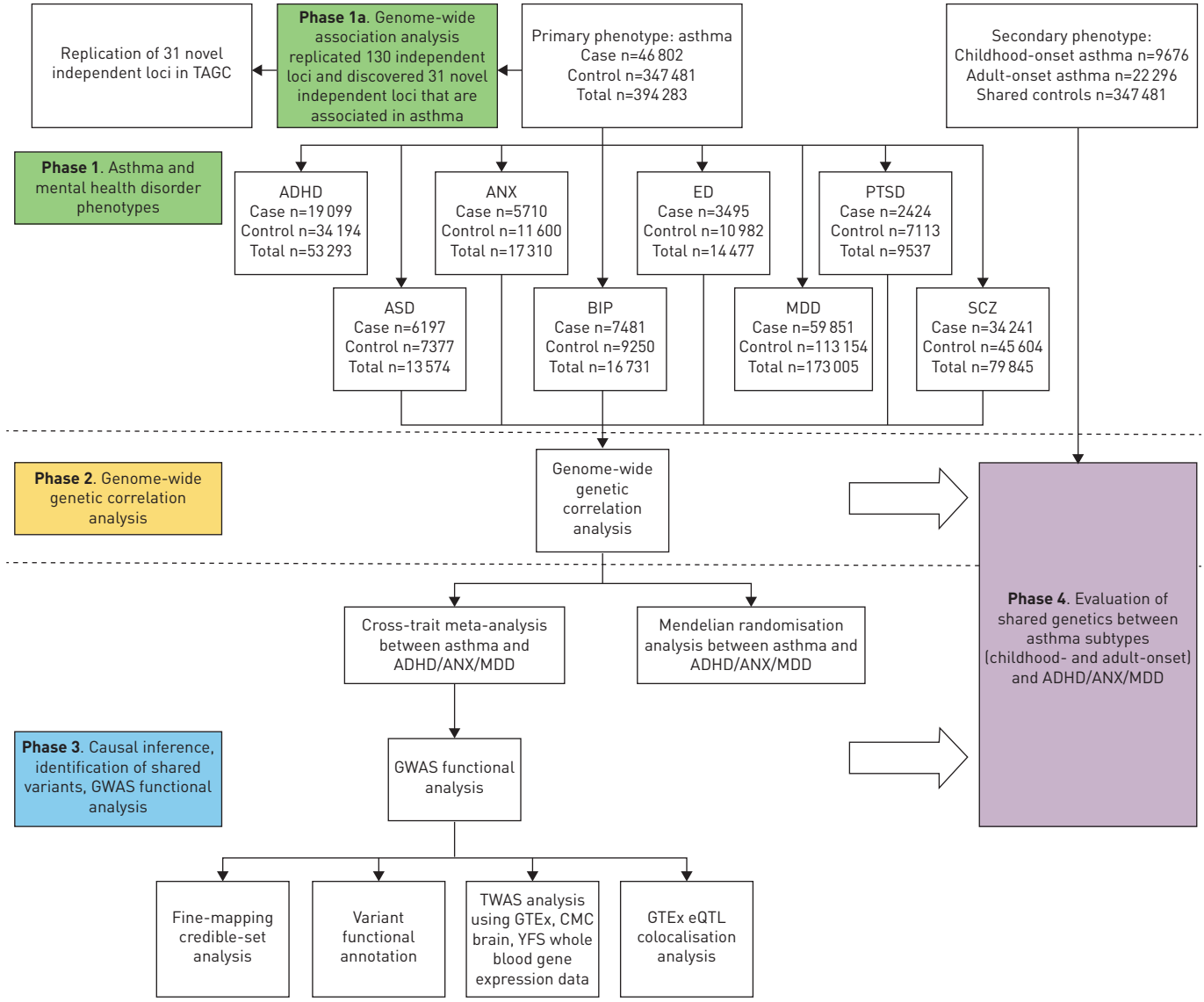

FIGURE 1 Overall study design. TAGC: Transnational Asthma Genetics Consortium; ADHD: attention deficit hyperactivity disorder; ANX: anxiety disorder; ASD: autism spectrum disorder; BIP: bipolar disorder; ED: eating disorder; MDD: major depressive disorder; PTSD: post-traumatic stress disorder; SCZ: schizophrenia; GWAS: genome-wide association study; GTEx: Genotype–Tissue Expression project; TWAS: transcriptome-wide association study; CMC: CommonMind Consortium; YFS: Young Finns Study; eQTL: expression quantitative trait loci.

