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A large-scale genome-wide association analysis of lung function in the Chinese population identifies novel loci and highlights shared genetic etiology with obesity

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Abstract

Lung function is a heritable complex phenotype with obesity being one of its important risk factors. However, the knowledge of their shared genetic basis is limited. Most genome-wide association studies (GWASs) for lung function have been based on European populations, limiting the generalizability across populations. Large-scale lung function GWAS in other populations are lacking.

We included 100,285 subjects from China Kadoorie Biobank (CKB). To identify novel loci for lung function, single-trait GWAS were performed on FEV1, FVC, FEV1/FVC in CKB. We then performed genome-wide cross-trait analysis between the lung function and obesity traits (body mass index [BMI], BMI-adjusted waist-to-hip ratio, and BMI-adjusted waist circumference) to investigate the shared genetic effects in CKB. Finally, polygenic risk scores (PRSs) of lung function were developed in CKB and its interaction with BMI's association on lung function were examined. We also conducted cross-trait analysis in parallel with CKB using 457,756 subjects from UK Biobank (UKB) for replication and investigation of ancestry specific effect.

We identified 9 genome-wide significant novel loci for FEV1, 6 for FVC and 3 for FEV1/FVC in CKB. FEV1 and FVC showed significant negative genetic correlation with obesity traits in both CKB and UKB. Genetic loci shared between lung function and obesity traits highlighted important pathways, including cell proliferation, embryo and tissue development. Mendelian randomization analysis suggested significant negative causal effect of BMI on FEV1 and on FVC in both CKB and UKB. Lung function PRSs significantly modified the effect of change-in-BMI on change-in-lung function during an average follow-up of 8 years.

This large-scale GWAS of lung function identified novel loci and shared genetic etiology between lung function and obesity. Change-in-BMI might affect change-in-lung function differently according to a subject's polygenic background. These findings may open new avenue for the development of molecular-targeted therapies for obesity and lung function improvement.

Introduction

Impaired lung function is associated with lung disease risk and mortality, such as chronic obstructive pulmonary disease (COPD) [1]. Clinical and epidemiological studies have shown many risk factors can affect lung function [2]. Among these risk factors, obesity has been one of the most rapidly growing public health issues with nearly tripled prevalence over the past 30 years [3]. Specifically, according to a population-based study on 121,965 subjects, obesity is associated with approximately 2 times higher risk of reduced lung function (e.g., forced expiratory volume in one second [FEV1] and forced vital capacity [FVC]) [4]. Obesity is also associated with increased risk of respiratory diseases, such as asthma and COPD [4, 5]. However, such findings have also raised new questions about whether the genetic risk factors can contribute to the coexistence of lung function reduction and obesity.

We and others have recently identified shared genetic architecture among respiratory diseases, including asthma and chronic obstructive pulmonary disease [6–9], indicating pleiotropic effects impacting both diseases. Lung function and obesity are both highly

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heritable traits, with an estimated heritability up to 70% [10–14]. The inverse association between lung function and obesity suggested potential shared genetic risk factors between these conditions [15]. However, the knowledge of shared genetic basis to lung function and obesity is limited.

To date, most lung function genome-wide association study (GWAS) participants are of European descent [13, 14, 16, 17]; only few studies include a small number of non-European participants [18, 19]. Thus, large-scale GWASs based on non-European populations are critical to extend our understanding of the genetic heterogeneity across different populations [20, 21]. In addition, it is critical to understand the shared genetic architecture of lung function with other complex traits (e.g., obesity), which is robust to environmental confounding [22]. Thus, in the current study, we conducted a large-scale GWAS and cross-trait/cross-population analysis in China Kadoorie Biobank (CKB) and UK Biobank (UKB) to address 3 aims: (1) to identify novel genetic risk loci for lung function traits that include FEV1, FVC and FEV1/FVC in the Chinese population; (2) to investigate shared genetic effects between the lung function traits and obesity traits (body mass index [BMI], BMI-adjusted waist-to-hip ratio [WHRadjBMI], and BMI-adjusted waist circumference [WCadjBMI]) in both Chinese and European populations; and (3) by using both CKB and UKB follow-up cohorts, to investigate whether the baseline BMI and longitudinal change in BMI from baseline would affect lung function, taking into account the polygenic background of lung function.

Methods

Study design, settings and participants

The overall study design can be found in Figure 1. In brief, this study has two analytical stages. The first stage is to identify novel loci for lung function in the Chinese population by using single-trait GWAS analysis. The second stage is to investigate shared genetic effects between lung function and obesity by using cross-trait GWAS analysis in both CKB and UKB. The CKB study is a prospective cohort study of >500,000 participants in China. Details of the CKB have been described previously [23]. In brief, the CKB recruited 512,715 adults aged 30-79 years from ten regions (Harbin, Qingdao, Suzhou, Liuzhou, Haikou, Henan, Gansu, Sichuan, Zhejiang, and Hunan) across China. All participants gave informed written consent. Questionnaire data, physical measurements, and blood samples were collected at the baseline survey during 2004-2008. Two follow-up surveys were taken in 2008 and during 2013-2014, respectively, which involved ~5% randomly chosen surviving participants.

The UKB study was described in detail elsewhere [7, 24]. In brief, the UKB study is a prospective cohort 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 (2004-2008) using questionnaires, and anthropometric assessments were performed. In UKB, we restricted to subjects of European ancestry. All detailed genotyping, quality control, and imputation procedures are described at the UK Biobank website (http://biobank.ctsu.ox.ac.uk). All participants provided informed consent to the UKB.

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Ascertainment of lung function and obesity traits

FEV1, FVC and FEV1/FVC were adjusted for age, age^2, sex, height, smoking status (ever vs. never) and assessment center in a linear regression model [14]. The resulting residuals were inverse normal transformed [14].

BMI, measured or self-reported weight in kg per height in meters squared was adjusted for age, age^2, sex, and assessment center in a linear regression model [14]. Waist and hip circumferences were also measured in CKB and UKB participants. The WHR and WC were adjusted for age, age^2, BMI, sex and assessment center in a linear regression model. The resulting residuals were inverse normal transformed. The detailed physical measurement procedures can be found in Supplementary Appendix, CKB previous study [25] and UKB website (https://www.ukbiobank.ac.uk/wp-content/uploads/2011/11/UK-Biobank-Protocol.pdf).

CKB genotyping procedure

The CKB has conducted three phases of genotyping. A custom-designed biobank array, to provide optimized genome-wide coverage for the Chinese population, was developed by University of Oxford's Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU) in collaboration with Beijing Genomics Institute (BGI, Shenzhen, China) and Affymetrix Inc. (now Thermo Fisher Scientific, Santa Clara, California, USA). This 700K-SNP array was used to genotype ~32,000 CKB participants in the first phase. A revised and updated version of the original array which covers ~803K SNPs was used to genotype ~69,000 participants in the second and third phase.

Variants with call rate>0.98, plate effect $P>10^{-6}$, batch effect $P>10^{-6}$, Hardy-Weinberg Equilibrium (HWE) deviations $P>10^{-6}$ (combined 10 df $\chi 2$ test from 10 regions), minor allele frequency (MAF) difference from 1000 Genomes East-Asian frequencies<0.2, resulting in genotypes for 532,415 biallelic variants present on both array versions. The qualified genotypes for each chromosome were phased with SHAPEIT. Then, imputation was performed for each 5-Mb interval with IMPUTE 4 based on haplotypes derived from the 1000 Genomes Phase III.

GWAS analysis

We selected variants that did not deviate from Hardy-Weinberg Equilibrium ($P>1\times10^{-12}$), per variant missing rates<10%, per-sample missing rate<10%, minor allele frequency (MAF)>1% and an imputation quality score>0.8. Detailed data summary, QC and imputation information can be found in the Supplementary Appendix. The genotype-phenotype association test was carried out in 100,285 samples from CKB and up to 457,756 from UKB. For lung function and obesity traits, we carried out linear mixed model (LMM) association analyses and adjusted for genotyping array, ten ancestry PCs in CKB and thirty ancestry PCs in UKB to assess association between the traits' Z-scores and imputed genotype dosages under an additive genetic model by using BOLT-LMM v2.3 [26]. After association analysis, we applied PLINK clumping function to determine top loci that are independent to each other. Specifically, variants with P-value less than 1×10^{-5}, has r2 more than 0.2 and less than 500 kb away from the peak were assigned to that peak's clump. The

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genes within each clump were identified by the overlap between gene regions and clump region. Novel loci were defined at two levels, clump and variant (Supplementary Appendix). In brief, if the independent clump region does not overlap with any loci in the GWAS catalog (search date: April 3, 2020) for the same trait, we defined it as a novel locus. If there is an overlap between clump region and GWAS catalog, we further checked if the sentinel variant is novel, which is defined by low linkage disequilibrium (LD) r2<0.2 between the sentinel variant and any variants within the clump region from GWAS catalog.

Cross-trait genetic correlation

We used cross-trait LD score regression (LDSC) to estimate genetic correlation between the causal effects of two traits (ranging from −1 to 1) based on summary statistics of each trait's GWAS [27]. We specified LDSC to estimate the regression intercept to account for shared subjects between different traits' GWAS [28]. We applied Bonferroni correction (P<0.05/9) to account for multiple testing in the LDSC analysis.

