Supplementary Appendix

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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Supplementary Method

Ascertainment of obesity and lung function traits in China Kadoorie Biobank (CKB)

In CKB, anthropometric measures (height, weight, waist circumference [WC], and hip circumference) were assessed by trained staff at baseline. Standing height was measured without shoes, to the nearest 0.1 cm, using stadiometer. Weight was measured without shoes but in light clothing, to the nearest 0.1 kg, using the TBF-300GS Body Composition Analyser (Tanita inc, Tokyo, Japan). The weight of clothing was estimated and subtracted according to the season. BMI was calculated as weight (kg) divided by the square of height (m^2). Waist and hip circumferences were measured to the nearest 0.1 cm using soft tape. WC was measured midway between the lowest rib and the iliac crest or, when this was not practicable, 1 cm above the umbilicus. Hip circumference was measured at the maximum circumference around the buttocks. WHR was calculated as the ratio of WC to HC.

Pre-bronchodilator FEV_1 and FVC were measured by trained health technicians following recommended procedure [1]. Two successful blows (judged by the technician) were recorded for each participant. The larger FEV_1 and FVC were used to calculate FEV_1/FVC ratio.

Ascertainment of obesity and lung function traits in UK Biobank (UKB)

In UKB, anthropometric measures (height, weight, WC, and hip circumference) were assessed by trained staff at baseline. Weight was measured using the Tanita BC-418 MA body composition analyser. Staff asked participants to remove shoes and heavy outer clothing and then step onto the footpads of the body composition analyser. Staff then pressed a button to start the analysis, during which weight (and several other variables) are measured. The readings then downloaded automatically to the UKB assessment center IT system. The analysers represent a

moderate capital expense but they are robust (requiring only infrequent recalibration), they accurately measure body weight to within 0.1 kg. Standing and sitting height (shoeless) was measured using a Seca 202 height measure. Staff read the measurements off analogue rulers and manually entered the readings into the assessment center IT system, which automatically and immediately flagged up impossible or implausible values. WC at the level of the umbilicus was measured using a Wessex non-stretchable sprung tape measure that has been used in previous large health studies (including the BRIGHT hypertension study [2]). Staff manually entered the readings into the assessment center IT system, which automatically and immediately warned staff of impossible or implausible values. Hip circumference was measured using the same tape measure as for WC.

Pre-bronchodilator FEV_1 and FVC were measured by trained health technicians following recommended procedure using Vitalograph Pneumotrac 6800 spirometer [1]. The Vitalograph Pneumotrac 6800 spirometer was chosen because it is extensively in observational studies and clinical trials, and fulfilled various key requirements (e.g. conformed to ATS requirements, validated, reliable, robust, easy to use, IT data download). Up to three measurements of lung function within a maximum of 6 minutes (since more attempts over a more prolonged period were not considered acceptable for participants) were conducted.

Ascertainment of asthma and COPD phenotypes in CKB and UKB

In UKB, we used the same procedure as our previous study to identify cases with asthma or COPD [3]. Specifically, we identified all UKB cases with asthma by using the data fields 6152 (self-reported physician-diagnosis of several conditions, including asthma and COPD), 20002 (non-cancer illness disease code), 41202 (ICD-10-CM primary diagnosis in the hospital), and 41204 (ICD-10-CM secondary diagnosis in the hospital). The ICD-10-CM diagnosis codes of

J45 were used for the identification of asthma. Cases with COPD were identified by data fields 6152 (self-reported physician-diagnosis of several conditions, including asthma and COPD), 20002 (non-cancer illness disease code), 22130 (self-reported physician-diagnosis of COPD), 41202 (ICD-10-CM primary diagnosis in the hospital), 41204 (ICD-10-CM secondary diagnosis in the hospital). The ICD-10-CM diagnosis codes of J43 and J44 were used for the identification of COPD. Data field 6152 is from the participant questionnaire to determine the doctor-diagnosed asthma phenotypes. This data field contains the question: "Has a doctor ever told you that you have had any of the following conditions?" Participants could select more than one answer from the following: Blood clot in the leg (DVT); blood clot in the lung; emphysema/chronic bronchitis; asthma; hayfever, allergic rhinitis or eczema; none of the above; prefer not to answer. If participants chose either "none of the above" or "prefer not to answer", they could not select other answers.

