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Lean mass, grip strength and risk of type 2 diabetes: a bi-directional Mendelian randomisation study

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Abstract

Aims/hypothesis Muscle mass and strength may protect against type 2 diabetes as a sink for glucose disposal. In randomised controlled trials, resistance training improves glucose metabolism in people with the metabolic syndrome. Whether increasing muscle mass and strength protects against diabetes in the general population is unknown. We assessed the effect of markers of muscle mass and strength on diabetes and glycaemic traits using bi-directional Mendelian randomisation.

Methods Inverse variance weighting estimates were obtained by applying genetic variants that predict male lean mass, female lean mass and grip strength, obtained from the UK Biobank GWAS, to the largest available case–control study of diabetes (DIAbetes Genetics Replication And Meta-analysis [DIAGRAM]; $n = 74{,}124$ cases and 824,006 controls) and to a study of glycaemic traits (Meta-Analyses of Glucose and Insulin-related traits Consortium [MAGIC]). Conversely, we also applied genetic variants that predict diabetes, HbA_{1c}, fasting glucose, fasting insulin and HOMA-B to UK Biobank summary statistics for genetic association with lean mass and grip strength. As sensitivity analyses we used weighted median, Mendelian randomisation (MR)-Egger and Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) and removed pleiotropic SNPs.

Results Grip strength was not significantly associated with diabetes using inverse variance weighting (OR 0.72 per SD increase in grip strength, 95% CI 0.51, 1.01, $p = 0.06$) and including pleiotropic SNPs but was significantly associated with diabetes using MR-PRESSO (OR 0.77, 95% CI 0.62, 0.95, $p = 0.02$) after removing pleiotropic SNPs. Female lean mass was significantly associated with diabetes (OR 0.91, 95% CI 0.84, 0.99, $p = 0.02$) while male lean mass was not significant but directionally similar (OR 0.94, 95% CI 0.88, 1.01, $p = 0.09$). Conversely, diabetes was inversely and significantly associated with male lean mass (β −0.02 SD change in lean mass, 95% CI −0.04, −0.00, $p = 0.04$) and grip strength (β −0.01, 95% CI −0.02, −0.00, $p = 0.01$).

Conclusions/interpretation Increased muscle mass and strength may be related to lower diabetes risk. Diabetes may also be associated with grip strength and lean mass. Muscle strength could warrant further investigation as a possible target of intervention for diabetes prevention.

Keywords Body composition · Diabetes mellitus · Grip strength · Hand strength · Lean mass · Mendelian randomisation · Muscle · Type 2 diabetes

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Abbreviations

DIAGRAM	DIAbetes Genetics Replication And Meta-analysis
GWAS	Genome-wide association study
InSIDE	Instrument Strength Independent of Direct Effect
MAGIC	Meta-Analyses of Glucose and Insulin-related traits Consortium
MR-Egger	Mendelian randomisation-Egger
MR-PRESSO	Mendelian Randomization Pleiotropy RESidual Sum and Outlier

Research in context

What is already known about this subject?

- Resistance training improves glucose metabolism in people with the metabolic syndrome but the protective effect of muscle mass and strength on diabetes in the general population is unknown

What is the key question?

- What are the effects of markers of muscle mass and strength on diabetes and glycaemic traits in the general population?

What are the new findings?

- In a bi-directional Mendelian randomisation study, higher grip strength was significantly associated with a decreased risk of diabetes

- Higher female lean mass was significantly associated with decreased risk of diabetes, while the association for male lean mass was not significant but was directionally similar

- Conversely, diabetes was significantly associated with lower male lean mass and lower grip strength

How might this impact on clinical practice in the foreseeable future?

