Impact of lung function on cardiovascular diseases and cardiovascular risk factors: a two sample bidirectional Mendelian randomisation study

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ABSTRACT

Introduction Observational studies suggested lung function is inversely associated with cardiovascular disease (CVD) although these studies could be confounded. We conducted a two sample Mendelian randomisation study using summary statistics from genome-wide association studies (GWAS) to clarify the role of lung function in CVD and its risk factors, and conversely the role of CVD in lung function.

Methods We obtained genetic instruments for forced expiratory volume in 1 s (FEV1; 260) and forced vital capacity (FVC; 320) from publicly available UK Biobank summary statistics (n=421 986) and applied to GWAS summary statistics for coronary artery disease (CAD) (n=184 305), stroke (n=446 696), atrial fibrillation (n=1 030 836) and heart failure (n=977 320) and cardiovascular risk factors. Inverse variance weighting was used to assess the impact of lung function on these outcomes, with various sensitivity analyses. Bidirectional Mendelian randomisation was used to assess reverse causation.

Results FEV1 and FVC were inversely associated with CAD (OR per SD increase, 0.72 (95% CI 0.63 to 0.82) and 0.70 (95% CI 0.62 to 0.78)), overall stroke (0.87 (95% CI 0.77 to 0.97), 0.90 (95% CI 0.82 to 1.00)) and some stroke subtypes. FEV1 and FVC were inversely associated with type 2 diabetes and systolic blood pressure. Sensitivity analyses produced similar findings although the association with CAD was attenuated after adjusting for height (eg, OR for 1SD FEV1 0.95 (0.75 to 1.19), but not for stroke or type 2 diabetes. There was no strong evidence for reverse causation.

Conclusion Higher lung function likely protect against CAD and stroke.

INTRODUCTION

Poorer lung function is associated with cardiovascular disease (CVD). However, these associations could be confounded by lifestyle factors, such as physical activity and smoking, and anthropometric characteristics, such as height, which are difficult to account for in observational studies.

Mendelian randomisation is potentially less vulnerable to residual confounding than observational studies because it uses genetic variants related to exposures which are randomly allocated during conception. A previous Mendelian randomisation study suggested higher forced expiratory volume in 1 s (FEV1) related to lower risk of coronary artery disease (CAD), while the relation for forced vital capacity (FVC) was less clear. However, that study used a relatively small number of genetic instruments (ie,16 instruments for FEV1 (variance explained (R2): 0.8%) and 10 instruments for FVC (R2: 0.4%)), did not consider other important CVDs, such as stroke and heart failure, and did not explore the possibility of bidirectional effects (ie, CVDs also having an effect on lung function). Furthermore, the study used genetic instruments extracted from genome-wide association studies (GWAS) which were adjusted for height and smoking and may introduce collider bias and hence potentially identify invalid instruments. Another Mendelian randomisation study provided evidence that lung function may protect against CAD although that study focused primarily on the mechanistic pathway between height and CAD risk instead of the etiologic role of lung function in CVDs.

The aim of this study was to determine the causal effect of FEV1, and FVC on a wide range of CVDs using two sample Mendelian randomisation with summary statistics. Our study adds to previous Mendelian randomisation studies by including more genetic instruments and more CVD outcomes and risk factors. We also explored whether genetic predisposition to CVDs might cause variation in lung function.
Table 1summarises the study design including the sources of GWAS summary data for exposure (FEV₁ and FVC—sample 1) and each CVD outcome and risk factors (sample 2). Given Mendelian randomisation has stringent assumptions (ie, relevance, independence and exclusion restriction), we also assessed whether the genetic instruments affected key confounders for CVD (education, body mass index (BMI), smoking, alcohol consumption and height) to check exclusion restriction. 9

Genetic determinants of FEV₁ and FVC (sample 1)