Sex specific genetic correlation

Previous studies showed the association between lung function and obesity could differ in male and female sex [29, 30]. Thus, we evaluated the genetic correlation between lung function and obesity in male and female sex separately.

Cross-population genetic correlation

To assess the genetic heterogeneity between Chinese and European populations, we also estimated genome-wide cross-population genetic correlation for lung function and obesity traits by applying S-LDXR [31] with the baseline-LD-X model annotations. We applied Bonferroni correction (P<0.05/6) to account for multiple testing in the S-LDXR analysis.

Cross-trait meta-analysis

Cross Phenotype Association (CPASSOC) combines effect estimate and standard error of the GWAS summary statistics to test hypothesis of association between the SNP with both traits [32]. A heterogeneous version of CPASSOC (SHet) was used in this study.

SHet is a cross-phenotype meta-analysis method based on fixed-effect model. It is more powerful when there is heterogeneous effect present across studies, which is common when testing multiple phenotypes [33]. SHet uses the sample size of a trait as the weight instead of using the effect standard error. It can also account for effect correlation due to overlapping or related subjects within and among different studies or cohorts.

Overrepresentation enrichment analysis

In order to understand the shared biological pathways between lung function and obesity, we extracted the genes from clumping procedure for both lung function and obesity and used the WebGestalt tool [34] to assess the enrichment of the identified genes in Gene Ontology (GO) biological pathway. If they are significantly enriched in both lung function and obesity, we consider them as the shared biological pathways. A false discovery rate (FDR) method was used to correct for multiple testing.

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Mendelian randomization (MR) analysis

We applied generalized summary data-based Mendelian randomization (GSMR) [35] under default settings to infer putative causal relationships between BMI and lung function traits from GWAS summary statistics. To avoid overlapping subjects in the MR analysis, we used BMI GWAS from Biobank Japan [BBJ] (n=158,284) [36] and the lung function GWAS from CKB; and we used the GIANT BMI GWAS (n_{max}=322,154) [12] and lung function GWAS from UKB. A more detailed description of the BBJ and GIANT GWAS data can be found in the Supplementary Appendix. Since GSMR requires a minimum of 10 LD-independent instruments with P-value less than 5×10^{-8}, we restricted our analyses to traits that satisfy this criterion. Prior to running GSMR, we removed SNPs with strand-ambiguity, imputation quality score INFO<0.9, and in the HLA region (chr6:25-34M). We applied Bonferroni correction (0.05/6) to account for the number of trait pairs in the MR analysis.

Lung function polygenic risk score and BMI interaction ($PRS_{lung\ function}$×BMI) analysis

We constructed the polygenic risk scores (PRSs) for three lung function traits using LDpred [37]. The details of PRS construction can be found in Supplementary Appendix. Besides, we constructed three additional lung function PRSs using weights of 279-SNPs reported by Shrine et al (only 275 SNPs were available in CKB data) [14]. To investigate interaction effect between lung function PRSs and baseline BMI or its longitudinal change (nCKB=21,791 and nUKB=12,019) on lung function, we fitted two linear regression models to test the $PRS_{lung\ function}$×BMI effect as following:

Baseline model:

$$Lung\ \ function_{t0} = BMI_{t0} + lung\ \ function\ \ PRS + BMI_{t0} \times lung\ \ function\ \ PRS + other\ \ covariates$$

Change model:

$$Lung\ \ function_{t1} - Lung\ \ function_{t0} = BMI_{t0} + (BMI_{t1} - BMI_{t0}) + lung\ \ function\ \ PRS + BMI_{t1} - BMI_{t0} \times lung\ \ function\ \ PRS + other\ \ covariates$$

where baseline (t_0) is at 2004-2010 and follow-up (t_1) is at 2012-2014; other covariates are PC1-PC10 for CKB and PC1-PC30 for UKB, age, age^2, sex, standing height, smoking status (ever/never), genotyping array and assessment center. For baseline model, we set normal BMI and deciles 2-9 group as reference, for change model, we set BMI stable and deciles 2-9 group as reference.

Results

GWAS and SNP-based heritability

The baseline demographic characteristics of the CKB and UKB cohorts are summarized in Table S1. GWAS results for all traits showed no evidence of inflation due to population stratification (Figures S1-S2). In CKB, LDSC estimates of SNP-based heritability on the observed scale were (mean ±SE) 13.07±0.88% for FEV1, 11.12±0.82% for FVC 5.12±0.67% for FEV1/FVC, 21.77±1.23% for BMI, 8.72±0.83% for WHRadjBMI and

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10.65±0.95% for WCadjBMI. We identified 28 genome-wide significant ($P<5\times10^{-8}$) loci for FEV1, 10 for FVC and 10 for FEV1/FVC (Figure 2). After comparing with GWAS Catalog results for FEV1, FVC and FEV1/FVC (Tables S2-S4), we determined a total of 18 novel loci for three lung function traits (Table 1). We further conducted the replication analysis for the novel loci in a recently published large-scale lung function GWAS (Table S5) [14]. A total of 11 loci were available in the Shrine et al.'s data. Among them, we found 4 were significant ($P<0.05/13$) with consistent effect size direction. The non-replicated loci were likely due to distinct effect allele frequency between CKB and Shrine et al. [14] (Table S5). For example, the MAF of sentinel SNP rs1861229 in CKB is 0.52, but 0.17 in Shrine et al.'s study. Among these previously reported loci showing genome-wide significant association with lung function in Shrine et al, *AGER, AP4M1, DIS3L2, FAM13A, FGF10, HLA-DQA1* and *HTR4* are notable genes that play important roles in lung function. In terms of novel loci, we identified *GPC5* as a novel gene for FEV1 (sentinel SNP: rs528366, $P=2.30\times10^{-8}$). In addition, we identified 20q11.23 as a novel region for FVC (sentinel SNP: rs6063386, $P=5.00\times10^{-10}$). The sentinel SNP is mapped to a long intergenic non-protein coding RNA (lncRNA), *LINC00489*. Among the novel loci for FEV1/FVC, two are within the 6p21.33 region, the sentinel SNP was mapped to *TNXB*, which was known for its association with lung function traits (FEV1, FEV1/FVC) and COPD [38, 39]. The detailed summary statistics information of genome-wide significant loci for three lung function traits can be found in Tables S6-S8.

In UKB, LDSC estimates of SNP-based heritability on the observed scale were (mean±SE) 20.13±0.76% for FEV1, 20.26±0.74% for FVC, 23.95±1.43% for FEV1/FVC, 27.41±1.07% for BMI, 13.88±0.94% for WHRadjBMI and 16.58±0.83% for WCadjBMI. The single-trait GWAS results are consistent with Shrine et al.'s study [14].

Genetic correlation between lung function and obesity traits

We investigated the genetic correlation between lung function and obesity traits in both CKB and UKB. As shown in Figure 3, we found that two lung function traits have significant negative genetic correlation with obesity traits in CKB (e.g., Rg =-0.26, $P=5.99\times10^{-9}$ for FEV1-WCadjBMI; Rg =-0.11, $P=5.44\times10^{-3}$ for FVC-BMI; and Rg =-0.28, $P=2.24\times10^{-10}$ for FVC-WCadjBMI). We found that the genetic correlation is generally stronger between lung function and central obesity traits than BMI. The UKB genetic correlations also showed consistent findings with CKB in most of the trait pairs, though different for one trait pair (e.g., Rg =0.15, $P=7.92\times10^{-24}$ for FEV1/FVC-BMI in UKB, but not significant in CKB) (Figure 3). Sex-specific analyses found stronger genetic correlation between lung function and obesity traits in females than in males (Tables S9-S10). In addition, the cross-population genetic correlation analysis showed that one of these traits had an estimated cross-population Rg significantly less than 1 ($Rg_{cross\text{-}population}=0.86$, $P=3.76\times10^{-6}$ for BMI) (Table S11).

Cross-trait meta-analysis

For the trait pairs that showed significant genetic correlation after Bonferroni correction (we also included BMI-FEV1 trait pair despite $P=0.038$), we applied CPASSOC for genome-wide cross-trait meta-analysis to identify shared genetic variants among each trait pairs ($P_{meta}<5\times10^{-8}$; single-trait $P<1\times10^{-5}$). A total of 6 trait pairs in CKB and 7 trait pairs in

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UKB were included for the cross-trait meta-analysis. In CKB, after pruning, we found 7 loci significantly associated with BMI and FEV1, 5 loci with WHRadjBMI and FEV1, 7 loci with WCadjBMI and FEV1, 4 loci with BMI and FVC, 1 locus with WHRadjBMI and FVC, and 1 locus with WCadjBMI and FVC. Among these loci, we highlighted three shared loci since they were shared loci in multiple pairs of lung function and obesity traits. The first locus is *DIS3L2* on 2q37.1 (BMI-FEV1, WCadjBMI-FEV1, BMI-FVC and WCadjBMI-FVC). The second locus is *HLA-DQA1* (BMI-FEV1 and BMI-FVC). The third locus consists of several sentinel SNPs that were all mapped within 12p13.2, with genes including *ATXN2* and *ACAD10* (Table 3). Out of the 25 shared loci identified in CKB, five of them were also identified in the same trait pairs in UKB (Table 2 and Tables S12-S18).