- Muscle strength could warrant further investigation as a possible target of intervention for improving glycaemic traits and preventing diabetes

Introduction

Type 2 diabetes is increasingly common globally, particularly in Asia, where rates of diabetes are high even in populations with comparatively low rates of obesity [1], suggesting the role of factors beyond adiposity. Low birthweight is a well-established cause of diabetes [2], but is difficult to modify, meaning that the consequences of low birthweight might be more effective and timely targets of intervention. Low birthweight is also associated with low muscle mass [3], which is modifiable and could mediate the effect of birthweight on diabetes. Muscle may act as a sink for glucose disposal [4], and muscle mass is inversely associated with diabetes observationally [5]. However, these observational studies could be confounded by many factors including health status, exercise habits and height, resulting in spurious associations [4, 5]. Randomised controlled trials have shown some benefits of resistance training for glucose metabolism in people with the metabolic syndrome [6]. However, these randomised controlled trials are primarily designed to investigate the therapeutic effects of resistance training in people with poor glucose metabolism or diabetes, rather than to assess whether muscle mass and strength are protective against diabetes in the general population.

In this situation, Mendelian randomisation studies may provide evidence to guide the search for effective interventions for preventing diabetes in the general population. Mendelian randomisation, as an instrumental variable analysis with genetic instruments, uses predicted levels of exposure experienced by an individual [7]. Given that genetic makeup is randomly allocated at conception, genotype is likely to be independent of the factors that may confound observational studies and can distinguish symptoms from causes (i.e. avoid reverse causality) [8]. Mendelian randomisation studies could be thought of as comparable with randomised controlled trials with random assortment of genotypes acting as a randomisation process to allocate individuals to different levels of exposure [8]. Specifically, we used a two-sample Mendelian randomisation design obtaining summary statistics for SNPs predicting exposure and applying them to summary statistics from a GWAS of the outcomes [9]. The use of a two-sample design has several advantages, such as limiting bias due to the 'winner's curse' [10]. The use of summary statistics from consortia also has the advantage of increased statistical power [9]. No association of grip strength with diabetes has been reported from a somewhat limited Mendelian randomisation study only using two SNPs for grip strength [11]. To our knowledge, no other Mendelian randomisation study has been conducted on this topic.

In order to test the hypothesis that there is a causal role of muscle mass and strength in diabetes and glycaemic traits, as well as to assess any potential reverse causality, we used a bi-directional two-sample Mendelian randomisation study design. We assessed whether genetically higher lean mass and grip strength (as proxies of muscle mass and muscle strength) were associated with diabetes and glycaemic traits. Conversely we also assessed whether genetically higher risk of diabetes or poor glycaemic traits were associated with lean mass and grip strength.

Methods

Influence of genetically predicted lean mass and grip strength on risk of diabetes and glycaemic traits

Whole body lean mass and grip strength Genetic predictors (SNPs) of whole body lean mass (fat-free mass) for men and women, as well as grip strength (right hand for both sexes) were obtained from the most up-to-date GWAS of the UK Biobank, which included 361,194 participants recruited in the UK [12]. Briefly, the UK Biobank recruited over 500,000 participants aged 40–69 years in 2006–2010, who provided comprehensive information, underwent extensive tests and provided biological specimens [12, 13]. Lean mass was measured using bioelectrical impedance analysis. Grip strength was measured isometrically using a calibrated hydraulic hand dynamometer adjusted for hand size [14]. Sex-specific genetic associations were adjusted for the first 20 principal components, age and age^2, while sex, sex×age and sex×age^2 were additionally adjusted for in analyses of both sexes. Sample and variant quality controls, such as restriction to white British genetic ancestry, genetic variant information metric (INFO score) >0.8 and minor allele frequency >0.0001 were also applied [15].

Lean mass represents lipid-free soft tissue including muscle, body water, protein, glycerol and soft tissue mineral mass [16], which is considered to be a valid measure of skeletal muscle mass [17]. For grip strength, we used absolute rather than relative grip strength (absolute grip strength/weight) as a proxy for muscle strength, because absolute grip strength may have a higher correlation with general muscle strength than relative grip strength [18, 19].