Genetic determinants of FEV₁ (in SD, GWAS ID: ukb-b-19657) and FVC (SD, GWAS ID: ukb-b-7953) were extracted from summary GWAS results in the UK Biobank, available in the Integrative Epidemiologic Unit (IEU) GWAS database (https://gwas.mrcieu.ac.uk/). 14 15 In brief, the UK Biobank is a large prospective cohort study where more than 500 000 participants were recruited in the United Kingdom (Great Britain only) from 2006 to 2010 (mean age: 56.5; 54% female). Prebronchodilation lung function testing was performed by trained healthcare staff using a Vitalograph Pneumotrac 6800 spirometer (Maids Moreton, UK). Genotyping was done using the Affymetrix UK BiLEVE Axiom array (~50 000 participants) and Affymetrix UK Biobank Axiom array (~450 000 participants). The summary statistics were generated using a linear mixed model to account for relatedness and population stratification, and adjusted for sex and genotyping array. The analyses were restricted to 421 986 participants of European descent. Quality controls included exclusion based on imputation quality (specific INFO scores based on minor allele frequency (MAF)) and MAF (≤1%) (online supplemental table 1).

Genetic associations with the outcomes (sample 2)

Complete summary GWAS results for CAD (CARDioGRAMplusC4D 1000 Genome based GWAS), 16 stroke and its subtypes (MEGASTROKE consortium), 17 atrial fibrillation, 18 heart failure (Heart Failure Molecular Epidemiology for Therapeutic Targets (HERMES) consortium), 19 systolic and diastolic blood pressure (UK Biobank associations obtained from IEU GWAS database), 20 LDL, HDL cholesterol and triglycerides (Global Lipids Genetics Consortium (GLGC)), 21 type 2 diabetes (Diabetes Genetics Replication and Meta-analysis (DIAGRAM)), 22 fasting glucose, insulin and glycated haemoglobin (HbA1c) (the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC)), 23 were generated using a linear mixed model to account for relatedness and population stratification, and adjusted for sex and genotyping array. The analyses were restricted to 421 986 participants of European descent. Quality controls included exclusion based on imputation quality (specific INFO scores based on minor allele frequency (MAF)) and MAF (≤1%) (online supplemental table 1).

Selecting genetic instruments from the exposure GWAS, identifying these in outcome GWAS and harmonising instruments across studies

We identified genetic instruments for lung function at genome wide significant p value (<5×10⁻⁸), and we excluded instruments which were in high linkage disequilibrium (LD) with other instruments (r² <0.001). We searched for the genetic instruments affected key confounders for CVD (education, body mass index (BMI), smoking, alcohol consumption and height) to check exclusion restriction. 9

 METHODS

Study design

We used two sample summary data Mendelian randomisation to assess the effect of FEV₁ (per SD) and FVC (per SD) on multiple CVD outcomes: (ie, CAD, stroke and its subtypes, heart failure, atrial fibrillation) and CVD risk factors (ie, systolic and diastolic blood pressure, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides, type 2 diabetes, fasting glucose, glycated haemoglobin and insulin). 9 Table 1 summarises the study design including the sources of GWAS summary data for exposure (FEV₁ and FVC—sample 1) and each CVD outcome and risk factors (sample 2).

| Data source (Pubmed ID (PMID)) | Sample size (% cases) | % European |
|--------------------------------|-----------------------|------------|
| Coronary artery disease CARDioGRAM (26343387) | 184 305 (33%) | 77 |
| Stroke MEGASTROKE (29531354) | 446 696 (9%) | 100 |
| Ischaemic stroke MEGASTROKE (29531354) | 440 328 (8%) | 100 |
| Cardioembolic stroke MEGASTROKE (29531354) | 211 763 (3%) | 100 |
| Small vessel stroke MEGASTROKE (29531354) | 198 048 (3%) | 100 |
| Large artery stroke MEGASTROKE (29531354) | 150 765 (3%) | 100 |
| Atrial fibrillation PMID: 30061737 | 1 030 836 (6%) | 100 |
| Heart failure HERMES (31919418) | 977 320 (5%) | 100 |
| Systolic blood pressure (SD) UK Biobank (EU GWAS) | 436 419 | 100 |
| Diastolic blood pressure (SD) UK Biobank (EU GWAS) | 436 424 | 100 |
| LDL cholesterol (SD) GLGC (24097068) | 173 082 | 100 |
| HDL cholesterol (SD) GLGC (24097068) | 187 167 | 100 |
| Triglycerides (SD) GLGC (24097068) | 177 861 | 100 |
| Glucose (mmol/L) MAGIC (22581228) | 58 074 | 100 |
| Hba1c (% MAGIC ABC (28898252) | 123 665 | 100 |
| Insulin (log) MAGIC (22581228) | 51 750 | 100 |
| Type 2 diabetes DIAGRAM (28566273) | 159 208 (17%) | 100 |