In CKB, prevalent COPD at baseline was defined as airflow obstruction (FEV1/FVC<0.7) or having self-reported emphysema/chronic bronchitis. Asthma was assessed using an interviewer-administered questionnaire which asked if the participant had ever been diagnosed with asthma.

Determination of novel loci in CKB

We have used the NHGRI/EBI GWAS category to determine reported lung function (FEV1, FVC and FEV1/FVC) loci. Novel lung function loci were based on two definitions: novel clump or novel variant. The novel clump is defined as the clump regions we identified for CKB lung function traits did not contain any previously-reported variants in the NHGRI-EBI GWAS catalog. If the clump contains variant from the NHGRI-EBI GWAS catalog, then we conducted further investigation to determine whether the sentinel variant in the clump is novel or not. Thus the novel variant is defined as the sentinel variant in the clump has never been reported in the

NHGRI-EBI GWAS catalog, and it is in low linkage disequilibrium (LD) (r2<0.2) with any other NHGRI-EBI GWAS catalog variants that are within the clump region. We identified 13 sentinel variants for FEV1, 5 for FVC and 5 for FEV1/FVC that need to be investigated for novel variant (table S2-S4).

Biobank Japan (BBJ) BMI GWAS dataset

Detailed information on the imputation and quality control (QC) procedures used in the BBJ data was described elsewhere [4]. In brief, the BBJ BMI GWAS data were imputed using the East Asian (EAS) samples of the 1000 Genomes Project Phase I v3 reference panel. The BBJ conducted genotyping QC using the following criteria: sample call rate < 0.98, SNV call rate < 0.99, HWE $P < 1x10^{-6}$. After imputation, variants with imputation quality score INFO < 0.7 were excluded.

Genetic Investigation of Anthropometric Traits (GIANT) Consortium BMI GWAS dataset

Detailed information on the imputation and QC procedures used in the Genetic Investigation of Anthropometric Traits (GIANT) Consortium data was described elsewhere [5]. In brief, the GIANT Consortium BMI GWAS data were imputed using the HapMap phase II CEU reference panel and then meta-analyzed based on fix-effect model. The genomic control was corrected for both individual GWAS results as well as GWAS meta-analysis results. In the current study, we used European only subjects from GIANT GWAS to be consistent with UK Biobank and minimize population stratification cofounding.

Lung function polygenic risk score in CKB and UKB

PRS is a score that aggregates genetic variants aiming to predict disease risk or trait level. Before computing PRSs, we used the base data (n_{CKB}=77,617 and n_{UKB}=357,244) to generate GWAS