We applied standardisation of GWAS summary statistics to minimise potential biases due to quality control procedures. We converted GWAS summary statistics with hg18 genome build to hg19 using the liftOver tool [24]. Indels and rare/low-frequency variants with minor allele frequency <1% were not included in this study. Additionally, we restricted our analysis to autosomal chromosomes.

GWAS analysis in the UK Biobank

In this study, we focused on common variants for the analysis with minor allele frequency >1%. We performed stringent GWAS quality control procedures. We included variants that did not deviate from Hardy–Weinberg equilibrium ($p>1\times10^{-6}$), with 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 linkage disequilibrium score regression (LDSC) intercept was used to evaluate genomic inflation due to population stratification. A total of 8 274 727 single nucleotide polymorphisms (SNPs) passed quality control on the whole genome, which were eligible for statistical association analyses.

We performed the three GWAS analyses for all asthma, childhood-onset asthma, adult-onset asthma and shared controls adjusting for age, sex, genotyping array, assess centre and 30 ancestry principal components. We did not remove any related samples in the UK Biobank since we used a 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 the 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 $p<1\times10^{-5}$, r^2 >0.05 and <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 National Human Genome Research Institute–European Bioinformatics Institute (NHGRI-EBI) GWAS Catalog (www.ebi.ac.uk/gwas; search date: July 1, 2019) for checking the previously reported status of genetic loci associating with asthma and identified novel loci. Novel asthma loci were defined as the clump regions that did not contain any previously reported variants in the NHGRI-EBI GWAS Catalog.

LDSC analysis

We conducted post-GWAS genome-wide genetic correlation analysis between asthma and mental health disorders using all SNPs after merging with HapMap3 SNPs 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 the Bonferroni method and a p-value of 0.00625 (0.05/8) was considered as the 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; www.bioconductor.org/packages/devel/bioc/html/ASSET.html) to combine the association evidence for asthma with ADHD, ANX and MDD at individual variants since it is designed for meta-analysis of binary traits [14, 28]. This method combines the effect estimate and standard error of the GWAS summary statistics to test the hypothesis of association between the SNP with any subset of studies.

We focused on shared sentinel variants satisfying $p_{meta}<5\times10^{-8}$ and clump-specific false discovery rate (FDR) <0.05 to account for multiple testing. We used Variant Effect Predictor based on the 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 500 kb 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 analysis

To identify association of asthma with ADHD, ANX and MDD with regard to transcriptome gene expression in specific tissues, we conducted a transcriptome-wide association study (TWAS) [31] using three sets of gene expression data sources: 43 post-mortem Genotype–Tissue Expression project (GTEx) tissues ($n_{average}$=214) [32], CommonMind Consortium (CMC) brain tissue (n=452) [33] and Young Finns Study (YFS) blood tissue (n=1264) [34]. Multiple testing correction for each mental health disorder was applied to account for all gene–tissue pairs based on TWAS p-values using the FDR Benjamini–Hochberg procedure (FDR <0.05). Detailed statistical information can be found in the supplementary material.

GTEx quantitative trait loci colocalisation analysis

Since the GTEx expression quantitative trait loci (eQTL) signals by themselves are pervasive, we further conducted the colocalisation analysis between signals from three 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 500 kb of the index SNP at each of the shared loci. We then 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 colocalised with *PPH4* >0.7. We conducted the tissue enrichment using permutation tests (1000 permutations) and calculated the permutation p-values for each tissue. We considered significant enrichment based on a p-value=0.001042 (0.05/48 tissues) after correcting for multiple testing of 48 tissues.