Confounders

| Body mass index (SD) GIANT (25673413) | 339 224 | 95 |
| Years education attained (SD) SSGAC (27225129) | 328 917 (Excluded 23andMe) | 100 |
| Alcohol (SD of Log transformed drinks per week) GSCAN (30643251) | 537 349 (Excluded 23andMe) | 100 |
| Smoking heandiness (SD of cigarettes per day) GSCAN (30643251) | 263 954 (Excluded 23andMe) | 100 |
| Height (SD) GIANT (25282103) | 253 288 | 100 |

GIANT, Genetic Investigation of Anthropometric Traits; GSCAN, GWAS & Sequencing Consortium of Alcohol and Nicotine use; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SSGAC, Social Science Genetic Association Consortium.
original instrument ($r^2 \geq 0.8$) was identified via MR-Base based on 1000 Genomes catalogue (CEU reference population).\textsuperscript{15} No proxy instruments were identified for outcomes not available in MR-Base. We aligned each genetic association for exposure and outcome on the same effect allele. We used effect allele frequency (values outside of 0.42–0.58) to ensure palindromic genetic instruments were aligned properly where that was possible.

**Statistical analysis**

We estimated the $R^2$ of each genetic instrument and summed them up to compute the overall $R^2$ and $F$ statistics using the sample size which the instruments for lung function was derived from ($n=421,986$). Higher $R^2$ and $F$ statistic values suggest lower risk of weak instrument bias.\textsuperscript{24} For our main Mendelian randomisation analyses, we used inverse variance weighting (IVW) with multiplicative random effects to obtain the causal effect of FEV$_1$ and FVC on CVD outcomes and their risk factors. IVW assumes there is no unbalanced horizontal pleiotropy.\textsuperscript{25} To assess the presence of potentially invalid instruments, we checked for evidence of heterogeneity across instrument-specific Wald ratios (ie, ratio of instrument–outcome association to instrument–exposure association) using Cochran’s Q test. Heterogeneity may result from horizontal pleiotropy.

**Additional analyses to explore potential violation of Mendelian randomisation assumptions**

MR assumes that genetic instruments do not affect confounders of the exposure-outcome association. We assessed the plausibility of this assumption by exploring whether the FEV$_1$ and FVC genetic instruments were related to key confounders defined as plausibly affecting lung function and CVDs (BMI, height, socioeconomic position, alcohol and smoking).\textsuperscript{9} This was done using publicly available summary GWAS data for: BMI,\textsuperscript{18} education (as a measure of socioeconomic position),\textsuperscript{22} number of drinks of alcohol per week and number of cigarette smoked per day,\textsuperscript{17} and height.\textsuperscript{23} Specifically, we meta analysed the estimate of each SNP–outcome association (per lung function increasing allele) using standard IVW method with additive random effects. For confounders which were associated with the genetic instruments, we then assessed whether these associations were a sign of vertical pleiotropy (causal role of lung function on confounders) or horizontal pleiotropy (causal role of confounders on lung function) using bi-directional Mendelian randomisation.\textsuperscript{9} We used multivariable Mendelian randomisation to control for potential horizontal pleiotropy by including estimates from the relevant confounders which were strongly associated with genetic instruments for lung function.\textsuperscript{9} Given the possibility of varying instrument strengths with increasing number of variables being adjusted for in multivariable Mendelian randomisation and hence limits the interpretation of the findings,\textsuperscript{26} we only considered variables which were strongly associated with the instruments for FEV$_1$ and FVC. We also approximated the conditional $F$ statistics to evaluate potential weak instrument bias,\textsuperscript{26} presented Cochran’s Q test to evaluate heterogeneity, and also provided estimates for multivariable MR-Egger to assess robustness of findings due to pleiotropy.\textsuperscript{27}