Pathway analysis

To gain biological insights of the shared genes, we assessed the enrichment of the independent loci for each trait and the identified set of shared gene between lung function and obesity traits in Gene Ontology (GO) biological process categories and observed many significant enrichments in the UKB results (FDR: q <0.05 for both traits) (Table S19). Consistent with the gene function of shared loci, GO biological process highlighted several common pathways for lung function and obesity traits, such as cell proliferation, embryo, skeletal and tissue development, and regulation of gene expression. However, we did not observe any significant enrichment in the CKB results.

Mendelian randomization

We applied GSMR to perform causal inference between BMI and lung function traits. In the East Asian population analysis, we observed significant negative causal effect of BMI (per standard deviation) on FEV1 (b_{xy}=-0.08, P=2.46×10^{-4}), and on FVC (b_{xy}=0.11, P=3.44×10^{-7}) (Table 3). We did not observe significant causal effect of BMI on FEV1/FVC. On the reverse direction, we observed either small magnitude or non-significant causal effect.

$PRS_{lung\ function}$×BMI analysis

We constructed seven PRS models from LDpred for each lung function trait and selected the PRS model with the highest discriminatory performance (R^2) for interaction analysis (Table S20). We found a significant interaction between baseline BMI and PRS of FEV1/FVC on FEV1/FVC (P=0.011) (Figure 4A and Table S21). Generally, compared with the reference group, the bottom PRS decile+underweight group has the lowest FEV1. For FVC, the largest reduction can be found in bottom PRS decile+obese group. For FEV1/FVC, we observed that the bottom PRS decile +underweight group has has the lowest FEV1/FVC, and overweight and obese groups have increases. In the change model, we found a significant interaction between change-in-BMI and PRS of FVC (P=0.038) on change-in-FVC or between change-in-BMI and PRS of FEV1/FVC (P=0.007) on change-in-FEV1/FVC (Figure 4B and Table S21). Overall, compared with the reference group, BMI increase group had reduced FEV1 and FVC and the effect was largest in top PRS decile. For UKB, we did not find a significant interaction effect in baseline model. However, we found a borderline significant interaction between change-in-BMI and PRS of FVC (P=0.068) on change-in-FVC (Table S22 and Figure S3). Finally, we constructed additional lung function

PRSs using weights of 275-SNPs from Shrine et al.'s study [14] and did not find significant $PRS_{lung\ function}$×BMI effect (Table S23 and Figure S4).

Discussion

To our knowledge, the current study is the largest GWAS of lung function in the Chinese population. We found strong genetic correlation and shared genetic loci between lung function and obesity traits. We replicated these Chinese findings in UKB and also identified population-specific genetic effects. We also found shared biological pathways between lung function and obesity traits, such as cell proliferation, embryo, skeletal and tissue development, and regulation of gene expression.

In this study, we identified 9 new loci for FEV1, 6 for FVC and 3 for FEV1/FVC. Of these, we highlighted a novel gene associated with FEV1, *GPC5* on 13q31.3. *GPC5* is a member of the glypican gene family. Evidence to date suggests that the main function of the glypicans is to regulate the signaling pathway of bone morphogenetic proteins, Wnt, hedgehog and fibroblast growth factors [40], which are involved in modulation of lung function [41], pulmonary fibrogenesis [42] and COPD pathobiology [43]. *GPC5* was also found to contribute to an increased risk of lung cancer in never smokers [44]. For FVC, we also found a novel independent region, 20q11.23, where the sentinel SNP is mapped to a lncRNA, *LINC00489*, although the function of this region needs to be further investigated. For FEV1/FVC, we note that several independent loci were within the 6p21 region, which was known for its association with lung function traits (FEV1, FEV1/FVC) and COPD [38, 39]. This region contains genes such as *AGER, ATF6B, NOTCH4* and *TNXB*, of which *AGER* has been reported to play potential functional role in lung function [45]. AGER protein, a receptor for advanced glycation end-products (RAGE), is a multiligand receptor of the immunoglobulin super-family and interacts with distinct molecules implicated in homeostasis, development, inflammation, diabetes and neurodegeneration [45]. RAGE signals depend on the cell type and the context. RAGE expression increases following cigarette smoke exposure and is partially responsible for inducing the proinflammatory signaling pathways (e.g., NF-κB) [46]. In addition, we noticed two novel loci (mapped genes *DIS3L2* and FGF10/FGF10-AS1) that are significant in both FEV1 and FVC, indicating their pleotropic effect between different lung function traits.

Our LDSC analysis showed strong genome-wide genetic correlation between lung function and obesity traits in both Chinese and European populations. We observed strong negative genetic correlation of obesity traits with FEV1 and FVC in both populations, but a non-significant genetic correlation between obesity traits and FEV1/FVC in the Chinese population. The genetic correlation results in the European population were consistent with those from the Chinese population, except for BMI-FEV1/FVC, which was also highly significant in the European population (Rg=0.15, $P=7.92\times10^{-24}$). Previous studies showed that FEV1 and FVC are reduced in the presence of obesity [47]. but FEV1/FVC ratio is usually unaffected [48]. There are several biological mechanisms that could potentially explain how lung function impairment and obesity are associated. First, the mechanical effects of obesity produce airway narrowing and closure, and increased respiratory system resistance. Compared to healthy weight individuals, airway narrowing in obesity correlates

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with airway closure and airway hyperresponsiveness (AHR) [49]. Airway narrowing and closure lead to air trapping and ventilation inhomogeneity [50]. In addition, we found that the genetic correlation is stronger between lung function and central obesity than with global obesity. Compared with global obesity, which does not take account of the fat distribution, abdominal and thoracic fat are more likely to play a role on the lung function impairment. This is because they have direct mechanical effects on the diaphragm and chest wall expansion during forced inspiration [51, 52], a typical symptom of restrictive lung disease [53].

Cross-trait meta-analysis identified significantly independent loci shared between lung function and obesity traits. In the Chinese population, the locus *DIS3L2* on 2q37.1 was found to be shared between multiple lung function and obesity traits (BMI-FEV1, WCadjBMI-FEV1, BMI-FVC, and WCadjBMI-FVC in the Chinese population; WC-FVC in the European population). A previous study found *DIS3L2* as a gene that contributes to an overgrowth syndrome (e.g., Perlman syndrome [54]), suggesting its critical role in the regulation of cell growth and division. Such function is also consistent with the findings from the pathway analysis, where the shared genes are mainly enriched in pathways related to cell proliferation, embryo, skeletal and tissue development. Notably, these shared pathways show the important role of growth for both lung function and obesity, and are partially distinct with a recent lung function GWAS study [14]. Unsurprisingly, we also found many loci in the *HLA* region that were shared by obesity traits and lung function in both populations. *HLA* is a gene complex that contains abundant pleiotropy for many complex diseases [6, 7, 9, 55], especially involved in immune related process [56]. In the European population, we also identified many shared loci between lung function and obesity traits. However, we found that most of the shared loci are distinct between the two populations.

Although the relationship between lung function and obesity was established in epidemiological studies [5, 15, 30, 57], it remains unclear whether obesity is a driving component in lung function or comorbidity of its presence. The MR estimates in the current study suggested a negative causal effect of BMI to FEV1 and FVC and a positive causal effect to FEV1/FVC. These estimates provide evidence that BMI might reduce lung function in both East Asian and European populations, although the causal relationship between BMI and FEV1/FVC can still be bi-directional. The results of causal association from BMI to lung function traits are consistent with Wielscher et al. showing negative causal associations of BMI with FEV1 and FVC and a positive causal association of BMI with FEV1/FVC [58]. Also, an observational study showed subjects with obesity have increased gastric and oesophageal pressures, which causes reduced lung function.

In this study, we found evidence of genetic heterogeneity in Chinese and European populations. At genome-wide level, the cross-population genetic correlation analysis showed that BMI had an estimated cross-population Rg statistically significant less than 1, indicating heterogeneity in genetic regulation BMI across Chinese and European populations. At variant level, the cross-trait meta-analysis showed majority of the shared variants are different in Chinese and European populations, which could be due to distinct genetic

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background and sample size in the two populations, and also gene environment interaction [31].

Several recent lung function PRS studies have focused on the association between lung function PRS and COPD risk, and interaction with smoking status [14, 59]. Our study investigated the $PRS_{lung\ function}$×BMI in both cross-sectional and longitudinal settings. Our interaction analysis showed that maintaining a normal BMI improved lung function and the beneficial effect is more profound in subjects with high lung function genetic profile. The results suggest that BMI might be a mediator of genetic effect on lung function, which is in consistent with the Mendelian randomization results showing that BMI is a causal risk factor of lung function. We also observed the top PRS group showed the most beneficial effect by BMI change. These findings have important implications for lung function improvement because they can provide potential intervention on BMI to individuals at risk before lung function reduction based on more precise risk stratification by using PRS.