Mendelian randomisation analysis

We applied generalised summary data-based Mendelian randomisation (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 exposure at the GWAS significance level ($p<5\times10^{-8}$) 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 major histocompatibility complex 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 childhood- and adult-onset asthma [12, 13]. Thus, we also investigated if the shared genetics between asthma and ADHD/ANX/MDD are different with respect to childhood- and adult-onset asthma, specifically in genetic correlation, cross-trait meta-analysis, TWAS and Mendelian randomisation analyses.

Results

Phenotypic association between asthma and mental health disorders in the UK Biobank

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

Genome-wide association and SNP-based heritability

There was no evidence of population stratification for three asthma GWASs (figure 2a, and supplementary figures S2 and S3). We identified 161 independent loci associated with asthma at the genome-wide significance level ($p<5\times10^{-8}$), comprised of 130 previously reported loci and 31 novel loci (figure 2b, and supplementary tables S3 and S4). For the 31 novel loci, we conducted replication analysis in the Transnational Asthma Genetics Consortium (TAGC) data (23 948 cases and 118 538 controls) [37]. 21 of these loci were not found in the TAGC data, likely because the TAGC meta-analysis was based on HapMap2 imputation. Thus, we used the most significant SNP in the clump region that was available from HapMap2/TAGC as the surrogate SNP and extracted the association results from the TAGC for replication purposes. As a result, we found surrogate SNPs for 14 loci, but the remaining seven loci were not applicable for replication. Thus, a total of 24 loci were sought for replication in the TAGC. Among them, we found 14 were nominally significant in the TAGC multi-ancestry or European population ($p<0.05$); 10 of the 14 loci had $p<0.001$ (supplementary table S3). In addition, we found the effect sizes of the 24 loci were highly consistent between the UK Biobank and the TAGC (supplementary figures S4 and S5). Estimates of SNP-based heritability on the observed scale using GWAS summary statistics were (mean±SE) 5.02±0.62% for asthma, 3.38±0.66% for childhood-onset asthma and 1.98±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 correlation (R_g) between asthma and ADHD ($R_g=0.197$, $p=1.21\times10^{-5}$), ANX ($R_g=0.406$, $p=1.61\times10^{-3}$) and MDD ($R_g=0.215$, $p=1.09\times10^{-8}$). 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 ($p_{meta}<5\times10^{-8}$, single-trait FDR <0.05). After pruning, we found seven 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. Furthermore, we found one 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 two regions shared by multiple traits: 5q21.2 and the *HLA* region shared by asthma, ADHD and MDD (table 2 and supplementary table S5).