To assess unbalanced horizontal pleiotropy bias, we undertook the following sensitivity analyses: MR-Egger,\textsuperscript{28} weighted median analyses\textsuperscript{25} and MR-PRESSO,\textsuperscript{30} that are more robust than IVW to the assumption that there is no effect of the genetic instrument on outcome other than through the exposures of interest (ie, no horizontal pleiotropy paths). Like IVW, MR-Egger and MR-PRESSO require that the InSIDE (‘instrument strength is independent of direct effect’) assumption is not violated. Specifically, InSIDE assumes there is no correlation between the strength of the instrument (association of FEV$_1$ or FVC on their respective genetic instruments) and the strength of any association of the genetic instruments on the outcome not via the exposures of interest (eg, any horizontal pleiotropy paths). The weighted median analyses assumed at least 50% of the weight of the genetic instruments is via the exposure of interest. Further details of these methods and their additional (and differing) assumptions are available in online supplemental material.

**Bidirectional Mendelian randomisation**

To assess potential reverse causation, that is, predisposition to CVDs affecting variation in FEV$_1$ or FVC, we also conducted a Mendelian randomisation using genetic predictors of risk of CAD, overall stroke, heart failure and atrial fibrillation as instruments.\textsuperscript{10–13} We used IVW to explore evidence of effects of genetic predispositions to these CVDs on FEV$_1$ or FVC.

All analyses were performed using R Version 4.0.4 (R Development Core Team, Vienna, Austria) using R packages (‘TwoSampleMR’) and (‘MRPRESSO’).\textsuperscript{15 30}

**RESULTS**

For FEV$_1$, up to 260 single nucleotide polymorphisms (SNPs) were used in the analyses, and these instruments explained up to 3.5% of FEV$_1$ variance (overall $F$ statistics: 58.8). For FVC, up to 320 SNPs were used in the analyses, and these instruments explained up to 4.8% of FVC variance (overall $F$ statistics: 66.4). (Online supplemental tables 2 and 3 show the summary statistics of the lung function instruments used in this study.

Figure 1 shows that higher FEV$_1$ was associated with lower risk of CAD, overall stroke and some subtypes (ie, ischaemic stroke, small vessel stroke, large artery stroke) and type 2 diabetes, but increased risk of atrial fibrillation and had no association with heart failure. FVC showed similar relation with these outcomes (figure 2). Regarding the association with cardiovascular risk factors, higher FEV$_1$ was mainly associated with lower systolic blood pressure and triglycerides (figure 3). FVC showed similar relations with these outcomes and FVC was also associated with lower LDL cholesterol, glucose and insulin (figure 4). Figures 1–4 show that between SNP Wald ratio heterogeneity was high for most of the outcomes although there was no strong evidence for directional horizontal pleiotropy based on the MR-Egger intercepts, with the exception of atrial fibrillation. Corresponding sensitivity analyses generally gave directionally similar estimates for most outcomes although differences were observed when using multivariable Mendelian randomisation analyses (figures 1–4 and Online supplemental tables 4 and 5).

