Genetic evidence strongly supports managing weight and blood pressure in addition to glycemic control in preventing vascular complications in people with type 2 diabetes

Type 2 diabetes and vascular complications

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Twitter Summary: Genetic evidence that managing weight and blood pressure may be as important as glycemic control in preventing vascular complications in type 2 diabetes.

Objective:

To investigate the causal association of type 2 diabetes and its components on the risk of vascular complications independent of shared risk factors obesity and hypertension, and to identify the main driver of this risk.

Study design and method

We conducted Mendelian randomization using independent genetic variants previously associated with type 2 diabetes, fasting glucose, HbA1c, fasting insulin, BMI, and systolic blood pressure as instrumental variables. We obtained summary-level data for 18 vascular diseases (15 for type 2 diabetes) from FinnGen and publicly available genome-wide association studies as our outcomes. We conducted univariable and multivariable Mendelian randomization, in addition to sensitivity tests to detect and minimize pleiotropic effects.

Results

Univariable Mendelian randomization analysis showed that type 2 diabetes was associated with 9 of 15 outcomes, BMI and systolic blood pressure with 13 and 15 of 18 vascular outcomes, fasting insulin with 4, and fasting glucose with 2. No robust association was found for HbA1c instruments. Adjusting for correlated traits in the multivariable test, BMI and systolic blood pressure maintained consistent causal effects, while five associations with type 2 diabetes (chronic kidney disease, ischemic heart disease, heart failure, subarachnoid haemorrhage, and intracerebral haemorrhage) were attenuated to null.

Conclusion

Our findings add strong evidence to support the importance of BMI and systolic blood pressure in the development of vascular complications in people with type 2 diabetes. Such findings strongly support the need for better weight and blood pressure management in type 2 diabetes, independent of glucose lowering, to limit important complications.

Article Highlight:

- The effectiveness of tight glycemic control vascular complications in trials has been modest. Shared risk factors may also be involved in increasing the risk of complications.
- We aimed to determine whether genetically predicted type 2 diabetes increases the risk of vascular complications independently of BMI and systolic blood pressure.
- We found genetic evidence that type 2 diabetes has at best modest independent effect on the risk of vascular complications when shared risk factors are accounted for.
- These data highlight a need for potentially greater focus on promoting healthy weight and blood pressure management to improve outcomes in this population.

Introduction

The link between type 2 diabetes and vascular complications has been subject to extensive research by both observational and randomized control trials studies with somewhat mixed findings. Multiple guidelines suggest tight glycaemic control is critical to the protection against macrovascular and microvascular complications associated with diabetes[1]. However, findings from randomized control trials show less significant benefits from tight glycaemic control than many expected, at least in the short to medium term [2].

The complex and heterogenic nature of type 2 diabetes makes it hard to reach a clear-cut conclusion regarding its role in the development of vascular complications. For instance, type 2 diabetes affects a broad range of organs within the human body and despite the mounting evidence provided by observational studies indicating its role in the development of several macrovascular and microvascular complications, to some extent, the effect of several tightly correlated risk factors, such as obesity and hypertension, makes the role of type 2 diabetes and glycaemic traits in the development of those complications uncertain[3]. Another source of complexity is the heterogeneity in underlying mechanisms. Type 2 diabetes may occur due to resistance to insulin actions in the insulin-sensitive tissues such as the liver, muscles and adipose tissues combined with insufficient insulin secretion as a result of β-cells dysfunction, both occurring in the early stages of the disease[4]. Hence, observational studies cannot determine relative contributions of differing risk pathways to diabetes complications. Also, excess adiposity and higher blood pressure[5] are known to predate the diagnosis of diabetes, sometimes by many years, with excess adiposity an upstream pathogenic factor for diabetes development in many[6]. Plus, there is the issue of aggregated weight exposure which could drive many vascular complications[7], a concept easily overlooked even though most may have many years of excess adiposity before diagnosis of type 2 diabetes.

In this study, we employed Mendelian randomisation, a method that leverages genetic variation to establish causal relationships between modifiable risk factors and outcomes[8], to investigate the causal association between type 2 diabetes and a range of macrovascular and microvascular complications. To elucidate the specific contribution of type 2 diabetes and shared risk factors to these associations, we conducted multivariable Mendelian randomization, adjusting for the genetically predicted effect of BMI and systolic blood pressure. We additionally looked at causal effects of higher HbA1c, fasting insulin and fasting glucose in their non-diabetic range against the risk of same vascular complications. A better

understanding of the causal risk factor driving vascular complications in individuals with type 2 diabetes and those with pre-diabetes could inform the development of targeted prevention strategies.