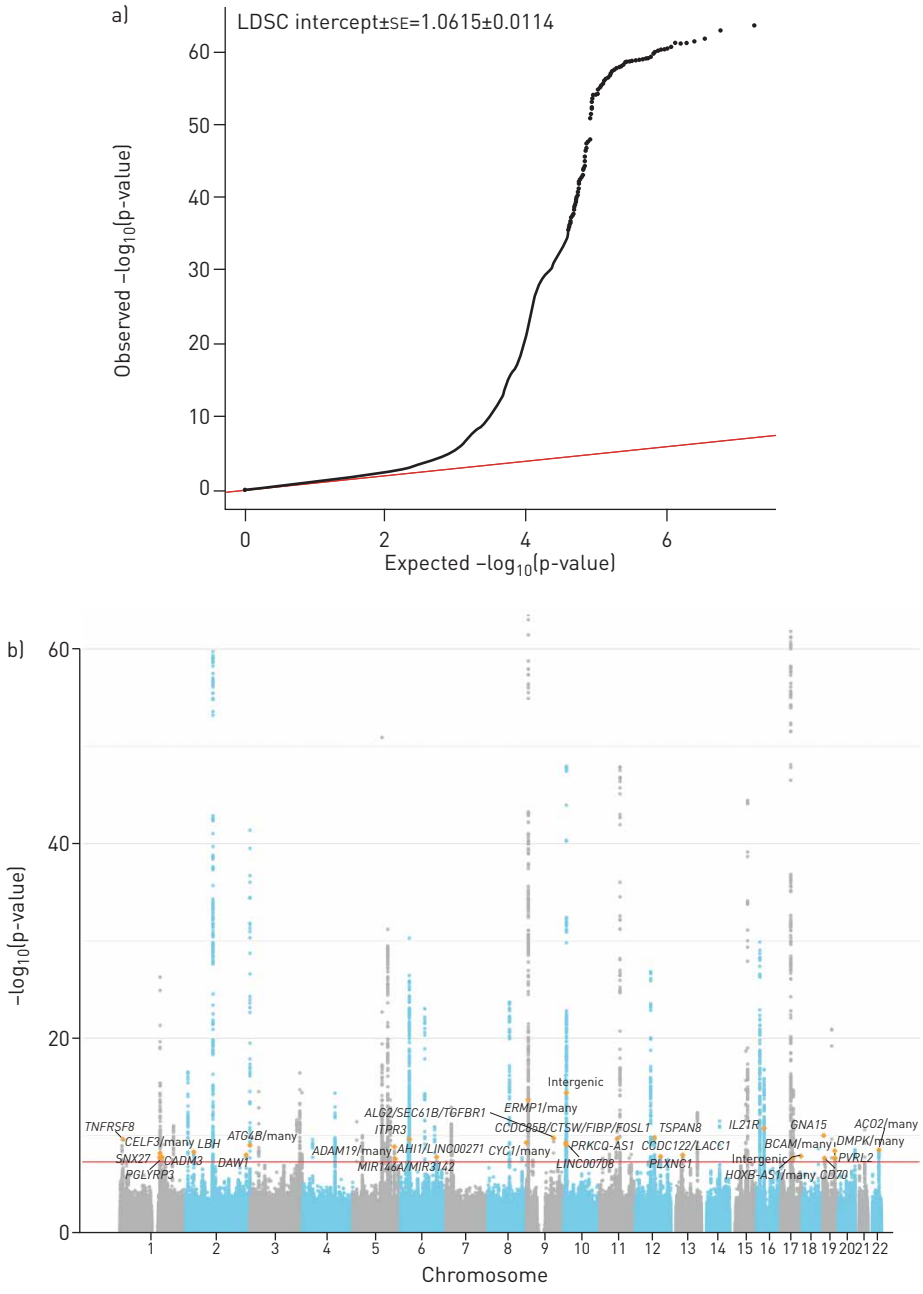

FIGURE 2 Results of genome-wide association analysis of the UK Biobank cohort for asthma. LDSC: linkage disequilibrium score regression. a) Association test quantile–quantile plot showing departure from the null hypothesis of no association. b) Manhattan plot for association test of 46 802 asthma cases and 347 481 controls. n=31 novel independent loci. The most significant novel single nucleotide polymorphism in each locus is highlighted with an orange diamond. The genome-wide significance level after accounting for multiple testing ($p=5\times10^{-8}$) is denoted by the red line.

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 was 99% likely to contain the causal variant. Lists of credible sets of SNPs for each locus are provided in supplementary tables S6–S8.

We found one locus (in *BX927320.1*) for asthma and MDD (supplementary 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 and ADHD or asthma and ANX (supplementary

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

Phenotype 1	Phenotype 2	R_g±SE	z	p-value
Asthma	ADHD	0.197±0.045	4.376	1.21×10^{-5}
	ANX	0.406±0.129	3.155	1.61×10^{-3}
	ASD	0.017±0.052	0.324	7.46×10^{-1}
	BIP	0.085±0.054	1.560	1.19×10^{-1}
	ED	0.003±0.055	0.045	9.64×10^{-1}
	MDD	0.215±0.038	5.717	1.09×10^{-8}
	PTSD	0.458±0.471	0.972	3.31×10^{-1}
	SCZ	0.012±0.026	0.471	6.38×10^{-1}

R_g: genetic correlation estimate; ADHD: attention deficit hyperactivity disorder; ANX: anxiety disorder; ASD: autism spectrum disorder; BIP: bipolar disorder; ED: eating disorder; MDD: major depressive disorder; PTSD: post-traumatic stress disorder; SCZ: schizophrenia.

tables S10 and S11), 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 colocalisation