We also acknowledge the limitations in current study. First of all, CKB GWAS sample size is only 1/4 of UKB's. This leads to some findings that may not be directly comparable between two cohorts. Second, the FVC and FEV1/FVC measurements for Haikou and Qingdao regions (n=14,000) have may be biased in comparison with other eight regions in CKB. Thus, we further conducted the sensitivity analysis removing the two regions. The sensitivity analysis (Figures S5-S6) showed the effect sizes of FVC and FEV1/FVC novel loci were highly consistent with the primary analysis (using full GWAS cohort) although the P-values modestly increased after removing the two regions due to less power. In addition, the results of sensitivity analysis for genetic correlation are consistent with the primary analysis (Table S24). The CKB FEV1/FVC PRS has also been used in a recent study and showed consistent results compared with other independent ancestry groups [14]. Third, we chose to use the lung function spirometry measures with two time points in UKB (data fields 3062 and 3063), thus the most cleaned lung function spirometry measures (data fields 20150 and 20151) cannot be used. However, we showed our GWAS results are in consistent with Shrine et al's results [14], which used the most cleaned lung function spirometry measures. Fourth, although the use of PRS allows researchers to effectively capture a useful fraction of genetic effects, the $PRS_{lung\ function}$×BMI analysis remains susceptible to confounding or bias due to LD between SNP markers in the PRS model and the causal variants of BMI [60, 61]. However, our sensitivity analyses showed that this potentially has little impact on the $PRS_{lung\ function}$×BMI analyses and adjusting height is not likely to introduce collider bias between BMI and lung function association (Tables S25-S27). Finally, the LD patterns in the HLA region is highly complex and that the signals we reported are likely tagging the causal variants instead of actually being the causal variants due to the limitation of imputation data. Sequencing data is recommended to identify causal variants in HLA region.

In conclusion, the current study is the first large-scale GWAS study of lung function in the Chinese population. Our study extends existing knowledge of the genetic landscape of lung function traits by leveraging large-scale Chinese and European genetic cohorts. We applied single- and cross-trait analyses and identified novel loci for lung function traits in the Chinese population, shared genetic effects between lung function and obesity traits, genetic heterogeneity in Chinese and European populations and $PRS_{lung\ function}$×BMI effect.

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These new findings provide greater knowledge of the genetic basis of lung function in the Chinese population and shared genetics between lung function and obesity, which will foster subsequent translational, clinical and public health research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Garcia-Aymerich J, Serra Pons I, Mannino DM, Maas AK, Miller DP, Davis KJ. Lung function impairment, copd hospitalisations and subsequent mortality. Thorax. 2011; 66 (7) :585–590. [PubMed: 21515553]
2. Ostrowski S, Barud W. Factors influencing lung function: Are the predicted values for spirometry reliable enough? J Physiol Pharmacol. 2006; 57 (Suppl 4) :263–271. [PubMed: 17072054]
3. World Health Organization. [cited 2020 July 1st] Obesity and overweight. 2020. Available from:https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight#:~:text=In%202016%2C%2039%25%20of%20adults,tripled%20between%201975%20and%202016
4. Leone N, Courbon D, Thomas F, Bean K, Jego B, Leynaert B, Guize L, Zureik M. Lung function impairment and metabolic syndrome: The critical role of abdominal obesity. Am J Respir Crit Care Med. 2009; 179 (6) :509–516. [PubMed: 19136371]
5. Li J, Zhu L, Wei Y, Lv J, Guo Y, Bian Z, Du H, Yang L, Chen Y, Zhou Y, Gao R, et al. Association between adiposity measures and copd risk in chinese adults. Eur Respir J. 2020; 55 (4)
6. Zhu Z, Guo Y, Shi H, Liu CL, Panganiban RA, Chung W, O'Connor LJ, Himes BE, Gazal S, Hasegawa K, Camargo CA Jr, et al. Shared genetic and experimental links between obesity-related traits and asthma subtypes in uk biobank. J Allergy Clin Immunol. 2020; 145 (2) :537–549. [PubMed: 31669095]
7. Zhu Z, Lee PH, Chaffin MD, Chung W, Loh PR, Lu Q, Christiani DC, Liang L. A genome-wide cross-trait analysis from uk biobank highlights the shared genetic architecture of asthma and allergic diseases. Nat Genet. 2018; 50 (6) :857–864. [PubMed: 29785011]
8. Zhu Z, Wang X, Li X, Lin Y, Shen S, Liu CL, Hobbs BD, Hasegawa K, Liang L, International CGC. Boezen HM, et al. Genetic overlap of chronic obstructive pulmonary disease and cardiovascular disease-related traits: A large-scale genome-wide cross-trait analysis. Respir Res. 2019; 20 (1) :64. [PubMed: 30940143]
9. Zhu Z, Zhu X, Liu CL, Shi H, Shen S, Yang Y, Hasegawa K, Camargo CA Jr, Liang L. Shared genetics of asthma and mental health disorders: A large-scale genome-wide cross-trait analysis. Eur Respir J. 2019; 54 (6)

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10. Palmer LJ, Knuiman MW, Divitini ML, Burton PR, James AL, Bartholomew HC, Ryan G, Musk AW. Familial aggregation and heritability of adult lung function: Results from the busselton health study. Eur Respir J. 2001; 17 (4) :696–702. [PubMed: 11401066]
11. Herrera BM, Lindgren CM. The genetics of obesity. Curr Diab Rep. 2010; 10 (6) :498–505. [PubMed: 20931363]
12. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, Powell C, Vedantam S, Buchkovich ML, Yang J, Croteau-Chonka DC, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature. 2015; 518 (7538) :197–206. [PubMed: 25673413]
13. Wain LV, Shrine N, Artigas MS, Erzurumluoglu AM, Noyvert B, Bossini-Castillo L, Obeidat M, Henry AP, Portelli MA, Hall RJ, Billington CK, et al. Genome-wide association analyses for lung function and chronic obstructive pulmonary disease identify new loci and potential druggable targets. Nat Genet. 2017; 49 (3) :416–425. [PubMed: 28166213]
14. Shrine N, Guyatt AL, Erzurumluoglu AM, Jackson VE, Hobbs BD, Melbourne CA, Batini C, Fawcett KA, Song K, Sakornsakolpat P, Li X, et al. New genetic signals for lung function highlight pathways and chronic obstructive pulmonary disease associations across multiple ancestries. Nat Genet. 2019; 51 (3) :481–493. [PubMed: 30804560]
15. Dixon AE, Peters U. The effect of obesity on lung function. Expert Rev Respir Med. 2018; 12 (9) :755–767. [PubMed: 30056777]
16. Loth DW, Soler Artigas M, Gharib SA, Wain LV, Franceschini N, Koch B, Pottinger TD, Smith AV, Duan Q, Oldmeadow C, Lee MK, et al. Genome-wide association analysis identifies six new loci associated with forced vital capacity. Nat Genet. 2014; 46 (7) :669–677. [PubMed: 24929828]
17. Soler Artigas M, Wain LV, Miller S, Kheirallah AK, Huffman JE, Ntalla I, Shrine N, Obeidat M, Trochet H, McArdle WL, Alves AC, et al. Sixteen new lung function signals identified through 1000 genomes project reference panel imputation. Nat Commun. 2015; 6 8658 [PubMed: 26635082]
18. Wyss AB, Sofer T, Lee MK, Terzikhan N, Nguyen JN, Lahousse L, Latourelle JC, Smith AV, Bartz TM, Feitosa MF, Gao W, et al. Multiethnic meta-analysis identifies ancestry-specific and cross-ancestry loci for pulmonary function. Nat Commun. 2018; 9 (1) 2976 [PubMed: 30061609]
19. Li X, Ortega VE, Ampleford EJ, Barr R Graham, Christenson SA, Cooper CB, Couper D, Dransfield MT, Han MLK, Hansel NN, Hoffman EA, et al. Genome-wide association study of lung function and clinical implication in heavy smokers. BMC Med Genet. 2018; 19 (1) :134. [PubMed: 30068317]
20. Sakaue S, Kanai M, Karjalainen J, Akiyama M, Kurki M, Matoba N, Takahashi A, Hirata M, Kubo M, Matsuda K, Murakami Y, et al. Trans-biobank analysis with 676,000 individuals elucidates the association of polygenic risk scores of complex traits with human lifespan. Nat Med. 2020; 26 (4) :542–548. [PubMed: 32251405]
21. Shi H, Burch KS, Johnson R, Freund MK, Kichaev G, Mancuso N, Manuel AM, Dong N, Pasaniuc B. Localizing components of shared transethnic genetic architecture of complex traits from gwas summary data. Am J Hum Genet. 2020; 106 (6) :805–817. [PubMed: 32442408]
22. Zhu Z, Hasegawa K, Camargo CA Jr, Liang L. Investigating asthma heterogeneity through shared and distinct genetics: Insights from genome-wide cross-trait analysis. J Allergy Clin Immunol. 2020
23. Chen Z, Chen J, Collins R, Guo Y, Peto R, Wu F, Li L, China Kadoorie Biobank collaborative g. China kadoorie biobank of 0.5 million people: Survey methods, baseline characteristics and long-term followup. Int J Epidemiol. 2011; 40 (6) :1652–1666. [PubMed: 22158673]
24. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, Liu B, et al. Uk biobank: An open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015; 12 (3) e1001779 [PubMed: 25826379]
25. Chen Z, Lee L, Chen J, Collins R, Wu F, Guo Y, Linksted P, Peto R. Cohort profile: The kadoorie study of chronic disease in china (kscdc). Int J Epidemiol. 2005; 34 (6) :1243–1249. [PubMed: 16131516]
26. Loh PR, Tucker G, Bulik-Sullivan BK, Vilhjalmsson BJ, Finucane HK, Salem RM, Chasman DI, Ridker PM, Neale BM, Berger B, Patterson N, et al. Efficient bayesian mixed-model analysis

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increases association power in large cohorts. Nat Genet. 2015; 47 (3) :284–290. [PubMed: 25642633]

27. Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh PR, ReproGen C, Psychiatric Genomics C, Genetic Consortium for Anorexia Nervosa of the Wellcome Trust Case Control C. Duncan L, Perry JR, Patterson N, Robinson EB, et al. An atlas of genetic correlations across human diseases and traits. Nat Genet. 2015; 47 (11) :1236–1241. [PubMed: 26414676]
28. Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J, Schizophrenia Working Group of the Psychiatric Genomics C. Patterson N, Daly MJ, Price AL, Neale BM. Ld score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet. 2015; 47 (3) :291–295. [PubMed: 25642630]
29. Forno E, Han YY, Mullen J, Celedon JC. Overweight, obesity, and lung function in children and adults-a meta-analysis. J Allergy Clin Immunol Pract. 2018; 6 (2) :570–581. e510 [PubMed: 28967546]
30. Sutherland TJ, McLachlan CR, Sears MR, Poulton R, Hancox RJ. The relationship between body fat and respiratory function in young adults. Eur Respir J. 2016; 48 (3) :734–747. [PubMed: 27471202]
31. Shi H, Gazal S, Kanai M, Koch EM, Schoech AP, Kim SS, Luo Y, Amariuta T, Okada Y, Raychaudhuri S, Sunyaev SR, et al. Population-specific causal disease effect sizes in functionally important regions impacted by selection. bioRxiv. 2019 803452
32. Zhu X, Feng T, Tayo BO, Liang J, Young JH, Franceschini N, Smith JA, Yanek LR, Sun YV, Edwards TL, Chen W, et al. Meta-analysis of correlated traits via summary statistics from gwass with an application in hypertension. Am J Hum Genet. 2015; 96 (1) :21–36. [PubMed: 25500260]
33. Zhu Z, Anttila V, Smoller JW, Lee PH. Statistical power and utility of meta-analysis methods for cross-phenotype genome-wide association studies. PLoS One. 2018; 13 (3) e0193256 [PubMed: 29494641]
34. Liao Y, Wang J, Jaehnig EJ, Shi Z, Zhang B. Webgestalt 2019: Gene set analysis toolkit with revamped uis and apis. Nucleic Acids Res. 2019; 47 (W1) :W199–W205. [PubMed: 31114916]
35. Zhu Z, Zheng Z, Zhang F, Wu Y, Trzaskowski M, Maier R, Robinson MR, McGrath JJ, Visscher PM, Wray NR, Yang J. Causal associations between risk factors and common diseases inferred from gwas summary data. Nat Commun. 2018; 9 (1) 224 [PubMed: 29335400]
36. Akiyama M, Okada Y, Kanai M, Takahashi A, Momozawa Y, Ikeda M, Iwata N, Ikegawa S, Hirata M, Matsuda K, Iwasaki M, et al. Genome-wide association study identifies 112 new loci for body mass index in the japanese population. Nat Genet. 2017; 49 (10) :1458–1467. [PubMed: 28892062]
37. Vilhjalmsson BJ, Yang J, Finucane HK, Gusev A, Lindstrom S, Ripke S, Genovese G, Loh PR, Bhatia G, Do R, Hayeck T, et al. Modeling linkage disequilibrium increases accuracy of polygenic risk scores. Am J Hum Genet. 2015; 97 (4) :576–592. [PubMed: 26430803]
38. Kim WJ, Lee MK, Shin C, Cho NH, Lee SD, Oh YM, Sung J. Genome-wide association studies identify locus on 6p21 influencing lung function in the korean population. Respirology. 2014; 19 (3) :360–368. [PubMed: 24387323]
39. Artigas MS, Wain LV, Shrine N, McKeever TM, BiLEVE UK. Sayers I, Hall IP, Tobin MD. Targeted sequencing of lung function loci in chronic obstructive pulmonary disease cases and controls. PLoS One. 2017; 12 (1) e0170222 [PubMed: 28114305]
40. Filmus J, Capurro M, Rast J. Glypicans. Genome Biol. 2008; 9 (5) :224. [PubMed: 18505598]
41. Verhamme FM, De Smet EG, Van Hooste W, Delanghe J, Verleden SE, Joos GF, Brusselle GG, Bracke KR. Bone morphogenetic protein 6 (bmp-6) modulates lung function, pulmonary iron levels and cigarette smoke-induced inflammation. Mucosal Immunol. 2019; 12 (2) :340–351. [PubMed: 30542109]
42. Chen X, Shi C, Cao H, Chen L, Hou J, Xiang Z, Hu K, Han X. The hedgehog and wnt/beta-catenin system machinery mediate myofibroblast differentiation of lr-mscs in pulmonary fibrogenesis. Cell Death Dis. 2018; 9 (6) :639. [PubMed: 29844390]
43. Kim YS, Hong G, Kim DH, Kim YM, Kim YK, Oh YM, Jee YK. The role of fgf-2 in smoke-induced emphysema and the therapeutic potential of recombinant fgf-2 in patients with copd. Exp Mol Med. 2018; 50 (11) :1–10.

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44. Li Y, Sheu CC, Ye Y, de Andrade M, Wang L, Chang SC, Aubry MC, Aakre JA, Allen MS, Chen F, Cunningham JM, et al. Genetic variants and risk of lung cancer in never smokers: A genome-wide association study. Lancet Oncol. 2010; 11 (4) :321–330. [PubMed: 20304703]
45. Miller S, Henry AP, Hodge E, Kheirallah AK, Billington CK, Rimington TL, Bhaker SK, Obeidat M, Melen E, Merid SK, Swan C, et al. The ser82 rage variant affects lung function and serum rage in smokers and srage production in vitro. PLoS One. 2016; 11 (10) e0164041 [PubMed: 27755550]
46. Robinson AB, Stogsdill JA, Lewis JB, Wood TT, Reynolds PR. Rage and tobacco smoke: Insights into modeling chronic obstructive pulmonary disease. Front Physiol. 2012; 3 :301. [PubMed: 22934052]
47. Zerah F, Harf A, Perlemuter L, Lorino H, Lorino AM, Atlan G. Effects of obesity on respiratory resistance. Chest. 1993; 103 (5) :1470–1476. [PubMed: 8486029]
48. Sin DD, Jones RL, Man SF. Obesity is a risk factor for dyspnea but not for airflow obstruction. Arch Intern Med. 2002; 162 (13) :1477–1481. [PubMed: 12090884]
49. Chapman DG, Berend N, King GG, Salome CM. Increased airway closure is a determinant of airway hyperresponsiveness. Eur Respir J. 2008; 32 (6) :1563–1569. [PubMed: 18653648]
50. Pellegrino R, Gobbi A, Antonelli A, Torchio R, Gulotta C, Pellegrino GM, Dellaca R, Hyatt RE, Brusasco V. Ventilation heterogeneity in obesity. J Appl Physiol (1985). 2014; 116 (9) :1175–1181. [PubMed: 24651986]
51. Canoy D, Luben R, Welch A, Bingham S, Wareham N, Day N, Khaw KT. Abdominal obesity and respiratory function in men and women in the epic-norfolk study, united kingdom. Am J Epidemiol. 2004; 159 (12) :1140–1149. [PubMed: 15191931]
52. Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. J Appl Physiol (1985). 2010; 108 (1) :206–211. [PubMed: 19875713]
53. Melo LC, Silva MA, Calles AC. Obesity and lung function: A systematic review. Einstein (Sao Paulo). 2014; 12 (1) :120–125. [PubMed: 24728258]
54. Astuti D, Morris MR, Cooper WN, Staals RH, Wake NC, Fews GA, Gill H, Gentle D, Shuib S, Ricketts CJ, Cole T, et al. Germline mutations in dis3l2 cause the perlman syndrome of overgrowth and wilms tumor susceptibility. Nat Genet. 2012; 44 (3) :277–284. [PubMed: 22306653]
55. Sivakumaran S, Agakov F, Theodoratou E, Prendergast JG, Zgaga L, Manolio T, Rudan I, McKeigue P, Wilson JF, Campbell H. Abundant pleiotropy in human complex diseases and traits. Am J Hum Genet. 2011; 89 (5) :607–618. [PubMed: 22077970]
56. Dendrou CA, Petersen J, Rossjohn J, Fugger L. Hla variation and disease. Nat Rev Immunol. 2018; 18 (5) :325–339. [PubMed: 29292391]
57. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Chen R, Decramer M, Fabbri LM, Frith P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: Gold executive summary. Eur Respir J. 2017; 49 (3)
58. Wielscher M, Minelli C, Amaral A, Auwinen J, Sebert S, Jarvis D, Jarvelin M-R. Cardio metabolic traits and lung function: A mendelian randomization study. 2018; 52 (suppl 62) PA1277
59. Moll M, Sakornsakolpat P, Shrine N, Hobbs BD, DeMeo DL, John C, Guyatt AL, McGeachie MJ, Gharib SA, Obeidat M, Lahousse L, et al. Chronic obstructive pulmonary disease and related phenotypes: Polygenic risk scores in population-based and case-control cohorts. Lancet Respir Med. 2020; 8 (7) :696–708. [PubMed: 32649918]
60. Aschard H, Vilhjalmsson BJ, Joshi AD, Price AL, Kraft P. Adjusting for heritable covariates can bias effect estimates in genome-wide association studies. Am J Hum Genet. 2015; 96 (2) :329–339. [PubMed: 25640676]
61. Dudbridge F, Fletcher O. Gene-environment dependence creates spurious gene-environment interaction. Am J Hum Genet. 2014; 95 (3) :301–307. [PubMed: 25152454]

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Take home message

The novel loci provide additional insights into the genetic basis of lung function. Understanding of shared genetic etiology between lung function and obesity may open new avenue for the development of molecular-targeted therapies for obesity and lung function improvement.