summary statistics for each of the three lung function traits: FEV1, FVC, FEV1/FVC; then, we used LDpred [6] to compute the PRS model coefficients based on ~1.74 million SNPs, and applied the selected model to the independent target data from the CKB (n=22,668) and UKB (n=14,507) to generate PRS value for participants in the target data. As opposed to removing SNPs with high LD, LDpred is a Bayesian method that adjusts the effect sizes from the GWAS by using a prior and LD information from an external reference panel to estimate the LD structure among SNPs. LDpred contains 3 typical steps. The first step is data synchronization. In this step, we used "ldpred coord" function to generate coordinate data that synchronizes the genotypes and GWAS summary statistics. The second step is LDpred SNP weights generation. In this step, we used "ldpred gibbs" function to generated re-weighted effect estimate for each SNP. We computed the SNP weights based on the HapMap 2 and 1000 Genome phase 3 version 5 SNPs [7]. The third step is individual PRS generation. We used "ldpred score" to generate the individual's PRS in the target data. For each of the lung function traits, we calculated 8 PRSs using 7 different proportion of causal variants models (1.0, 0.1, 0.01, 0.001, 0.3, 0.03, 0.003) and an infinitesimal model. We selected a PRS with the maximum R2 to discriminate the risk of outcome. Lastly, we investigated the PRS and BMI interaction between the derived lung function PRSs and baseline BMI and its longitudinal changes and their association with the lung function level changes by fitting linear regression models 21,791 participants in CKB and 12,019 participants in UKB (after excluding those with missing lung function or BMI data). For BMI, we used it as continuous variable in the baseline and change models. We further categorized baseline BMI into four categories to investigate the overall effect of $PRS_{\text{lung function}}$×BMI interaction (Figure 4): 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, obesity: BMI ≥30.0 kg/m^2. In addition, we defined three

categories for BMI change: BMI decrease, BMI stable, BMI increase to investigate the overall effect of the $PRS_{lung\ function}$×BMI interaction (Figure 4). 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, BMI increase is defined as BMI_{t1}-BMI_{t0} > 1 kg/m^2.

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Figure S1. QQ plots of lung function and obesity traits in CKB