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 three gene expression data sources. We investigated the overlap of significant tissue–gene pairs in asthma and ADHD, MDD and ANX. There was an overlap in 18 significant tissue–gene pairs in GTEx and three 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 sizes than GTEx, for tissues of brain and blood we considered CMC and YFS as discovery datasets and GTEx as the replication dataset. We additionally extracted the association statistics of four significant tissue–gene pairs between asthma and mental health disorders (*CISD2*, *KATNA1* and *MANBA* from CMC brain; *POLI* from YFS blood) from the GTEx results. We replicated all of them in the GTEx dataset accounting for multiple testing for the available genes ($p<0.05$/three genes) except for *KATNA1*, which is not available in GTEx brain tissues (supplementary table S12).

We further conducted colocalisation 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 the *HLA* region were the potential causal eQTL variants in many tissues (supplementary table S13). Notably, in asthma and MDD, *HLA* was also the major causal eQTL colocalised region (supplementary table S14). Through the permutation analysis, we observed a significant amount of colocalised signals between asthma and ADHD/MDD in some specific tissues, belonging mainly to the exocrine/endocrine, digestive, respiratory and haemic/immune systems (supplementary figures S6 and S7).

Mendelian randomisation results

We observed a small but significant positive causal effect of ADHD on asthma ($\beta_{ADHD\rightarrow Asthma}=0.054$, $p=0.036$), but not *vice versa* (table 4), corroborating the putative model that ADHD causally increases the risk of asthma. We also observed a strongly significant positive causal effect of MDD on asthma ($\beta_{MDD\rightarrow Asthma}=0.21$, $p=1.80\times10^{-5}$). However, since there is a small fraction of overlapping samples between MDD and asthma GWAS data (~6.7%) and potential unobserved confounders, our Mendelian randomisation 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 (supplementary table S15). In terms of the 18 shared genetic sentinel variants, we found some of them have stronger associations with childhood-onset asthma, but others have stronger associations with adult-onset asthma (supplementary table S16). For shared genes in the TWAS, we found most of them have approximately even associations between childhood- and adult-onset asthma, except for *POLI*, which has a much stronger association with childhood-onset asthma (supplementary table S17). Finally, we identified a

TABLE 2 Genome-wide significant loci by cross-trait meta-analysis associated with asthma and attention deficit hyperactivity disorder (ADHD), anxiety disorder (ANX) or major depressive disorder (MDD) ($p<5\times10^{-8}$; single-trait false discovery rate (FDR) <0.05)