Diabetes Genetic associations with diabetes were obtained from the DIAMANTE (European) meta-analysis of type 2 diabetes from the DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) consortium [20]. The study is a meta-analysis of diabetes case–control studies ($n = 74,124$ cases and 824,006 controls) of people of European ancestry from 32 studies (49.6% cases and 48.0% controls were women; mean age cases 55.2 years, controls 52.7 years) adjusted for study specific covariates and principal components for ancestry [20].

Glycaemic traits Genetic associations with glycaemic traits were obtained from the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) [21–23]. We used a meta-analysis of GWAS results including HbA_{1c} (in % units) for 123,665 people (European ancestry only, 61.4% women), fasting glucose for 58,074 people (51.3% women, mean age men 55.5 years; women 54.1 years), fasting insulin for 51,750 people (49.7% women, mean age men 56.9 years, women 55.3 years) and indices of insulin resistance (HOMA-IR, 55.5% women, mean age men 51.4 years; women 50.9 years) and beta cell function (HOMA-B, 55.6% women, mean age men 51.3 years; women 50.8 years) for up to 46,186 people [21, 22]. All studies were adjusted for age, sex and study specific covariates [21–23]. The GWAS of HbA_{1c} also accounted for population structure using genomic control [21]. Paired fasting glucose and insulin measures were used to calculate HOMA-B and HOMA-IR with the homeostasis model assessment [24].

Influence of genetically predicted diabetes risk and glycaemic traits on lean mass and grip strength

Diabetes and glycaemic traits Genetic predictors of diabetes, HbA_{1c} and HOMA-B were obtained from DIAGRAM and MAGIC. Significant SNPs for diabetes were extracted from the original summary statistics provided by DIAGRAM [20]. The SNPs for HbA_{1c} (European ancestry only) were obtained from published supplementary files [21]. For fasting glucose and fasting insulin, we obtained genetic associations reaching genome-wide significance ($p < 5 \times 10^{-8}$) from the GWAS by Scott et al of up to 133,010 individuals (fasting glucose: 51.6% men, mean age men 51.35 years; women 50.0 years; fasting insulin: 52.7% men, mean age men 50.7 years; women 49.2 years) adjusted for age, study site and geographical covariates, with genomic control [25].

Lean mass and grip strength Genetic associations with whole body lean mass (fat-free mass) and grip strength were obtained from genetic summary statistics of the UK Biobank [12, 13].

Selection of genetic predictors

We used all SNPs that independently (linkage disequilibrium $r^2 < 0.01$) and strongly, at genome-wide significance ($p < 5 \times 10^{-8}$), predicted an exposure. For whole body lean mass, grip strength and diabetes, we used a lower cut-off (p value = 0.05/ number of SNPs examined) for genome-wide significance to avoid false positives given the large number of SNPs in these GWASs. We computed the F statistic for SNPs on exposures to assess the overall and individual instrument strength [26–28]. If the variance explained by the SNPs (r^2) was not available, we estimated the pooled variance for calculating the r^2, as given in the electronic supplementary material (ESM) Methods. To assess the exclusion restriction assumption in Mendelian randomisation, we searched the curated SNP-to-phenotype databases PhenoScanner (Version 2; http://www.phenoscanner.medschl.cam.ac.uk/) and the GWAS Catalog (https://www.ebi.ac.uk/gwas) [29, 30], for other genome-wide significant ($p < 5 \times 10^{-8}$) phenotypes related to the chosen SNPs and their correlated SNPs, which may affect the outcomes via paths other than the exposures of interest (i.e. pleiotropic SNPs). We also used Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) to identify and remove pleiotropic SNPs [31].