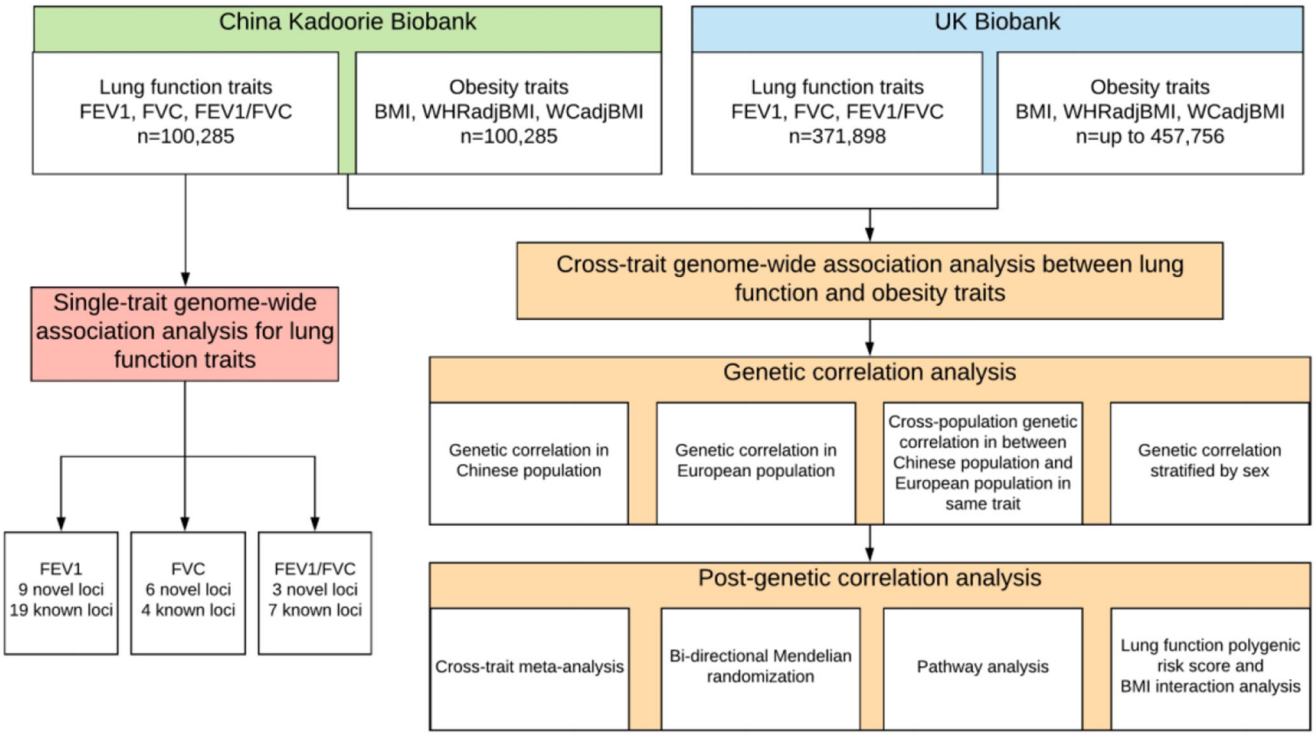

Figure 1. Overall study design.

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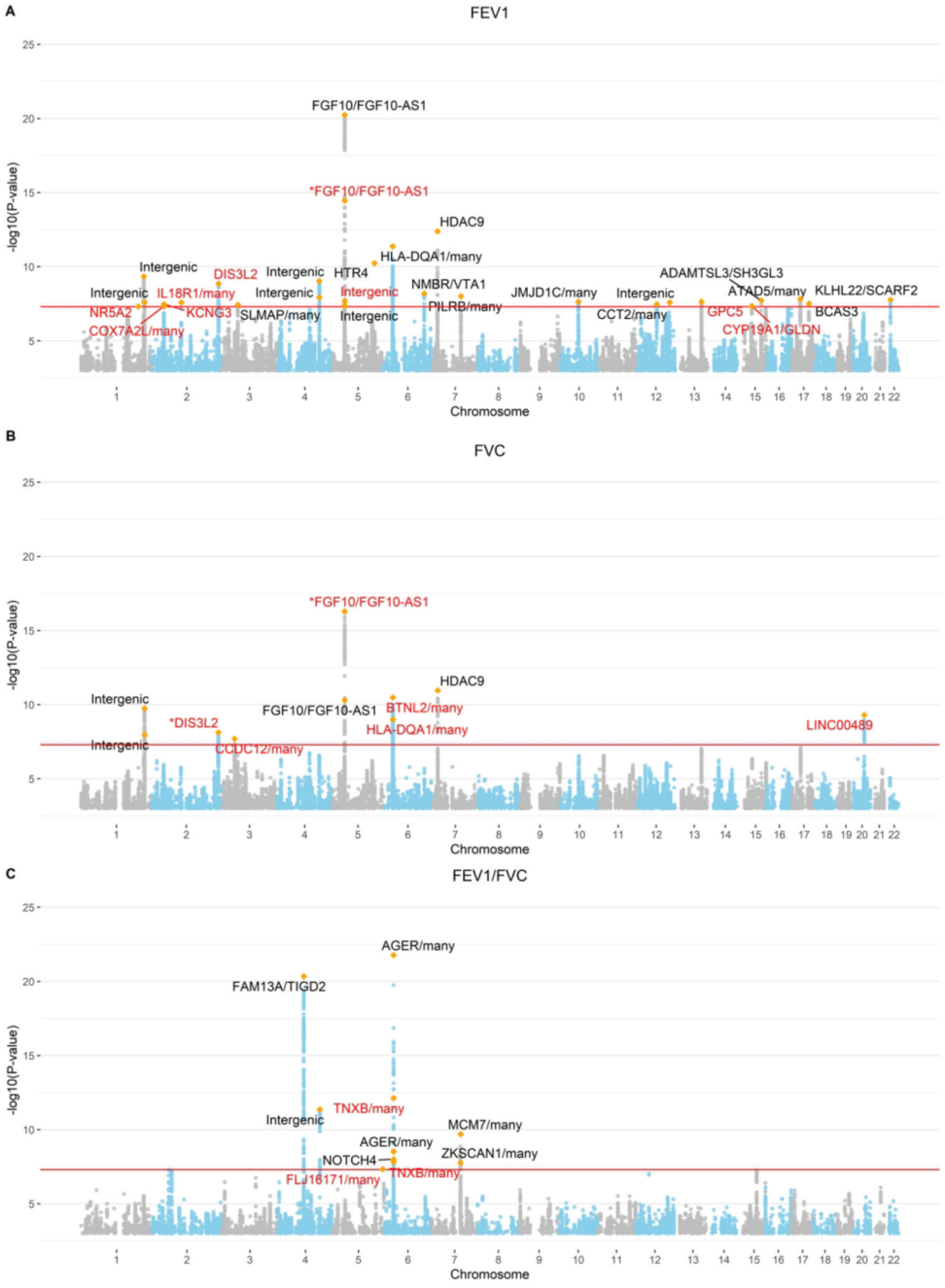

Figure 2.

Manhattan plot for genome-wide association analysis of 100,285 Chinese subjects in CKB cohort for three lung function traits, FEV1 (panel A), FVC (panel B), and FEV1/FVC (panel C). X-axis denotes the genomic position (chromosomes 1-22), Y-axis denotes the $-\log_{10}$(P-value) of association test and starts at $-\log_{10}$(P-value)=3. The most significant novel variant in each independent clump is highlighted in yellow orange diamond shape. Genes that are labeled in black font are previously reported, and genes that are labeled in red

font are novel. Asterisk on some genes means novel variant. Genome-wide significance level (P=5×10-8) is denoted by red line.