Materials and Methods

Study design

We designed a Mendelian randomization study to dissect the causal role of type 2 diabetes in vascular complications (supplementary Fig.1). Mendelian randomizationis is a statistical method that uses genetic variants as instrumental variables to estimate the causal effect of an exposure (e.g., type 2 diabetes) on an outcome (e.g., vascular disease). Since genetic variants are randomly assorted at conception, this method can significantly reduce confounding and reverse causation.

We used genetic instruments for type 2 diabetes, three glycaemic traits in their non-diabetic range (fasting glucose, HbA1c, and fasting insulin), BMI and systolic blood pressure as our exposures and 18 vascular complications as outcomes in a univariable Mendelian randomization model (supplementary Fig.1A). We excluded diabetic nephropathy, neuropathy and retinopathy from the analysis of type 2 diabetes and in multivariable Mendelian randomizationmodels to avoid collider bias as these complications follow the diagnosis of type 2 diabetes. Since obesity and hypertension are shared risk factors and can confound the association between type 2 diabetes and vascular complications, we performed multivariable Mendelian randomization to try to exclude the confounding effect of BMI and systolic blood pressure (supplementary Fig.1B). The causal effects estimated by multivariable Mendelian randomization differs from those estimated by the univariable method. Univariable Mendelian randomization estimates the total causal effect of exposure on an outcome, while the multivariable method estimates the independent direct causal effect of each exposure on the outcome of interest[9].

Genetic instrument selection:

To construct a genetic instrument for type 2 diabetes, we used the recent genome-wide association study (GWAS) of type 2 diabetes[10] (74,124 cases and 824,006 controls). For glycaemic traits fasting glucose, fasting insulin, and HbA1c, we obtained the genetic instruments from the Meta-Analysis of Glucose and Insulin-related Traits Consortium (MAGIC) (281,416 non-diabetic individuals)[11]. The association tests for fasting glucose and fasting insulin in the GWAS were adjusted for BMI, which may produce collider bias. Therefore, to ensure that the issue of collider bias was addressed, we performed a sensitivity

analysis using instruments obtained from BMI-unadjusted GWAS (140,595 and 98,210 non-diabetic individuals for fasting glucose and fasting insulin, respectively)[12]. For BMI instrument, we used data from the GWAS of 694,649[13], and for systolic blood pressure from the GWAS of 757,601 individuals[14]. All GWAS were in individuals of European ancestry.

To create the genetic instruments, we first selected variants associated with each exposure ($p<5x10^{-8}$) and then identified a set of independent variants for each exposure using linkage disequilibrium pruning ($r^2>0.001$) within a window of 10Mb using unrelated white Europeans from the 1000 genomes reference panel. The summary of each exposure GWAS, including definitions, numbers of cases and controls and covariates adjusted for in the GWAS model can be found in Supplementary Table 1.

For multivariable Mendelian randomization, we used genetic variants from the same GWAS of exposure data and divided them into four instruments. Each instrument included genetic variants independently associated with BMI and systolic blood pressure in addition to one of type 2 diabetes, fasting glucose, HbA1c and fasting insulin. The purpose of this step was to understand the causal effect of each exposure after adjusting for the genetically predicted higher BMI and systolic blood pressure.

Outcome data sources

We selected a broad range of diabetes associated cardiovascular (including stroke, heart failure, and atrial fibrillation) and microvascular (including chronic kidney disease, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, and retinal vascular occlusion) outcomes. We obtained genome-wide summary level data for 18 outcomes from FinnGen consortium release 6 (https://www.finngen.fi/en/). For 6 outcomes (ischemic stroke[15], ischemic heart disease[16], heart failure[17], atrial fibrillation[18], myocardial infarction[19], and chronic kidney disease[20]), data from another independent published GWAS was available. For these 6 outcomes we meta-analysed results from FinnGen and published GWAS. All outcomes were obtained from the MRC Integrative Epidemiology Unit at the university of Bristol GWAS database (available from https://gwas.mrcieu.ac.uk/) to ensure the homogeneity of study population and accuracy of the obtained result. Detailed information on outcome data sources (e.g., outcome definitions, numbers of cases and controls and covariates adjusted for in the GWAS model) can be found in Supplementary Table 2.