Traits	Sentinel SNP	Genome position	A1	A2	FDR1	FDR2	p-value	Genes within clumping region
Asthma and ADHD	rs2025758	chr10:8 777 640–8 855 244	T	C	1.29×10^{-14}	1.09×10^{-3}	4.52×10^{-18}	Intergenic region
	rs7094182	chr10:8 452 766–8 543 732	G	C	1.09×10^{-9}	4.89×10^{-3}	5.15×10^{-12}	Intergenic region
	rs325485	chr5:103 769 738–104 048 590	A	G	2.64×10^{-5}	5.31×10^{-5}	1.94×10^{-8}	Intergenic region
	rs227283	chr4:103 550 006–103 885 568	C	G	8.60×10^{-5}	5.58×10^{-6}	2.67×10^{-8}	*CISD2*, *MANBA*, *SLC9B1*, *UBE2D3*
	rs3117006	chr6:33 096 426–33 124 972	G	A	6.61×10^{-7}	3.13×10^{-2}	2.81×10^{-8}	*HLA-DPB2*
	rs6736411	chr2:63 508 703–63 906 628	G	A	1.71×10^{-6}	3.45×10^{-2}	2.91×10^{-8}	*MDH1*, *WDPCP*
	rs71565398	chr6:33 581 633–33 775 446	C	G	9.68×10^{-7}	2.18×10^{-2}	3.70×10^{-8}	*IP6K3*, *ITPR3*, *LEMD2*, *MLN*, *UQCC2*
Asthma and ANX	rs1709393	chr3:101 684 480–101 713 472	C	T	2.30×10^{-4}	2.06×10^{-6}	4.29×10^{-8}	*LOC152225*
Asthma and MDD	rs2855812	chr6:31 078 809–31 835 164	G	T	7.64×10^{-13}	1.07×10^{-5}	2.09×10^{-16}	*ABHD16A*, *AIF1*, *APOM*, *ATP6V1G2*, *ATP6V1G2-DDX39B*, *BAG6*, *C6orf15*, *C6orf25*, *C6orf47*, *C6orf48*, *CCHCR1*, *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*, *SNORD117*, *TCF19*, *TNF*, *VARS*, *VWA7*
	rs2854275	chr6:32 606 970–32 808 299	C	A	1.18×10^{-13}	1.31×10^{-2}	3.47×10^{-13}	*HLA-DOB*, *HLA-DQA1*, *HLA-DQA2*, *HLA-DQB1*, *HLA-DQB2*, *TAP2*
	rs396755	chr5:103 791 044–104 088 117	C	G	3.80×10^{-5}	9.59×10^{-8}	1.55×10^{-11}	Intergenic region
	rs150814685	chr6:28 207 991–29 196 418	T	G	9.84×10^{-9}	1.78×10^{-4}	1.91×10^{-11}	*C6orf100*, *GPX5*, *GPX6*, *HCG14*, *LOC401242*, *LOC100129636*, *NKAPL*, *OR2B3*, *OR2J2*, *OR2J3*, *OR2W1*, *PGBD1*, *TRIM27*, *ZBED9*, *ZKSCAN3*, *ZKSCAN4*, *ZNF311*, *ZSCAN12*, *ZSCAN23*, *ZSCAN26*, *ZSCAN31*
	rs149702363	chr6:29 218 513–29 448 128	T	G	1.33×10^{-8}	2.50×10^{-3}	3.55×10^{-1}	*OR2H1*, *OR5V1*, *OR10C1*, *OR11A1*, *OR12D2*, *OR12D3*, *OR14J1*
	rs493161	chr6:27 357 414–28 304 384	A	T	9.84×10^{-5}	9.38×10^{-7}	9.69×10^{-1}	*HIST1H1B*, *HIST1H2AI*, *HIST1H2AJ*, *HIST1H2AK*, *HIST1H2AL*, *HIST1H2AM*, *HIST1H2BL*, *HIST1H2BM*, *HIST1H2BN*, *HIST1H2BO*, *HIST1H3H*, *HIST1H3I*, *HIST1H3J*, *HIST1H4J*, *HIST1H4K*, *HIST1H4L*, *LINC01012*, *LOC100131289*, *NKAPL*, *OR2B2*, *OR2B6*, *PGBD1*, *TOB2P1*, *ZKSCAN4*, *ZKSCAN8*, *ZNF165*, *ZNF184*, *ZNF192P1*, *ZNF391*, *ZSCAN9*, *ZSCAN12P1*, *ZSCAN16*, *ZSCAN16-AS1*, *ZSCAN26*, *ZSCAN31*
	rs301817	chr1:8 415 235–8 847 380	C	A	1.59×10^{-9}	4.59×10^{-2}	2.94×10^{-9}	*RERE*
	rs148696809	chr6:28 934 352–28 934 352	T	C	1.53×10^{-3}	1.96×10^{-7}	4.78×10^{-9}	Intergenic region
	rs147121091	chr6:27 174 557–27 765 899	A	G	1.87×10^{-4}	4.58×10^{-5}	2.63×10^{-8}	*LINC01012*, *LOC100131289*, *POM121L2*, *PRSS16*, *VN1R10P*, *ZNF184*, *ZNF204P*, *ZNF391*
	rs10789340	chr1:72 565 800–72 945 128	A	G	1.44×10^{-3}	3.36×10^{-6}	2.68×10^{-8}	*NEGR1*

SNP: single nucleotide polymorphism; A1: effect allele; A2: reference allele; FDR: false discovery rate.

modest but nonsignificant causal effect between ADHD and childhood/adult-onset asthma. We also observed a strong positive causal effect of MDD on adult-onset asthma ($\beta_{MDD\rightarrow Adult\text{-}onset\ asthma}=0.26$, $p=3.00\times10^{-4}$) (supplementary table S18).