Statistical analysis

In the main analysis, we present estimates with 95% CI and
p values from inverse variance weighting with multiplicative
random effects, which essentially combines the SNP-specific
Wald estimates assuming balanced pleiotropy. Wald estimates
were calculated as the SNP-outcome estimate divided by the
SNP-exposure estimate. We aligned palindromic SNPs (allele
pairs coded as A/T or C/G) on allele and effect allele frequency.
For fasting glucose, fasting insulin, HOMA-B and HOMA-IR,
we excluded palindromic SNPs before removing SNPs in link-
age disequilibrium because effect allele frequency is not given
so they cannot be unequivocally aligned with outcome SNPs.
Heterogeneity of the Wald estimates was assessed using I^2,
where a high I^2 may indicate the presence of invalid instru-
ments. Given that it is difficult to verify the exclusion restric-
tion assumption, we conducted several sensitivity analyses that
rely on different assumptions for valid estimation. A p value
<0.05 was considered to be statistically significant. No correc-
tion for multiple comparison was performed as the primary
analysis essentially focused on testing the one hypothesis that
muscle mass and strength are associated with risk of diabetes.
Power calculations were performed [32]. We assessed whether
association differed by sex from the differences in slope [33].
There were 41 tests of sex differences altogether and therefore
we applied a Bonferroni corrected significance level (0.05/
41 = 0.001) to account for multiple comparisons.

All analyses were performed using R Version 3.4.2 with the
R package (TwosampleMR) [34, 35].

Sensitivity analysis

Weighted median We present weighted median estimates
which are valid estimates when at least 50% of information
is derived from valid SNPs [36].

MR-Egger Mendelian randomisation (MR)-Egger regression
provides valid estimates even when all the SNPs are invalid,
provided that the Instrument Strength Independent of Direct
Effect (InSIDE) assumption holds [37]. An MR-Egger inter-
cept where the $p < 0.05$ indicates the presence of directional
pleiotropy. However, MR-Egger has lower statistical power
compared with inverse variance weighting and hence we fo-
cused more on the consistency of the estimate direction be-
tween MR-Egger and inverse variance weighting.

MR-PRESSO MR-PRESSO detects horizontal pleiotropy by
assessing outliers among the included SNPs contributing to
the Mendelian randomisation estimate. This method assumes
that at least 50% of the SNPs are valid SNPs, have balanced
pleiotropy and the InSIDE assumption holds. MR-PRESSO
also identifies the outlier SNPs and provides adjusted

estimates [31]. We used this method as a statistical procedure
to locate and remove possible pleiotropic SNPs.

Removal of pleiotropic SNPs We repeated the analyses after
excluding potentially pleiotropic SNPs. Considering the close
relation between lean mass and grip strength and the difficulty
of unequivocally identifying pleiotropic SNPs, we used two
different approaches: strict and lenient. Briefly, in the strict
approach we removed all SNPs related to any aspect of body
composition except the relevant exposure, while in the lenient
approach we removed all pleiotropic SNPs including those
related to fat mass, on the assumption that fat causes diabetes
[38], but not the SNPs related to body composition, which may
be associated with lean mass or grip strength, e.g. height and
weight. The lenient approach has the advantages of removing
key pleiotropic SNPs while preserving statistical power but
risks including some pleiotropic SNPs. The strict approach
removes all invalid SNPs but possibly also some valid SNPs.

Ethics approval

We used publicly available summary data where no ethical
approval is required.

Results

Influence of genetically predicted lean mass and grip strength on risk of diabetes and glycaemic traits

We obtained 313 SNPs for male whole body lean mass, 311
for female whole body lean mass and 130 for grip strength
after removing correlated SNPs. The F statistics for individual
SNPs were all larger than 10, with overall F statistics and
variance explained by SNPs of 117 and 8% for male whole
body lean mass, 101.9 and 6.9% for female whole body lean
mass and 26.4 and 0.7% for grip strength [13]. Attributes of
the SNPs are shown in ESM Tables 1–3. ESM Table 4 shows
the phenotypes related to the potentially pleiotropic SNPs
using the strict and lenient definitions.