Statistical Analysis

We used different Mendelian randomization methods. A robust Mendelian randomization study must satisfy three assumptions. First, the relevance assumption where the instrument variables must be associated with the exposure. Second, the independence assumption which states that instrument variable must have no association with a confounder. Third, the exclusion restriction assumption that suggest that the relation between the instrument variable and the outcome should only be through the exposure. Invalidation of any of those three core assumptions could invalidate the Mendelian randomization. Therefore, the three assumptions must be evaluated in advance[21].

For the main analysis, we used Inverse Variance Weighted method (IVW). The IVW method combines the Wald ratio estimates of each SNP into one causal estimate. However, the IVW result could be affected by instrumental variable bias or horizontal pleiotropy. An instrumental variable with weaker association with the exposure tends to produce bias in the direction of the observational confounded association proportional to the strength of the association. On the other hand, horizontal pleiotropy occurs when an instrument variable has direct effect on the outcome that is bypassing the exposure via a different pathway to the exposure, violating Mendelian randomization's third assumption. Therefore, we used MR-Egger as a method of sensitivity test and for determining presence of horizontal pleiotropy based on Egger intercept in addition to weighted median, simple mode, and weighted mode.

For the estimation of the independent effect of each exposure, we used multivariable Mendelian randomization (MVMR) IVW method. This method utilizes several phenotypes as one exposure into the model. Since type 2 diabetes, BMI and systolic blood pressure are correlated, we created a model that includes all these three exposures to identify which one drives the risk of vascular complications.

All Mendelian randomization analysis were performed using R (version 4.2.2). The univariable and multivariable Mendelian randomization were conducted using "TwoSampleMR" package[22]. We used "metafor" package for meta-analysis of MR results from FinnGen and published GWAS.

We used Benjamini-Hochberg–adjusted *P* value (BHP) to classify significant causal associations (BHP < 0.05). Those associations with IVW p-value < 0.05 and BHP > 0.05 are presented as suggestive associations.

Data and Resource Availability

All data used in this paper are accessible through *ieu* open gwas project database, available at (https://gwas.mrcieu.ac.uk/), and FinnGen R6 release available at (https://www.finngen.fi/en/access_results). All data generated in this study are included in the published article and its online supplementary files.

Results

To conduct univariable Mendelian randomization, we selected 186, 70, 75, 38, 456 and 543 genetic variants associated with type 2 diabetes, fasting glucose, HbA1c, fasting insulin, systolic blood pressure and BMI, respectively, as instrumental variables. The F-statistics for these instrument were between 51 and 122 indicating the instrument strength[23] (supplementary table 3).

The causal effect of type 2 diabetes on risk of vascular complications

Genetically predicted type 2 diabetes was associated with 9 of the 15 cardiovascular and microvascular outcomes including ischemic stroke, ischemic heart disease, heart failure, myocardial infarction, chronic kidney disease, peripheral atherosclerosis and peripheral artery disease (Fig. 1, supplementary table 4). There was also a suggestive protective effect against aortic aneurysm (odds ratio (OR) 0.91; 95% confidence interval (CI) [0.85-0.99]; p-value = 0.024) (Fig.1, supplementary Fig.2, supplementary table 4). MR-Egger sensitivity analysis indicated no evidence of horizontal pleiotropy (supplementary table 5). The effects from all the sensitivity tests were consistent with the IVW estimates (supplementary table 6). After adjusting for the genetically predicted effect of BMI and systolic blood pressure in the multivariable Mendelian randomization test, genetically predicted type 2 diabetes lost its effect on chronic kidney disease, ischemic heart disease, heart failure, subarachnoid haemorrhage, and intracerebral haemorrhage. However, an association with a diluted effect size remained with ischemic stroke, myocardial infarction, while the association and the effect size with peripheral atherosclerosis and peripheral artery disease remained unchanged (Fig.1, supplementary table 7).