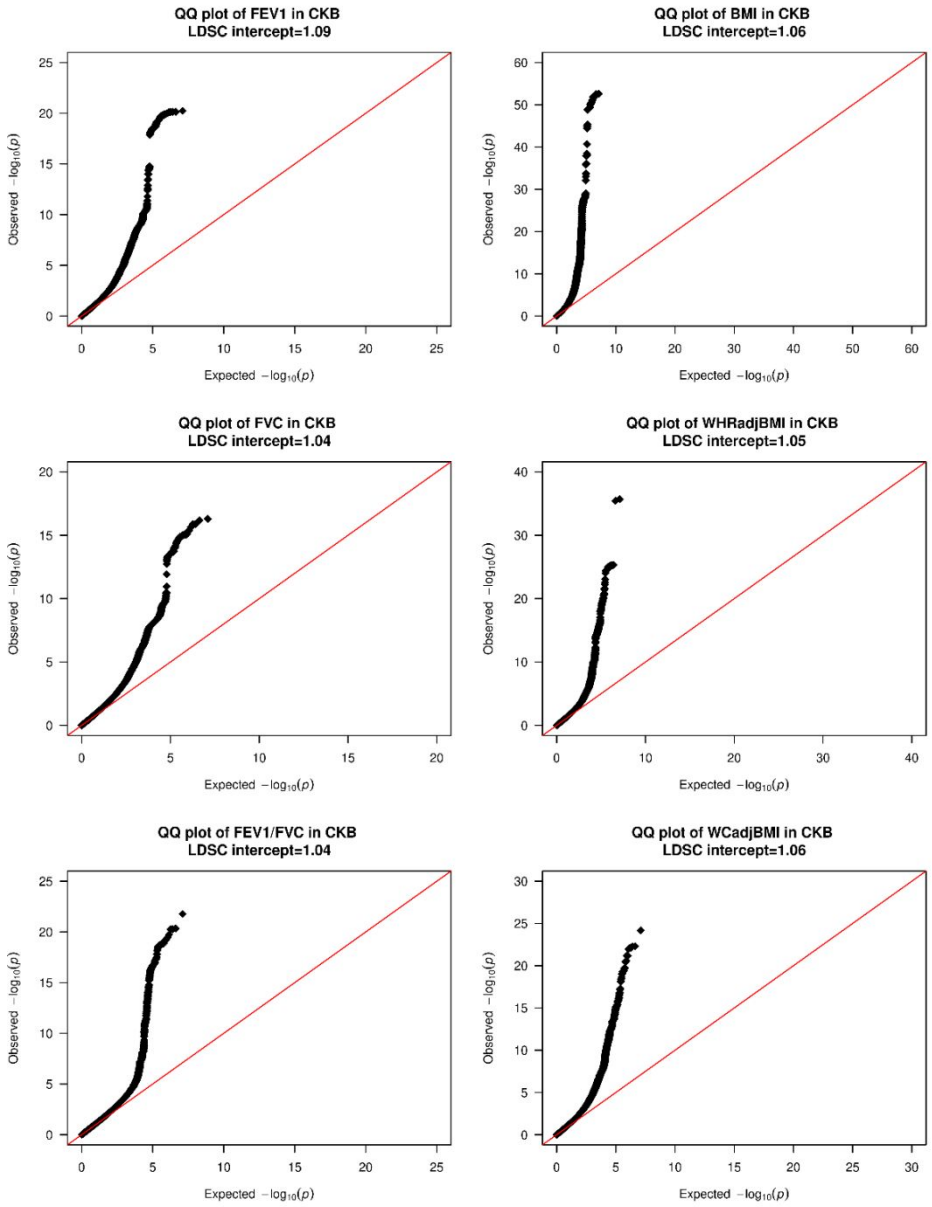

Figure S2. QQ plots of lung function and obesity traits in UKB

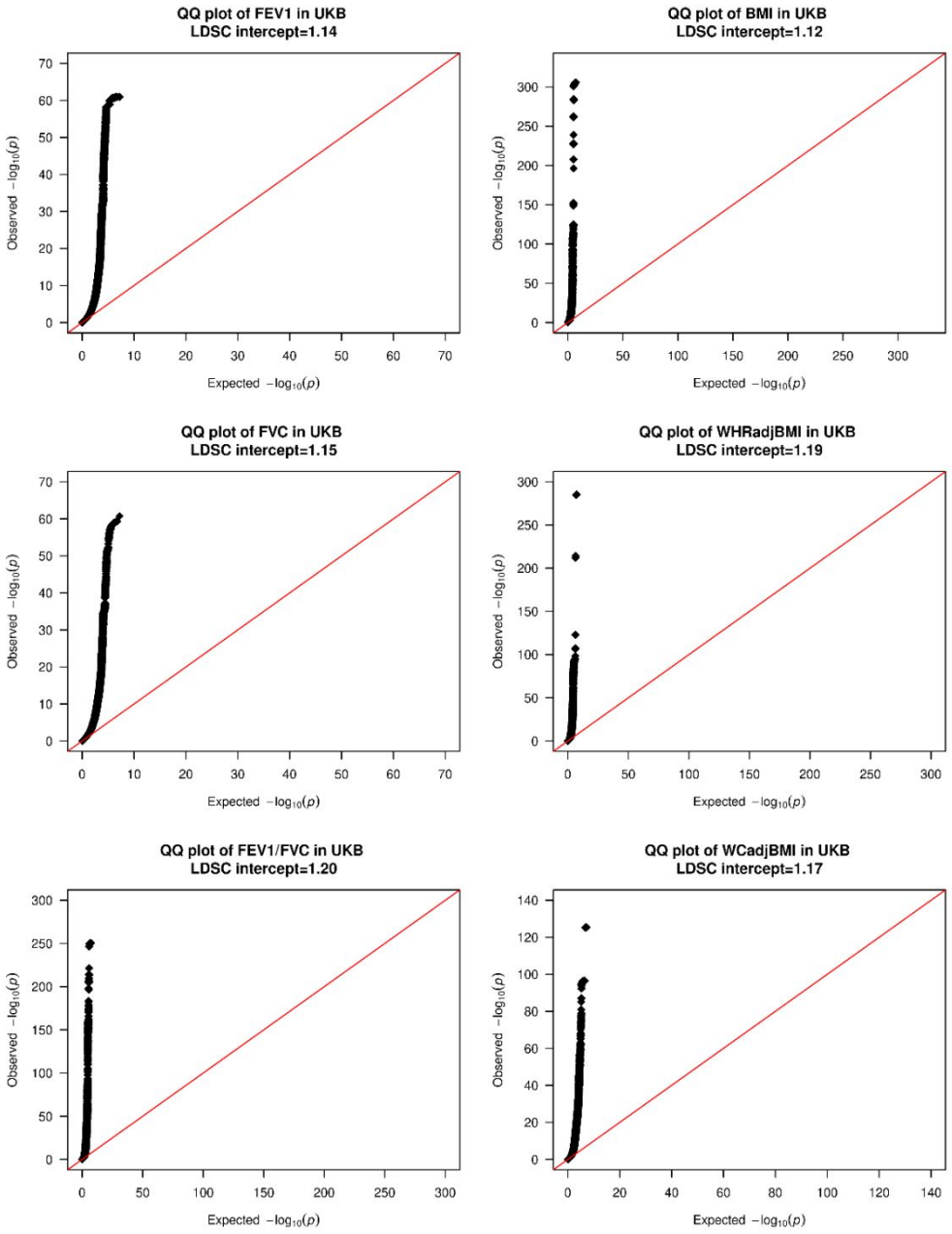

Figure S3. Relationship of three lung function PRSs distribution with BMI (panel A: baseline model; panel B: change model) in UKB. For baseline model, we set normal BMI and deciles 2-9 group as reference, for