Table 1 shows no association of male whole body lean mass
with any outcome robust to sensitivity analysis based on 180
SNPs using the lenient definition of pleiotropic SNPs or on
eight SNPs using the strict definition, although it is associated
with fasting glucose using inverse variance weighting and the
lenient approach. Female lean mass was inversely and signif-
icantly associated with diabetes using the lenient pleiotropy
definition with consistent estimates in all sensitivity analyses
but was not significantly associated with any outcome using
the strict pleiotropy definition SNPs. No significant sex-
specific effect was found after correcting for multiple compari-
sons as shown in Table 2. Grip strength was inversely and
significantly associated with diabetes using the lenient

Table 1 Association of male lean mass, female lean mass and grip strength with diabetes and glycaemic traits using Mendelian randomisation

Exposures	Outcomes	SNP selection[a]	No. of SNPs	Inverse variance weighting with multiplicative random effects Estimates (95% CI)	p	I^2 [b]	MR-Egger Estimates (95% CI)	p	Intercept	Intercept p	Weighted median Estimates (95% CI)	p	MR-PRESSO Global test p	Estimates (95% CI)	p
Male lean mass	Diabetes	All	267	1.10 (1.00, 1.20)	0.049*	0.86	0.89 (0.64, 1.24)	0.50	0.006	0.21	1.02 (0.96, 1.09)	0.48	$<2\times10^{-5}$	1.03 (0.97, 1.10)	0.29
		Lenient	180	0.92 (0.85, 1.00)	0.06	0.76	0.86 (0.64, 1.15)	0.31	0.002	0.63	0.96 (0.89, 1.04)	0.33	$<2\times10^{-5}$	0.94 (0.88, 1.01)	0.09
		Strict	8	0.92 (0.56, 1.50)	0.74	0.86	1.84 (0.29, 11.8)	0.55	−0.022	0.48	1.33 (0.97, 1.83)	0.08	$<2\times10^{-5}$	0.95 (0.65, 1.38)	0.80
	HbA₁c (% units)	All	95	0.03 (0.01, 0.05)	0.003**	0.32	0.04 (−0.08, 0.15)	0.53	−0.00	0.91	0.02 (−0.00, 0.04)	0.10	<0.001	0.03 (0.01, 0.05)	0.01*
		Lenient	62	0.01 (−0.02, 0.03)	0.46	0.31	0.05 (−0.08, 0.19)	0.45	−0.001	0.53	0.01 (−0.02, 0.04)	0.56	<0.01[c]		
		Strict	3[d]	−0.01 (−0.09, 0.08)	0.91	0	0.12 (−0.19, 0.43)	0.59	−0.004	0.57	0.01 (−0.09, 0.11)	0.84			
	HbA₁c (mmol/mol)	All	95	0.33 (0.11, 0.55)	0.003**	0.32	0.44 (−0.88, 1.65)	0.53	−0.00	0.91	0.22 (0.00, 0.44)	0.10	<0.001	0.33 (0.11, 0.55)	0.01*
		Lenient	62	0.11 (−0.22, 0.33)	0.46	0.31	0.55 (−0.88, 2.09)	0.45	−0.001	0.53	0.11 (−0.22, 0.44)	0.56	<0.01[c]		