Genetically predicted higher BMI was associated with higher risk of 13 out of 18 cardiovascular and microvascular diseases, including ischemic stroke, ischemic heart disease, diabetic retinopathy, diabetic nephropathy and diabetic neuropathy. Outcomes for which we found no evidence of a causal association included retinal haemorrhage, retinal vascular occlusion, subarachnoid haemorrhage, cerebral aneurysm, non-ruptured and intracerebral haemorrhage (Fig. 1, supplementary Fig.3, supplementary table 8). These effects were consistent across all sensitivity test (supplementary table 9) and we found no evidence of horizontal pleiotropy from the MR-Egger intercept (supplementary table 10). In the multivariable model, adjusting for the genetically predicted effect of type 2 diabetes and

systolic blood pressure removed association with peripheral artery disease (Fig.1, supplementary table 7), but not other outcomes.

Genetically predicted higher systolic blood pressure was associated with higher risk of 15 out of the 18 vascular outcomes, including ischemic stroke, cerebral aneurysm, ischemic heart disease and myocardial infarction (Fig.1, supplementary Fig.4, supplementary table 11). These effects were consistent across all sensitivity test (supplementary table 12), and we found no evidence of horizontal pleiotropy from the MR-Egger intercept (supplementary table 13). Adjusting for the genetically predicted effect of BMI and type 2 diabetes removed the association with pulmonary embolism (Fig.1, supplementary table 7) and attenuated the effect for chronic kidney disease, heart failure, ischemic heart disease, subarachnoid haemorrhage and intracerebral haemorrhage towards the null.

The causal effect of higher levels of glycaemic traits in their normal range on risk of vascular complications

One mmol/l increase of genetically predicted fasting glucose was associated with higher risk of ischemic heart disease (OR 1.26 [1.12-1.41], BHP= 2 $x10^{-03}$) and higher risk of diabetic nephropathy (OR 1.98 [1.35-2.91], BHP= 8 $x10^{-3}$) There was suggestive evidence of association with diabetic retinopathy (1.36 [1.06-1.75]), peripheral atherosclerosis (1.68 [1.18-2.38]), and peripheral artery disease (1.57 [1.15-2.16]); (Fig. 2, supplementary Fig.5, supplementary table 14). These effects were consistent across all sensitivity test (supplementary table 15), and we found no evidence of horizontal pleiotropy from the MR-Egger intercept (supplementary table 16). In the multivariable model, adjusting for the genetically predicted effect of BMI and systolic blood pressure, the effect on ischemic heart disease was attenuated towards the null, while the suggestive association with peripheral atherosclerosis and peripheral artery disease remained unchanged (Fig. 2). Adjusting for the genetically predicted effect of fasting glucose in the multivariable model did not change the associations between BMI or systolic blood pressure and vascular outcomes

There was no multiple testing adjusted evidence for an association between HbA1c but we observed suggestive association between 1% increase in genetically predicted HbA1c and higher risk of ischemic heart disease (1.26 [1.04-1.51]), diabetic retinopathy (1.54 [1.14-2.07]) and diabetic nephropathy (1.87 [1.16-3.02]) (Fig.3, supplementary Fig.6, supplementary table 17). These effects were consistent across all sensitivity test (supplementary table 18) and we found no evidence of horizontal pleiotropy from the MR-Egger intercept (supplementary table

19). After adjusting for the genetically predicted effect of BMI and systolic blood pressure in the multivariable model, genetically predicted HbA1c suggestive association with ischemic heart disease remained plus a new suggestive association with myocardial infarction (1.26 [1.05-1.67]). Adjusting for the genetically predicted effect of HbA1c in the multivariable model did not change the associations between BMI or systolic blood pressure and vascular outcomes.

One pmol/l increase in genetically predicted fasting insulin was associated with higher risk of ischemic heart disease (OR 1.88 [1.45-2.44]), myocardial infarction (2.06 [1.55-2.73]), diabetic nephropathy (3.86 [1.87-7.98]), and diabetic neuropathy (4.76 [1.85-12.26]) (Fig.4, supplementary Fig. 7, supplementary table 20). There was also evidence of suggestive association with higher risk of ischemic stroke (1.35 [1.05-1.75]), chronic kidney disease (1.63 [1.15-2.31]), peripheral atherosclerosis (2.60 [1.32-5.13]), and peripheral artery disease (2.41 [1.31 - 4.44]) (Fig.4, supplementary Fig. 7). These effects were consistent across all sensitivity tests (supplementary table 21) and we found no evidence of horizontal pleiotropy from the MR-Egger intercept test (supplementary table 22). Adjusting for the genetically predicted effect of BMI and SBP in the multivariable model, genetically predicted fasting insulin lost its association with ischemic heart disease, while its association with myocardial infarction was downgraded towards suggestive as the effect size attenuated towards the null (Fig. 4). Adjusting for the genetically predicted effect of fasting insulin in the multivariable model did not change the associations between BMI or systolic blood pressure and vascular outcomes.