Discussion

To the best of 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 a genome-wide significance level, which contains 130 previously reported loci and 31 novel loci. More than half of the novel loci were replicated in the TAGC cohort. We also

TABLE 3 Significant overlap transcriptome-wide association analysis results between asthma and attention deficit hyperactivity disorder (ADHD) or major depressive disorder (MDD) (false discovery rate (FDR) <0.05)

Tissue	Gene	Chromosome	SNPs n[#]	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
Artery_Aorta	*CISD2*	4	326	rs227375	0.038	rs227369	0.035	ADHD
Cells_Transformed_fibroblasts	*MANBA*	4	389	rs227375	0.009	rs227369	0.001	ADHD
Cells_Transformed_fibroblasts	*UBE2D3*	4	343	rs227375	0.045	rs227369	0.036	ADHD
Colon_Sigmoid	*CISD2*	4	326	rs227375	0.046	rs227369	0.025	ADHD
Colon_Transverse	*CISD2*	4	326	rs227375	0.027	rs227369	0.006	ADHD
Esophagus_Gastroesophageal_Junction	*CISD2*	4	326	rs227375	0.049	rs227369	0.036	ADHD
Esophagus_Muscularis	*CISD2*	4	326	rs227375	0.022	rs227369	0.025	ADHD
Lung	*CISD2*	4	326	rs227375	0.038	rs227369	0.025	ADHD
Muscle_Skeletal	*CISD2*	4	326	rs227375	0.004	rs227369	0.004	ADHD
Ovary	*CISD2*	4	326	rs227375	0.032	rs227369	0.032	ADHD
Pancreas	*MANBA*	4	389	rs227375	0.013	rs227369	0.039	ADHD
Pancreas	*UBE2D3*	4	343	rs227375	0.007	rs227369	0.021	ADHD
Skin_Not_Sun_Exposed_Suprapubic	*CISD2*	4	326	rs227375	0.045	rs227369	0.042	ADHD
Skin_Sun_Exposed_Lower_leg	*CISD2*	4	326	rs227375	0.034	rs227369	0.028	ADHD
Small_Intestine_Terminal_Ileum	*CISD2*	4	326	rs227375	0.025	rs227369	0.022	ADHD
Spleen	*MANBA*	4	389	rs227375	0.038	rs227369	0.005	ADHD
Uterus	*CISD2*	4	326	rs227375	0.038	rs227369	0.007	ADHD
CMC								
Brain	*CISD2*	4	322	rs227375	0.003	rs227369	0.010	ADHD
Brain	*KATNA1*	6	469	rs112225	0.010	rs2342764	0.048	ADHD
Brain	*MANBA*	4	390	rs228617	0.009	rs227369	0.009	ADHD
YFS								
Blood	*POLI*	18	347	rs3730783	0.016	rs4801003	0.046	MDD

SNP: single nucleotide polymorphism; GWAS: genome-wide association study; ID: identifier; CMC: CommonMind Consortium; YFS: Young Finns Study. [#]: number of SNPs in the locus.

showed a strong positive genetic correlation between asthma and three mental health disorders (ADHD, ANX and MDD).

We also identified the genetic overlap between asthma and ADHD, ANX or MDD at the individual variant level, including seven loci shared by asthma and ADHD, one loci shared by asthma and ANX, and 10 loci shared by asthma and MDD from cross-trait meta-analysis. We highlighted the *HLA* region (several sentinel SNPs) for its significant role in between asthma and mental health disorders. The *HLA* region harbours 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 those involved in immune-related

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

Phenotype 1	Phenotype 2	Direction	Causal effect size±SE	p-value	Instruments n
ADHD	Asthma	→	0.054±0.026	0.036	10
		←	−0.034±0.025	0.16	126
ANX	Asthma	→[#]	NA	NA	NA
		←	−0.014±0.055	0.8	159
MDD	Asthma	→[¶]	0.21±0.049	1.80×10^{-5}	20
		←	0.012±0.015	0.45	124