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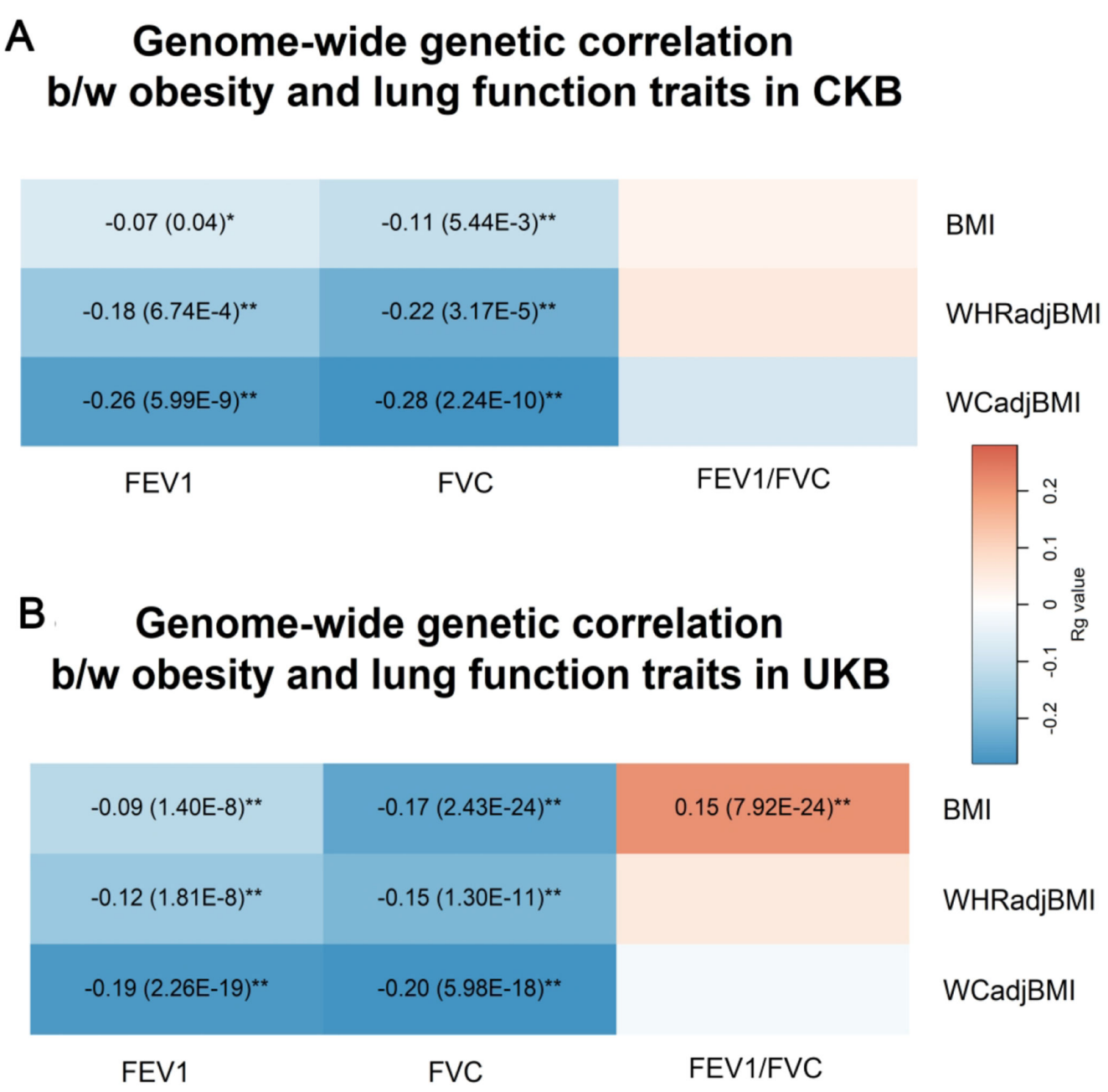

Figure 3.

Genome-wide genetic correlation between three lung function traits and three obesity traits in both CKB (panel A) and UKB (panel B) cohorts. The color of each box scales with the magnitude of the genetic correlation. Pairs of traits with nominal significant genetic correlation ($p < 0.05$) are marked by 1 asterisk, and pairs of traits with significant genetic correlation after correcting for multiple testing ($p < 0.05/9$) are marked by 2 asterisks. Boxes without labelling are trait pairs with non-significant genetic correlation.

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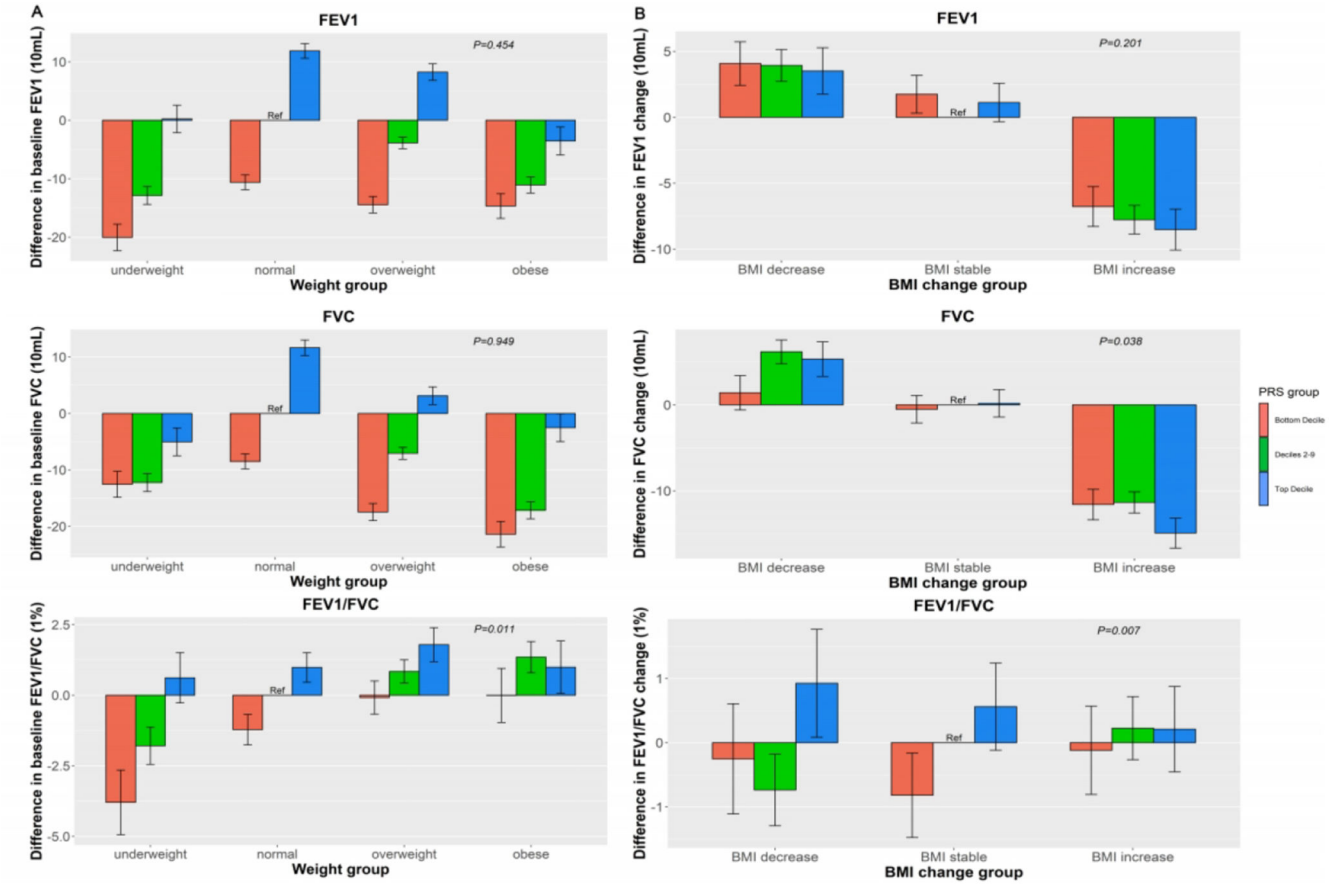

Figure 4.

Relationship of three lung function PRSs distribution with BMI (panel A: baseline model; panel B: change model) in CKB. For baseline model, we set normal BMI and deciles 2-9 group as reference, for change model, we set BMI stable and deciles 2-9 group as reference. For panel A, X-axis denotes different BMI categories by following definition: underweight: BMI <18.5 kg/m^2; normal: BMI 18.5-24.9 kg/m^2, overweight: BMI 25.0-29.9 kg/m^2, and obesity: BMI ≥30.0 kg/m^2. Y-axis denotes the differences between lung function measurements for each group with the reference group. For panel B, X-axis denotes different BMI change categories. BMI decrease is defined as BMI_{t1}-BMI_{t0} ≤ -1 kg/m^2, BMI stable is defined as -1 kg/m^2 < BMI_{t1}-BMI_{t0} ≤ 1 kg/m^2, and BMI increase is defined as BMI_{t1}-BMI_{t0} > 1 kg/m^2. Y-axis denotes the differences between lung function measurements change (lung $function_{t1}$-lung $function_{t0}$) for each group with the reference group. The PRS groups were defined as: bottom decile, deciles 2–9, and top decile. The P-value on each plot represents the lung function and baseline BMI or BMI change interaction P-value from baseline or change models.