Based on the results in Online supplemental tables 6 and 7, we identified BMI, height and education as possible horizontal pleiotropic effects which may bias the main analyses. Given height had a much stronger association with the instruments and knowledge that height is an established cause of lung function, we undertook multivariable MR adjusting for height only. With adjustment for height, the effect estimates were directionally similar to the main analyses although estimates for CAD attenuated substantially, while the effect estimate for stroke and type 2 diabetes remained similar. Given the lower statistical power in these analyses the confidence intervals are wider, as expected,
Respiratory epidemiology

and in the case of stroke included the null value (figures 1 and 2). The positive association with atrial fibrillation disappeared and lung function was potentially associated with lower risk of heart failure although with CI overlapping null (figures 1 and 2). Similar findings were observed when we used multivariable MR-Egger method (online supplemental figures 1–4). However, these analyses need to be treated with some caution as the conditional F statistics were small, ranging from 7.8 to 9.9 for FEV1 and 10.0 to 11.6 for FVC.

Figure 5 shows the association of predisposition to CVD with FEV1 and FVC, using genetic instruments for CVD (online supplemental table 8). Predisposition to CAD, stroke, atrial fibrillation and heart failure was not associated with FEV1 or FVC. This provides evidence against possible reverse causation when assessing the relation of lung function with CVDs.

DISCUSSION

In this Mendelian randomisation study which we explored the impact of lung function on the risk of CVDs and risk factors which may mediate any observed effects on CVDs (blood pressure, lipids, glycaemic traits). Our study provides suggestive evidence that better lung function is cardioprotective. These findings were consistent across a range of sensitivity analyses used to explore possible bias due to horizontal pleiotropy, except for CAD where the association was attenuated after adjusting for height. We also found novel evidence that better lung function

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**Figure 1** The impact of forced expiratory volume in 1 s (FEV1, per SD) on cardiovascular disease and type 2 diabetes using Mendelian randomisation. *IVW, inverse variance weighting; MVMR: multivariable Mendelian randomisation (adjusted for height); WM, weighted median.

**Figure 2** The impact of forced vital capacity (FVC, per SD) on cardiovascular disease and type 2 diabetes using Mendelian randomisation. *IVW, inverse variance weighting; MVMR, multivariable Mendelian randomisation (adjusted for height); WM, weighted median.

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Au Yeung SL, et al. Thorax 2022;77:164–171. doi:10.1136/thoraxjnl-2020-215600
Respiratory epidemiology protects against stroke and type 2 diabetes, with these effects being consistent across sensitivity analyses, including adjustment for height. The positive association between lung function and atrial fibrillation in our main Mendelian randomisation is in the opposite direction to that seen for other CVD outcomes but attenuated to the null with adjustment for height. The impact of lung function on heart failure is also less clear than that seen for CAD, stroke and type 2 diabetes, as the protective effect is only evident when adjusting for height in the multivariable Mendelian randomisation. Lastly, our study also suggested that genetic susceptibility to CVD is unlikely to affect lung function.

Previous observational studies have suggested poorer FEV₁ and FVC increase CVD.¹⁻⁴ Our study suggests these observed associations are likely causal for CAD and stroke. Multiple pathways may explain the protective effect, with our study suggesting systolic blood pressure is a possible mechanism, but with weaker evidence of an effect of lung function on diastolic blood pressure. This may imply poorer lung function primarily acts on arterial stiffness,³¹ and hence may contribute to systemic hypertension. We also found better lung function associated with lower triglycerides and LDL cholesterol, lower insulin and type 2 diabetes. As previous Mendelian randomisation studies support a causal effect of hypercholesterolaemia, hyperglycaemia, type 2 diabetes and higher insulin on CAD,³²⁻³⁵ these are possibly also mediators of the effect of lung function on CAD. With the exception of an inverse association with triglycerides, we did not

Figure 3  The impact of forced expiratory volume in 1 s (FEV₁, per SD) on cardiovascular risk factors using Mendelian randomisation. *IVW, inverse variance weighting; MVMR: multivariable Mendelian randomisation (adjusted for height); WM, weighted median.