"→" refers to the phenotype 1→phenotype 2 causal direction; "←" refers to the phenotype 2→phenotype 1 causal direction. ADHD: attention deficit hyperactivity disorder; ANX: anxiety disorder; MDD: major depressive disorder; NA: not available; GWAS: genome-wide association study. [#]: the ANX GWAS does not have enough single nucleotide polymorphisms at the genome-wide significance level for constructing the instrument variable; [¶]: the MDD GWAS data include 23andMe.

process [39]. Wang *et al.* [40] also identified that the *HLA* region showed the strongest role contributing to the pleiotropic effect between psychiatric and immune disorders, although asthma was not assessed in their study. For example, with the inclusion of the *HLA* region, the pleiotropy significance between SCZ and rheumatoid arthritis was around 280 times stronger than with the exclusion of the *HLA* region [40].

Furthermore, we investigated whether genes shared between asthma and mental health disorders have a potential functional connection with human tissues. In the TWAS analysis, we found multiple shared tissue–gene pairs between asthma and ADHD, including the exocrine/endocrine, digestive, respiratory and nervous systems. Of them, *CISD2* was found to be shared between asthma and ADHD in most of the tissues and potentially have a significant biological function. CDGSH iron sulfur domain 2 (*CISD2*) deficiency causes mitochondrial breakdown and dysfunction, and drives premature ageing [41]. A transmission electron microscopy study revealed that mitochondrial degeneration occurs in brain cells and skeletal muscle cells in *Cisd2*$^{-/-}$ mice [41]. Mitochondrial dysfunction was associated with allergic asthma [42] and affected the 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 the *POLI* gene in YFS whole blood tissue was shared by asthma and MDD. One possible mechanism for such a connection is through DNA polymerase η, which arises from a gene duplication from DNA polymerase ί encoded by the *POLI* gene. DNA polymerase η is the sole contributor of A/T modifications during immunoglobulin gene hypermutation in the mouse [44]. IgE is a key component in the pathology of asthma. Recognition of allergens by IgE depends on a combination of choice of human immunoglobulin heavy chain variable genes, utilisation of certain mutational hotspots and improvement of affinity *via* additional mutations in complementarity determining regions [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 Mendelian randomisation. 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 Mendelian randomisation for ANX and asthma. In addition, our Mendelian randomisation analyses using a more exclusive outlier p-value threshold of 0.1 showed most of the Mendelian randomisation analysis results remain unchanged (supplementary table S19). We emphasise that our inferred causal relationships are putative as all Mendelian randomisation analyses in this study are based on GWAS summary statistics; unobserved confounders and overlapping samples may lead to false conclusions. Further analysis, such as gene function biological experiments and 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 a genetic correlation with any of the mental health disorders, whereas several studies observed robust phenotypic correlations between asthma and ADHD in children and adults [3, 47]. Such findings suggest the phenotypic correlation between asthma and ADHD in children maybe more attributed to environmental factors, but not substantially from genetic origins [47]. Furthermore, our genetic correlation results suggest the genetic predisposition on ADHD (the majority are children) might have more impact on the genetic predisposition of adult-onset asthma. However, there is limited research demonstrating the phenotypic correlation between childhood-onset ADHD and adult-onset asthma, which could be investigated by longitudinal studies in the future. However, 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 suggests the shared genetics among complex diseases may be different at the genome-wide polygenic level and top association level. Also, Lehto *et al.* [5] 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. Complementary with the Lehto *et al.* [5] study, we further examined the shared genetics at the variant, gene and tissue function levels for both childhood- and adult-onset asthma, and we fully utilised the genetic effect to infer the potential genetic causality of the observed associations.

We acknowledge several potential limitations in this study. First, the statistical power of our GWAS analysis was restricted to the sample sizes of each of the mental health disorders; genetic correlation between asthma and additional mental health disorders may be discovered with larger sample sizes. Second, the asthma information in the 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. In addition, other asthma endotypes, such as by IgE (allergic status) and eosinophil level (type 2 inflammation) [48], may provide additional insights into the pathophysiological connection between asthma and mental health disorders. Finally, it is important to evaluate the common nongenetic 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 the UK Biobank data, may have 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.

Conclusions

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 three 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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