change model, we set BMI stable and deciles 2-9 group as reference. For panel A, X-axis denotes 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.

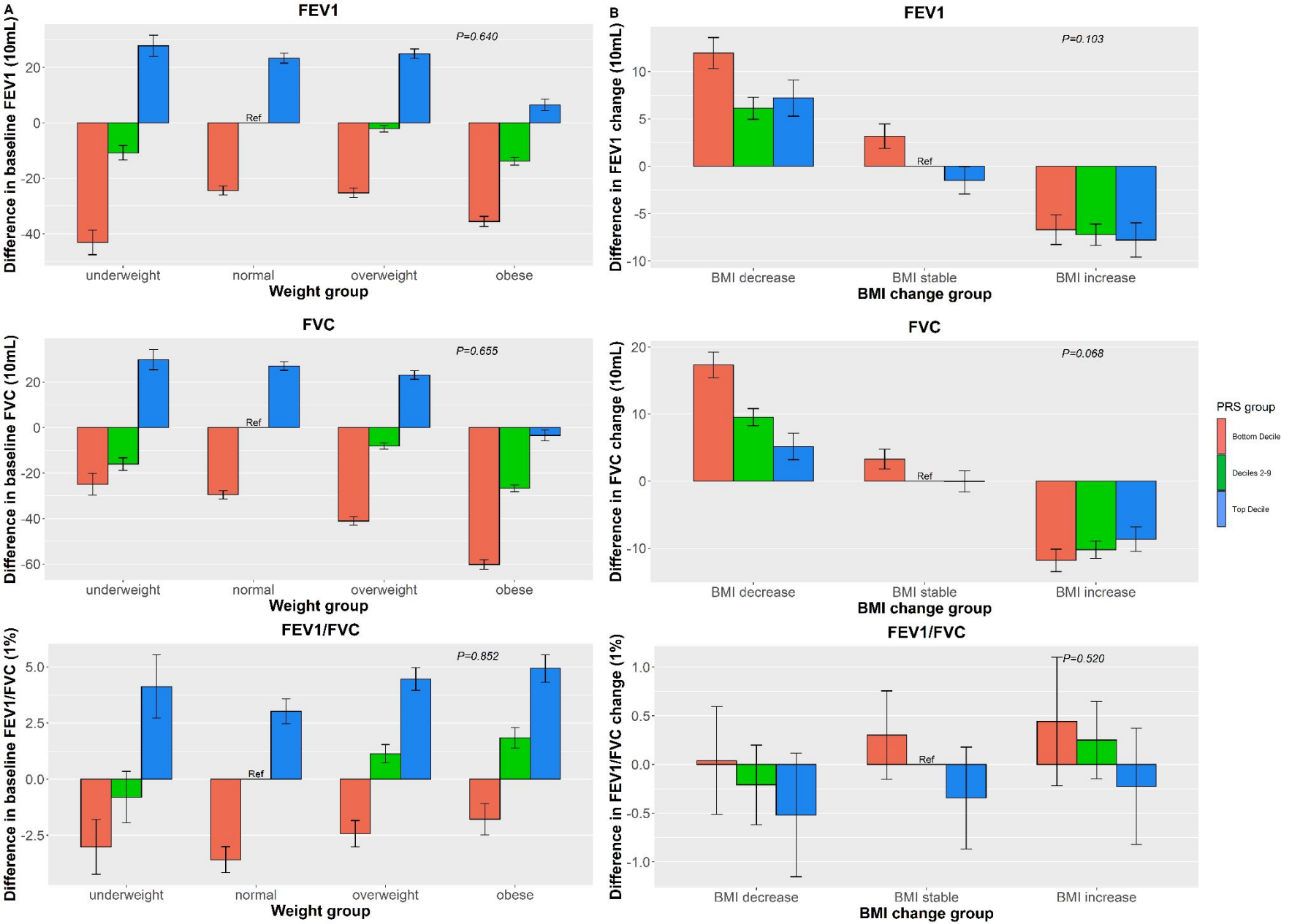
A
FEV1
Difference in baseline FEV1 (10mL)
P=0.640
Ref
underweight
normal
overweight
obese
Weight group
B
FEV1
Difference in FEV1 change (10mL)
P=0.103
Ref
BMI decrease
BMI stable
BMI increase
BMI change group
FVC
Difference in baseline FVC (10mL)
P=0.655
Ref
Weight group
FVC
Difference in FVC change (10mL)
P=0.068
Ref
BMI change group
PRS group
Bottom Decile
Deciles 2-9
Top Decile
FEV1/FVC
Difference in baseline FEV1/FVC (1%)
P=0.852
Ref
Weight group
FEV1/FVC
Difference in FEV1/FVC change (1%)
P=0.520
Ref
BMI change group