Figure 4  The impact of forced vital capacity (FVC, per SD) on cardiovascular risk factors using Mendelian randomisation. *IVW, inverse variance weighting; MVMR: multivariable Mendelian randomisation (adjusted for height); WM, weighted median.
Respiratory epidemiology

find strong evidence for a causal effect of lung function on lipids. Our study also indicated the importance of height as a horizontal pleiotropic effect, given the associations with CAD were attenuated in the multivariable Mendelian randomisation. Nevertheless, further investigation would be needed as attenuation may reflect weak instrument bias and was sensitive to where the SNP-height estimates in the multivariable Mendelian randomisation were extracted from (GIANT in online supplemental figure 1 vs UK Biobank in online supplemental figure 5).

In our main analyses, we found evidence of a protective effect of lung function on overall, ischaemic, small vessel and large artery stroke, but not cardioembolic stroke. The underlying mechanisms may include reduced blood pressure, reduced risk of type 2 diabetes, while the role of lipid is not as clear. The lack of large GWAS with publicly available data on haemorrhagic stroke mean that we were not able to explore this outcome and it is not included in the overall stroke outcome. Sensitivity analyses were largely supportive of these causal effects, apart for MR-Egger for some stroke subtypes. Although the estimates for stroke were smaller than those for CAD and CIs were wider, the apparently weaker effect of lung function on stroke (compared with that observed for CAD) could be an underestimation because of selection bias. For example, if lung function is also related to survival then those who survive to have a stroke (which tend to occur at older ages than CAD) will likely be the ones with better lung function.

In contrast to CAD and stroke, results for heart failure in the main analysis were very close to the null, which could suggest lung function is not causally related to heart failure. However, after adjusting for height, FEV\(_1\) and FVC were possibly associated with lower risk of heart failure (figures 1 and 2). Although this could be a reflection of adjustment removing possible selection bias, reasons underpinning the differences would require further investigation.

Our study, using a design that is less likely to be confounded than conventional multivariable regression, indicates a possible role of lung function on cardiovascular health. From a clinical perspective, our results support further exploration of the effectiveness of monitoring cardiovascular and type 2 diabetes risk in patients with poor lung function. They also support interventions which improve lung function, such as tobacco cessation and increased physical activity, to prevent CVD.

We have not been able to fully explore the relation of the FEV\(_1\)/FVC ratio with CVDs or its risk factors. Nevertheless, exploratory analyses, using up to 97 SNPs strongly associated with FEV\(_1\)/FVC extracted from a recent GWAS (F statistic: 144), suggested no strong evidence for an effect of FEV\(_1\)/FVC on any of the outcomes (online supplemental figures 9 and 10). However, the interpretation of the findings for FEV\(_1\)/FVC ratio is potentially more challenging given any change in the ratio may also have reflected the varying magnitude of changes of both FEV\(_1\) and FVC, which could have explained the differences with our main findings.

Although we used Mendelian randomisation which is less susceptible to confounding by key traits, such as smoking, height and socioeconomic position, there are some limitations. One of the limitations is that the validity of our study depends on the three main instrumental variable assumptions. The F-statistics...
and proportion of variation in FEV1 and FVC make a major impact of weak instrument bias on our main IVW results unlikely, which if present, would bias our estimates towards the null for majority of the outcomes. Previous studies suggested possible biases related to the use of Wald ratio to estimate causal effects for disease outcomes. However, we expected such biases would be small given the large sample sizes used. We also explored associations of instruments with confounders (e.g., smoking and height) which can constitute violation of the assumptions, where we found height as a main pleiotropic effect. Although consistent findings were observed using standard sensitivity analyses, we noticed attenuations of estimates for CAD on adjusting for height in the multivariable Mendelian randomisation. However, the degree of attenuation depends on the choice of GWAS where height instruments were extracted from (online supplemental figures 1–8), which could possibly be a reflection of weak instrument bias and warrant further investigations. Another limitation is that we were unable to explore the possibility of non-linear effects between lung function and CVD, which can only be explored in one sample Mendelian randomisation in large biobanks with individual level data. A final limitation is that we were unable to disentangle the independent effects of FEV1 and FVC on the outcomes. Whist exploratory analyses using multivariable Mendelian randomisation suggested FVC may be more relevant than FEV1 (online supplemental figures 11 and 12), these results are susceptible to weak instrument bias (conditional F statistics <2.1 for both exposures) and so should be interpreted with caution.