Discussion

We conducted a Mendelian randomization study to try to investigate the causal association between type 2 diabetes, BMI and systolic blood pressure with cardiovascular and microvascular complications. Type 2 diabetes, BMI and systolic blood pressure genetic instruments were associated with most of the outcomes tested in a univariable analysis. However, in a multivariable model the associations between genetically predicted type 2 diabetes and several of the vascular outcomes attenuated to the null, while the majority of associations between genetically determined BMI and systolic blood pressure remained significant. To understand the causal role of 'glycaemic' traits in their non-diabetic range, we followed the same approach. Genetically predicted fasting insulin showed the most significant causal association with vascular outcomes in the univariable model, but notably all causal effects disappeared when corrected for the effect of genetically predicted higher BMI and systolic blood pressure.

Type 2 diabetes and vascular complications

Our findings are consistent with previous observational[24,25] and Mendelian randomization studies[3,26] highlighting type 2 diabetes as a causal risk factor for most of the common cardiovascular and microvascular complications including peripheral artery disease, peripheral atherosclerosis, myocardial infarction, heart failure, chronic kidney disease, ischemic stroke and ischemic heart disease. We additionally provided evidence that the causal role of type 2 diabetes in mechanisms that lead to these complications is independent of higher BMI and systolic blood pressure. The association with chronic kidney disease, heart failure, ischemic heart disease, subarachnoid haemorrhage, and intracerebral haemorrhage attenuated to the null after adjusting for the genetically predicted effect of BMI and systolic blood pressure suggesting that the association reported in the observational studies for the link between type 2 diabetes and these complications may largely be mediated through obesity and hypertension.

Our results indicated a suggestive protective effect of type 2 diabetes against aortic aneurysm consistent with observations from animal models and human studies suggesting diabetes exerts protective effect against aortic aneurysms[27]. There was no evidence of such effect against cerebral aneurysm. We also found no evidence of a causal association between genetically predicted type 2 diabetes and atrial fibrillation consistent with findings reported

by previous Mendelian randomization studies[3,28]. By contrast, BMI instruments were strongly linked to this outcome.

Glycaemic traits and vascular complications

Hyperglycaemia has long been linked to the progression of diabetes associated microvascular complications and several studies recommended intensive glycaemic control as protective approach[29]. We did not find any robust evidence for the causal role of hyperglycaemia in its normal range and higher risk of vascular complication. It is known that risk for many complications accelerates meaningfully only once glucose or HbA1c levels move into the diabetes range[30]. We did not find any association between fasting glucose and chronic kidney disease consistent with previous studies. These findings suggest the impact of glucose on chronic kidney disease may be a threshold effect with impact only evidence once frank diabetes develops.

Our findings are consistent with a previous report on causal link between fasting insulin and increased risk of coronary artery disease, ischemic stroke and myocardial infarction[31]. Observational studies have generally not focused on the association of fasting insulin and insulin resistance with cardiovascular and microvascular complications because of the general assumption that hyperglycaemia is the main reason for the development of those complications. However, our genetic findings suggest that the positive association of fasting insulin as an independent risk factor is greater than that of hyperglycaemic markers. Of course, this does not mean insulin per se is harmful – the ORIGIN trial[32] did not suggest harm for basal insulin in diabetes - but the factors that lead to higher insulin levels (so tissue insulin resistance due to ectopic fat) may be harmful, or else related factors such as dyslipidaemia or lower activity levels may be relevant.

BMI, systolic blood pressure and vascular complications

In the univariable Mendelian randomization, genetically predicted higher BMI was causally associated with the majority of the vascular complications including diabetic nephropathy, diabetic retinopathy and diabetic neuropathy.