Figure S4. Relationship of three lung function 275-SNP PRSs (from Shrine et al.) 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.

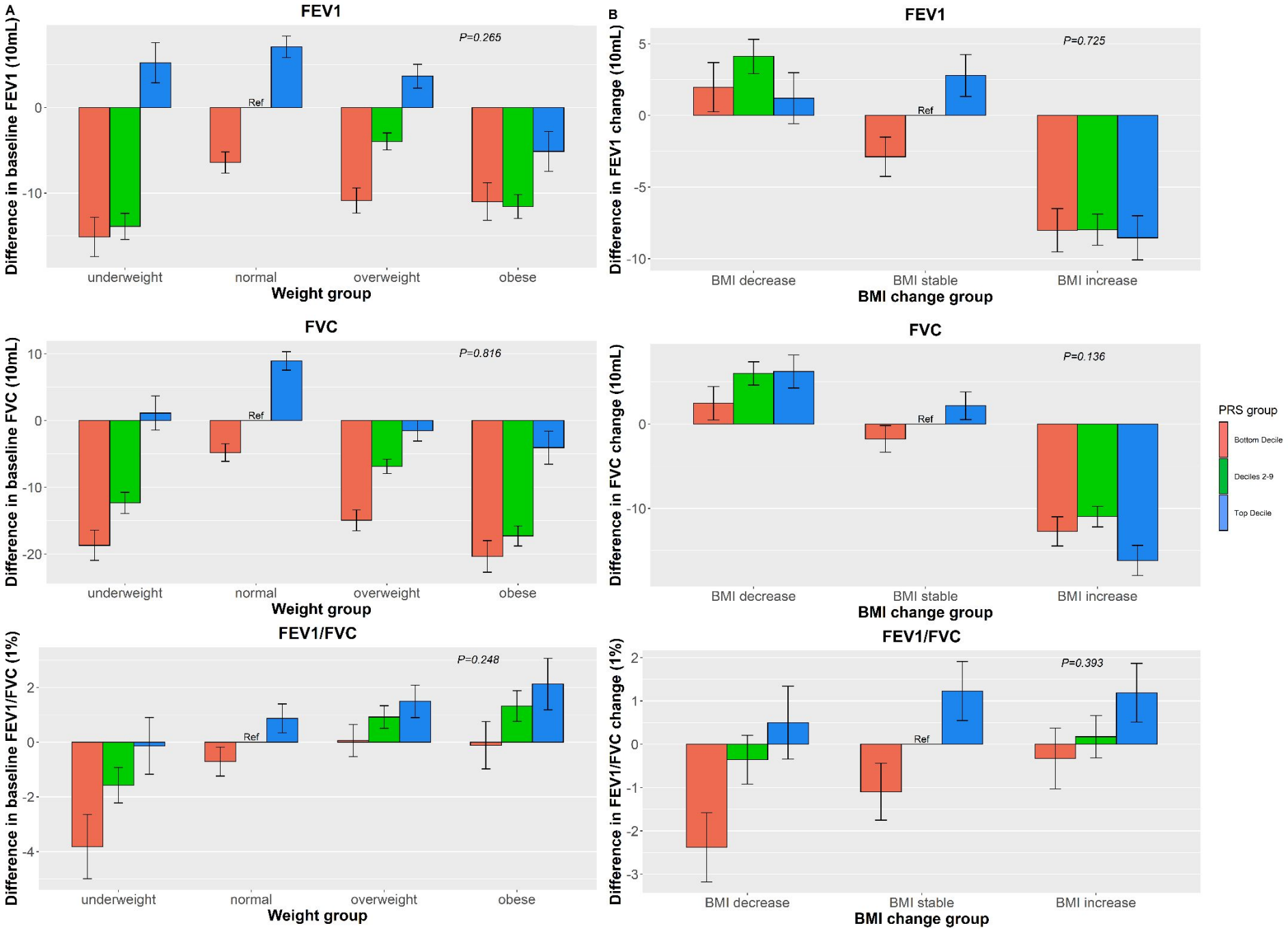
A
FEV1
Difference in baseline FEV1 (10mL)
P=0.265
Ref
underweight
normal
overweight
obese
Weight group
B
FEV1
Difference in FEV1 change (10mL)
P=0.725
Ref
BMI decrease
BMI stable
BMI increase
BMI change group
FVC
Difference in baseline FVC (10mL)
P=0.816
Ref
underweight
normal
overweight
obese
Weight group
FVC
Difference in FVC change (10mL)
P=0.136
Ref
BMI decrease
BMI stable
BMI increase
BMI change group
PRS group
Bottom Decile
Deciles 2-9
Top Decile
FEV1/FVC
Difference in baseline FEV1/FVC (1%)
P=0.248
Ref
underweight
normal
overweight
obese
Weight group
FEV1/FVC
Difference in FEV1/FVC change (1%)
P=0.393
Ref
BMI decrease
BMI stable
BMI increase
BMI change group

Figure S5. Sensitivity analysis for 6 FVC novel loci's effect size and P-value by comparing primary cohort (n=100,285) and sensitivity cohort after removing the two CKB regions (n=86,285)