In conclusion, our Mendelian randomisation study provides some evidence concerning the protective role of lung function on CAD, stroke, type 2 diabetes and lower systolic blood pressure. Future studies should explore the underlying mechanisms, including the role of height in these relationships and hence help identify additional targets of intervention for CVD prevention. Future GWAS and Mendelian randomisation studies exploring causes of haemorrhagic stroke are also important, particularly for settings where haemorrhagic stroke is prevalent, such as China.

Acknowledgements Data on coronary artery disease have been contributed by CARDIoGRAMplusC4D investigators and have been downloaded from www.CARDIoGRAMplusC4D.ORG. We thank the investigators of the atrial fibrillation GWAS for providing the summary statistics, which have been downloaded from http://csg.sph.umich.edu/willer/public/afib2018/. We thank MEGASTROKE for providing the summary statistics for stroke, which have been downloaded from http://www.megastroke.org/index.html. The MEGASTROKE project received funding from sources specified at http://www.megastroke.org/acknowledgements.html. The list of authors in the MEGASTROKE Consortium can be found in the Supplemental materials. We thank HERMES Consortium for providing the summary statistics for heart failure, which have been downloaded from http://www.broadcdri.org/informational/data. We thank GLGC for providing summary statistics for lipids, which have been downloaded from http://csg.sph.umich.edu/willer/public/cliplips2013/. We thank MAGIC for providing summary statistics for glycemic traits, which have been downloaded from https://www.magicinvestigators.org. We thank DIAGRAM for providing the summary statistics for type 2 diabetes, which have been downloaded from https://www.diagрам-consortium.org. We thank GIANT consortium for providing the summary statistics for body mass index and height, which have been downloaded from https://portals.broadinstitute.org/collaboration/giant/index.php/ GIANT_consortium_data_files. We thank SGAC for providing the summary statistics for years of education attainment, which have been downloaded from https://www.thessgac.org/data. We thank GSCAN for providing the summary statistics for alcohol and cigarette use phenotypes, which have been downloaded from https://conservancy.umn.edu/handle/11299/201564. Data on FEV1, and FVC, systolic and diastolic blood pressure were extracted from summary genome-wide association study results in the UK Biobank, available in the IEU GWAS database [https://great.anci.ac.uk]. We thank Mr KN Wong and VAC Wong for summarising the descriptive information regarding the GWAS used in this study. We thank Dr Eleanor Sanderson for helpful discussion concerning the multivariable Mendelian randomisation.

Contributors SLAY designed the study, wrote the analysis plan and interpreted the results. SLAY undertook analyses with feedback from MCB, DAL and CMS. SLAY wrote the first draft of the manuscript with critical feedback and revisions from MCB, DAL and CMS. All authors gave final approval of the version to be published. SLAY had primary responsibility for final content.

Funding MCB is supported by MRC Skills Development Fellowship (MR/P014054/1). MCB and DAL’s contribution to this study is supported by the British Heart Foundation (AA18/7/34219) and MCB and DAL work in a Unit receives funding from the University of Bristol and UK Medical Research Council (MRC) (MC_UU_000116).

Competing interests DAL receives support from several national and international government and charitable research funders, as well as from Medtronic Ltd and Roche Diagnostics for research unrelated to that presented here. All other authors declared they have no conflict of interest, financial or otherwise.

Patient consent for publication Not required.

Ethics approval This study only used publicly available summary statistics from relevant genome-wide association studies (GWAS) and UK Biobank and hence no ethics approval was required. Respective ethics approval have been obtained by the GWAS and the UK Biobank investigators.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. All data used to generate the results can be found in the URLs given in the acknowledgement, online supplemental tables and references.

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