In the multivariable Mendelian randomization we excluded (retinopathy, nephropathy and neuropathy) to avoid bias. The associations remained significant for 8 out of 13 outcomes after adjusting for the genetically predicted effect of type 2 diabetes and systolic blood

pressure, suggesting an independent causal role for higher BMI in diabetes related vascular complications but the association was lost for peripheral artery disease and peripheral atherosclerosis. These results are consistent with those reported previously[33], but in contrast, we did not find an independent causal effect of BMI on subarachnoid haemorrhage. These results are also consistent with the fact that many individuals will have had excess adiposity for a long period of time before frank type 2 diabetes develops, such that overall exposure to excess adiposity would have been extensive, operating over many years to accelerate the risk of many adiposity-sensitive complications, before and after diabetes develops[7]. This is an important fact given that chronic complications like chronic kidney disease take time to develop from aggregated exposure to risk factors such as excess adiposity[34]. Interestingly, in a recently reported 10 year observational follow-up of a trial comparing two forms of bariatric surgery with medical treatment in diabetes, the difference in weights by around 20kg in surgery recipients versus medical treated participants for around 10 years was associated with a remarkable apparent difference in macro/microvascular complication rates (6% versus 71%)[35]. Of course, this was a small study and the results of the ongoing SURPASS CVOT in over 12,000 patients with type 2 diabetes will be interesting given it is testing the cardiovascular benefits of one incretin-based therapy (Tirzepatide) that yields around a 10kg greater weight loss than another incretin-based therapy (Dulaglutide)[36]. This trial should report in 2-years' time.

Genetically predicted higher systolic blood pressure was associated with majority of the outcomes. All these associations remained significant when we corrected for the genetically instrumented effect of type 2 diabetes and BMI. Our findings support those reported by various previous observational studies which suggested that cardiovascular complications are common among people with type 2 diabetes and hypertension, while microvascular complications risk is induced by hypertension[37]. An independent study investigated the causal effect of hypertension on the risk of cardiovascular diseases and found that 10 mm/Hg increase in genetically predicted systolic blood pressure increased the risk of total cardiovascular disease (OR 1.32 [95% CI, 1.25-1.40]), ischemic heart disease (OR 1.33, [1.24-1.41]) and stroke (OR 1.35, [1.24-1.48])[38], which is in line with the findings of our study. These findings also fit with evidence for the benefit of blood pressure reduction in diabetes on many vascular complications[39].

Evidence from Non-European populations:

Limited availability of genome-wide association data has resulted in a scarcity of Mendelian randomization studies conducted on non-European populations. Nevertheless, a notable Mendelian randomization study examined 45 risk factors for chronic kidney disease in both European and East Asian populations[40]. The results revealed that genetically predicted type 2 diabetes was associated with an increased risk of chronic kidney disease in European, Japanese, and Chinese populations; while genetically predicted BMI was found to be associated with an increased risk of chronic kidney disease in European and Japanese populations, but not in the Chinese population.[40] This inconsistency may be attributed to a lack of chronic kidney disease cases among the Chinese population or potential ethnic variations[41]. Furthermore, genetically predicted systolic blood pressure was associated with chronic kidney disease in Europeans but not in the East Asian population, suggesting a potential effect based on ancestry[41]. Another study investigated the causal effect of type 2 diabetes on the risk of coronary artery disease and atrial fibrillation in the East Asian population and revealed a causal association with coronary artery disease but not with atrial fibrillation[42].

Strengths and limitations

This study covered a broad range of vascular complications associated with type 2 diabetes. We used strong instrumental variables associated with each exposure (F-statistic >10) which indicates a good strength of our genetic instruments. The novelty of our study arises from the fact that we investigated the causal effect of type 2 diabetes and glycaemic traits while looking at the mediating effect of the shared risk factors: BMI and systolic blood pressure appear to be lacking. We included genetic instruments for type 2 diabetes, BMI and systolic blood pressure in a multivariable model to adjust for the genetically predicted independent effect of each phenotype and try to help answer which component drives the risk of vascular complications. Our study had some limitations. First, our source of data was restricted to individuals of European ancestry, which makes the generalisability of our findings to other ethnic groups unclear. Given the excess risk of type 2 diabetes and vascular complications in non-Europeans, we hope the availability of non-European GWAS will make it possible to follow up our findings. Second, the pleiotropic effect of genetic variants we used as instrument could violate the Mendelian randomization assumption. To address this, we performed various sensitivity analyses and adjusted for the correlation between type 2 diabetes, BMI and systolic

blood pressure in our multivariable Mendelian randomization test. Third, we had data from two different source, FinnGen and an independent published GWAS, for only 6 out of 19 vascular outcomes where the same ICD definition was used to define cases and controls. For the other 13 outcomes where results were only available in FinnGen, it would be necessary to validate the findings in non-Finnish populations. Finally, our work on glycaemic trait instruments was necessarily restricted to the non-diabetes range and elevated glucose beyond the diabetes diagnostic thresholds accelerates vascular and kidney harm over many years, as is seen in patients living with type 1 diabetes but without obesity. This means these data are somewhat limited.