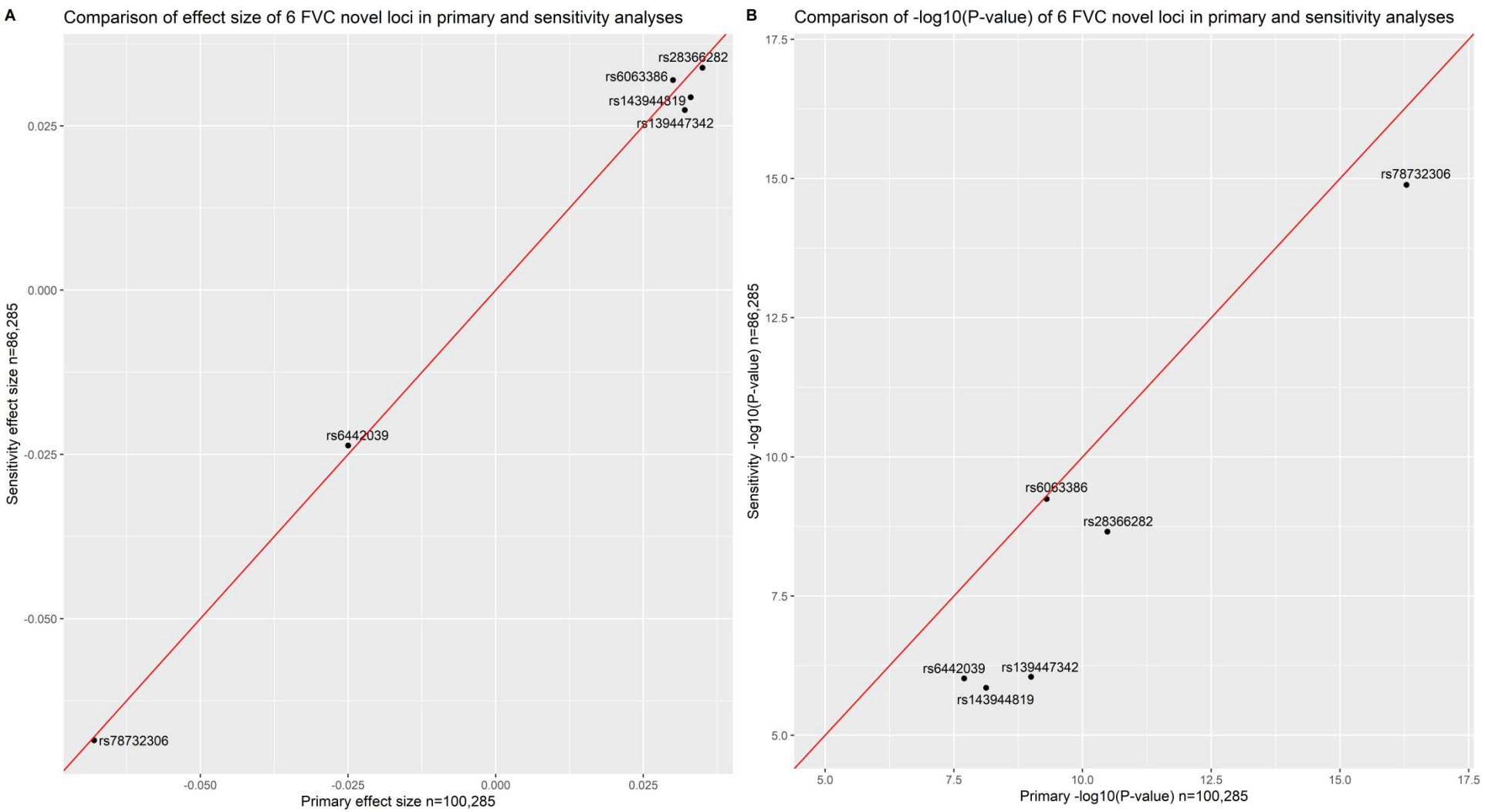

Figure S6. Sensitivity analysis for 3 FEV1/FVC novel loci's effect size and P-value by comparing primary cohort (n=100,285) and sensitivity cohort after removing the two CKB regions (n=86,285)