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Table 1
Eighteen novel loci associated with FEV1, FVC and FEV1/FVC in CKB

Trait	Sentinel SNP	Clump region	N	A1	A2	A1 FREQ	BETA	SE	P	Genes within clump region
FEV1	rs145972739	chr1:200031115-200031115	1	A	G	0.97	-0.083	0.015	4.90E-08	*NR5A2*
FEV1	rs1861229	chr2:102992079-103208610	28	A	G	0.52	0.026	0.005	2.60E-08	*IL18R1,IL18RAP,MIR4772,SLC9 A4*
FEV1	rs28695435	chr2:232797462-233092939	181	G	A	0.31	-0.029	0.005	1.40E-09	*DIS3L2*
FEV1	rs222482	chr2:42391012-42703861	188	C	T	0.27	-0.028	0.005	4.70E-08	*COX7A2L,EML4,KCNG3,LOC10 2723824*
FEV1	rs112952987	chr2:42638788-42703942	21	G	A	0.94	0.050	0.009	3.40E-08	*KCNG3*
FEV1	rs117331805	chr5:43813683-44687091	96	A	G	0.94	-0.076	0.010	3.50E-15	*FGF10,FGF10-AS1*
FEV1	rs117675260	chr5:44474070-44623745	28	G	A	0.96	-0.069	0.012	2.10E-08	Intergenic region
FEV1	rs528366	chr13:92381450-92572381	224	T	C	0.78	-0.030	0.005	2.30E-08	*GPC5*
FEV1	rs77578670	chr15:51607186-51645049	23	C	T	0.75	-0.028	0.005	4.60E-08	*CYP19A1,GLDN*
FVC	rs143944819	chr2:232797462-233101499	185	A	G	0.77	0.033	0.006	7.50E-09	*DIS3L2*
FVC	rs6442039	chr3:46902129-47410564	158	C	G	0.52	-0.025	0.004	2.00E-08	*CCDC12,KIF9,KIF9-AS1,KLHL18,MYL3,NBEAL2,I ADDP,PTH1R,SETD2*
FVC	rs78732306	chr5:44048662-44583962	177	T	C	0.91	-0.068	0.008	5.10E-17	*FGF10,FGF10-AS1*
FVC	rs28366282	chr6:32196697-32713674	1767	C	T	0.76	0.035	0.005	3.30E-11	*BTNL2,C6orf10,HCG23,HLA-DQA1,HLA-DQA2,HL DRA,HLA-DRB1,HLA-DRB5,HLA-DRB6*
FVC	rs139447342	chr6:32396905-32636434	661	C	T	0.3	0.032	0.005	1.00E-09	*HLA-DQA1,HLA-DQB1,HLA-DRA,HLA-DRB1,HLA*
FVC	rs6063386	chr20:36206453-36273380	127	C	T	0.33	0.030	0.005	5.00E-10	*LINC00489*
FEV1/ FVC	rs186784089	chr5:174393318-174393318	1	G	A	0.99	0.120	0.022	4.70E-08	*FLJ16171*
FEV1/ FVC	rs149101418	chr6:31944375-32113312	17	T	G	0.55	0.035	0.005	7.50E-13	*ATF6B,C4A,C4B,C4B_2,CYP21A1P,CYP21A2,FKBP*
FEV1/ FVC	rs200214283	chr6:31976290-32133380	4	C	T	0.9	-0.045	0.008	1.50E-08	*ATF6B,C4A,C4B,C4B_2,CYP21A1P,CYP21A2,EGFL C100507547,PPT2,PPT2-EGFL8,PRRT1,STK19,TNX*

Note: N is number of variants meet the criteria of P-value<1×10^{-5} and r2>0.2 within the clump region; A1 is effect allele; A2 is non-effect allele; BETA is BOLT-LMM regression effect size.

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Table 2

Twenty-five shared genetic loci between lung function (FEV1, FVC) and obesity (BMI, WHRadjBMI, WCadjBMI) traits in CKB

Trait pair	Sentinel SNP	Clump region	N	A1	A2	BETA1	P1	BETA2	P2	P	Genes within clump region
FEV1 and BMI	rs73995038	chr2:232797462-233165478	193	A	G	-0.027	2.40E-09	-0.024	1.30E-07	1.15E-15	*DIS3L2*
	rs801170	chr5:139973696-140230371	303	C	T	0.023	3.70E-07	0.022	7.20E-07	9.11E-13	*CD14,DND1,HARS,HARS2 VTRNA1-1,VTRNA1-2,VT*
	rs9271730	chr6:32397794-32667412	1728	G	A	0.022	3.10E-06	0.029	3.30E-10	7.72E-15	*HLA-DQA1,HLA-DQB1,H*
	rs11066001	chr12:111629389-112119171	19	T	C	0.024	7.60E-06	0.028	3.40E-07	1.99E-11	*ATXN2,BRAP,CUX2,FAM*
	rs144504271	chr12:112140669-113117897	16	G	A	0.028	1.00E-06	0.029	3.20E-07	1.88E-12	*ACAD10,ADAM1A,ALDH*
	rs2078863	chr12:111846028-112355472	137	T	C	0.020	5.60E-06	0.020	9.50E-06	5.20E-10	*ACAD10,ADAM1A,ALDH*
	rs5742653	chr12:102397730-102910374	339	C	T	0.021	4.50E-06	0.022	1.10E-06	2.03E-11	*CCDC53,IGF1,NUP37,PAR*
FEV1 and WHRadjBMI	rs11066325	chr12:112834586-113150735	7	T	C	0.036	2.00E-09	0.031	2.30E-07	5.44E-16	*PTPN11,RPL6*
	rs3809297	chr12:111293470-111718231	88	G	T	0.029	8.80E-07	0.026	6.80E-06	2.53E-11	*CCDC63,CUX2,LOC10013*
	rs4646776	chr12:111886967-112678697	19	G	C	0.037	5.60E-11	0.029	2.20E-07	1.51E-17	*ACAD10,ADAM1A,ALDH 5,SH2B3,TMEM116,TRAF*
	rs7175531	chr15:51415799-51556959	49	T	C	0.027	1.60E-07	0.022	7.80E-06	2.01E-12	*CYP19A1,MIR4713*
	rs6142351	chr20:33864484-34336720	302	G	A	-0.032	5.20E-11	-0.024	1.20E-06	5.03E-16	*C20orf173,CEP250,CPNE1, AS1,NFS1,RBM12,RBM39,*
FEV1 and WCadjBMI	rs12048493	chr1:149922960-149995265	4	A	C	-0.023	1.00E-06	0.022	6.10E-06	1.92E-10	*OTUD7B*
	rs6604614	chr1:218568359-218690948	71	C	G	-0.030	5.10E-09	-0.027	1.90E-07	1.06E-16	*TGFB2*
	rs16828537	chr2:232797462-233211117	264	A	G	0.033	3.90E-13	-0.025	3.30E-08	3.91E-19	*DIS3L2*
	rs11066065	chr12:111846028-112824473	707	C	G	0.025	2.20E-08	0.024	1.20E-07	1.92E-16	*ACAD10,ADAM1A,ALDH 5,SH2B3,TMEM116,TRAF*
	rs11066325	chr12:112834586-113150735	7	T	C	0.053	6.70E-19	0.031	2.30E-07	5.08E-27	*PTPN11,RPL6*
	rs4646776	chr12:111827203-112678697	31	G	C	0.055	4.90E-23	0.029	2.20E-07	7.56E-31	*ACAD10,ADAM1A,ALDH 5,SH2B3,TMEM116,TRAF*
	rs78572043	chr12:111293470-111718231	94	A	G	0.046	1.10E-13	0.029	2.70E-06	4.58E-20	*CCDC63,CUX2,LOC10013*
FVC and BMI	rs6730783	chr2:219890663-220051676	63	A	G	-0.023	2.00E-07	-0.021	4.00E-06	2.73E-12	*CCDC108,CNPPD1,FAM13*
	rs73995038	chr2:232797462-233201328	207	A	G	-0.027	2.40E-09	-0.024	7.10E-08	4.13E-16	*DIS3L2*
	rs801170	chr5:139791506-140230371	327	C	T	0.023	3.70E-07	0.022	1.30E-06	8.74E-13	*ANKHD1,ANKHD1-EIF4E PCDHA4,PCDHA5,PCDHA*
	rs9271730	chr6:32397794-32667412	2271	G	A	0.022	3.10E-06	0.028	1.30E-09	2.21E-14	*HLA-DQA1,HLA-DQB1,H*
FVC and WHRadjBMI	rs2425059	chr20:33847253-34412049	326	T	C	0.033	3.70E-11	0.022	9.10E-06	1.61E-14	*C20orf173,CEP250,CPNE1, AS1,NFS1,PHF20,RBM12,*
FVC and WCadjBMI	rs16828537	chr2:232797462-233211117	257	A	G	0.033	3.90E-13	-0.025	1.40E-08	5.78E-17	*DIS3L2*

Note: N is number of variants meet the criteria of P-value<1×10^{-5} and r2>0.2 within the clump region; A1 is effect allele; A2 is non-effect allele; BETA1 is lung function trait effect size; P1 is lung function trait P-value; BETA2 is obesity trait effect size; P2 is obesity trait P-value; P is cross-trait meta-analysis P-value. Overlap with UKB means if the cross-trait meta-analysis clump region is overlapped with the same trait pair results in UKB.

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Table 3
Estimates of causal effect size for BMI and lung function traits

Population	Trait 1	Trait 2	Direction	Causal effect size	SE	P	nsnp
East Asian	BMI	FEV1	→	-0.0773	0.021	2.46E-04	68
			←	0.0884	0.033	6.53E-03	17
		FVC	→	-0.1084	0.021	3.44E-07	67
			←*	NA	NA	NA	6
		FEV1/FVC	→	0.0332	0.021	0.115732	69
			←*	NA	NA	NA	3
European	BMI	FEV1	→	-0.1057	0.012	4.65E-18	50
			←	0.0250	0.012	0.0308	411
		FVC	→	-0.1564	0.012	1.23E-37	50
			←	-0.0180	0.013	0.154475	379
		FEV1/FVC	→	0.1622	0.014	8.01E-33	48
			←	0.0393	0.009	4.75E-06	599

Note: "→" refers to the trait 1→trait 2 causal direction; "←" refers to the trait 2→trait 1 causal direction; nSNP is number of SNPs in the instrumental variable; causal effect sizes are in unit of per standard deviation increase in exposure.

*the FVC and FEV1/FVC GWASs do not have enough SNPs at the genome-wide significance level for constructing the instrument variable;