Conclusion:

We provided genetic evidence for causal effects of type 2 diabetes, BMI and systolic blood pressure on risk of vascular complications. Our findings provide evidence that even though tight glycaemic control is considered important for lowering the risk of vascular complications, such an approach alone is unlikely to be enough. Rather, additional weight and blood pressure management should have meaningful impacts to lower the risk of multiple complications, including heart failure, important arrythmias and chronic kidney disease in those living with type 2 diabetes.

Acknowledgement

The authors acknowledge the participants and investigators of the FinnGen study.

Funding

H.Y. is funded by Diabetes UK RD Lawrence fellowship (grant 17/0005594). N.S. is supported by the British Heart Foundation Research Excellence Award (RE/18/6/34217).

Conflict of interest

NS has received grant and personal fees from AstraZeneca, Boehringer Ingelheim, and Novartis; grant from Roche Diagnostics; and personal fees from Abbott Laboratories, Afimmune, Amgen, Eli Lilly, Hanmi Pharmaceuticals, Merck Sharp & Dohme, Novo Nordisk, Pfizer, and Sanofi outside the submitted work.

Data Access and Responsibility: Guarantor Statement

Hanieh Yaghootkar is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior presentation:A prior presentation in abstract form was submitted to the Diabetes UK 2023 conference.

Author Contributions and Guarantor Statement

A.A. analysed the data. H.Y. designed the study. A.A., H.Y. and N.S. wrote the manuscript. H.A. and F.D. reviewed and edited the manuscript. H.Y. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure legends

Figure 1. Comparison of the causal effect of type 2 diabetes, BMI and systolic blood pressure from univariable (UVMR) and multivariable (MVMR) Mendelian randomization tests. This plot shows the total causal effect of type 2 diabetes, body mass index and systolic blood pressure on 15 and 18 vascular complications respectively, and the independent causal effect of each exposure after adjusting for the genetically predicted effect of other two. The colour and intensity of the colour corresponds to the direction and value of Z-scores (from IVW test). Benjamini-Hochberg p-values < 0.05 are given. The star symbol indicates when meta-analysed results from FinnGen and a published GWAS were available.

Figure 2. Comparison of the causal effect of fasting glucose, BMI and systolic blood pressure from univariable (UVMR) and multivariable (MVMR) Mendelian randomization tests. This plot shows the total causal effect of fasting glucose, body mass index and systolic blood pressure on 18 vascular complications, and the independent causal effect of each exposure after adjusting for genetically predicted effect of the other two. The colour and intensity of the colour corresponds to the direction and value of Z-scores (from IVW test). Benjamini-Hochberg p-values < 0.05 are given. The star symbol indicates when meta-analysed results from FinnGen and a published GWAS were available.

Figure 3. Comparison of the causal effect of HbA1c, BMI and systolic blood pressure from univariable (UVMR) and multivariable (MVMR) Mendelian randomization tests. This plot shows the total causal effect of HbA1c, body mass index and systolic blood pressure on 18 vascular complications, and the independent causal effect of each exposure after adjusting for genetically predicted effect of the other two. The colour and intensity of the colour corresponds to the direction and value of Z-scores (from IVW test). Benjamini-Hochberg p-values < 0.05 are given. The star symbol indicates when meta-analysed results from FinnGen and a published GWAS were available.

Figure 4. Comparison of the causal effect of fasting insulin, BMI and systolic blood pressure from univariable (UVMR) and multivariable (MVMR) Mendelian randomization tests. This plot shows the total causal effect of fasting insulin, body mass index and systolic blood pressure on 18 vascular complications, and the independent causal effect of each exposure after adjusting for the genetically predicted effect of the other two. The colour and intensity of the colour corresponds to the direction and value of Z-scores (from

IVW test). Benjamini-Hochberg p-values < 0.05 are given. The star symbol indicates when meta-analysed results from FinnGen and a published GWAS were available.