		Strict	3[d]	−0.11 (−0.99, 0.88)	0.91	0	1.32 (−2.09, 4.73)	0.59	−0.004	0.57	0.11 (−0.99, 1.21)	0.84			
	Fasting glucose	All	102	0.06 (0.02, 0.10)	0.003**	0.54	−0.06 (−0.30, 0.18)	0.62	0.003	0.31	0.02 (−0.02, 0.06)	0.24	$<2\times10^{-5}$	0.05 (0.02, 0.08)	0.003**
		Lenient	62	0.04 (0.00, 0.09)	0.049*	0.30	−0.11 (−0.34, 0.13)	0.37	0.004	0.20	0.02 (−0.03, 0.08)	0.39	0.01[c]		
		Strict	3[d]	0.04 (−0.10, 0.19)	0.55	0.00	−0.29 (−0.80, 0.23)	0.47	0.010	0.41	0.01 (−0.16, 0.17)	0.95			
	Fasting insulin	All	102	0.04 (0.01, 0.08)	0.01*	0.26	−0.10 (−0.29, 0.09)	0.30	0.004	0.13	0.04 (−0.01, 0.08)	0.10	0.01[c]		
		Lenient	62	0.01 (−0.03, 0.04)	0.75	0.02	−0.12 (−0.32, 0.07)	0.23	0.003	0.20	0.02 (−0.03, 0.07)	0.49	0.37		
		Strict	3[d]	−0.02 (−0.16, 0.13)	0.84	0.00	0.04 (−0.47, 0.55)	0.90	−0.002	0.85	−0.02 (−0.18, 0.14)	0.80			
	HOMA-B	All	100	0.00 (−0.03, 0.03)	0.86	0.08	−0.03 (−0.21, 0.16)	0.77	0.001	0.74	0.00 (−0.04, 0.04)	1.00	0.21		
		Lenient	60	−0.03 (−0.07, 0.01)	0.20	0.03	−0.02 (−0.24, 0.20)	0.86	−0.000	0.95	−0.02 (−0.08, 0.04)	0.48	0.34		
		Strict	3[d]	−0.01 (−0.20, 0.19)	0.95	0.00	0.39 (−0.16, 0.94)	0.39	−0.013	0.38	−0.06 (−0.25, 0.13)	0.53			
	HOMA-IR	All	100	0.04 (0.00, 0.09)	0.03*	0.22	−0.11 (−0.35, 0.13)	0.39	0.004	0.21	0.04 (−0.01, 0.10)	0.12	0.02[c]		
		Lenient	60	−0.01 (−0.06, 0.04)	0.81	0.07	−0.12 (−0.39, 0.15)	0.40	0.003	0.42	0.00 (−0.07, 0.07)	0.97	0.26		
		Strict	3[d]	0.07 (−0.11, 0.26)	0.44	0.00	0.42 (−0.23, 1.08)	0.42	−0.011	0.47	0.07 (−0.14, 0.28)	0.51			
Female lean mass	Diabetes	All	261	1.08 (0.99, 1.19)	0.09	0.85	0.80 (0.55, 1.15)	0.23	0.008	0.09	1.01 (0.94, 1.09)	0.71	$<2\times10^{-5}$	1.04 (0.97, 1.12)	0.28
		Lenient	174	0.89 (0.81, 0.99)	0.03*	0.79	0.58 (0.39, 0.87)	0.01*	0.011	0.03*	0.89 (0.82, 0.97)	0.01*	$<2\times10^{-5}$	0.91 (0.84, 0.99)	0.02*
		Strict	10	0.76 (0.46, 1.24)	0.27	0.80	2.99 (0.33, 27.06)	0.36	−0.036	0.25	0.80 (0.59, 1.09)	0.15	$<2\times10^{-5}$	0.94 (0.73, 1.20)	0.62
	HbA₁c (% units)	All	112	0.02 (−0.01, 0.04)	0.15	0.44	−0.06 (−0.19, 0.06)	0.30	0.002	0.19	0.01 (−0.01, 0.04)	0.32	$<2\times10^{-5}$	0.01 (−0.01, 0.03)	0.44
		Lenient	86	−0.00 (−0.02, 0.02)	0.89	0.30	−0.16 (−0.31, −0.02)	0.03*	0.004	0.03*	−0.00 (−0.03, 0.02)	0.73	0.01[c]		
		Strict	7	0.01 (−0.07, 0.08)	0.88	0	0.57 (−0.07, 1.21)	0.14	−0.013	0.14	0.02 (−0.08, 0.11)	0.70	0.71		
	HbA₁c (mmol/mol)	All	112	0.22 (−0.11, 0.44)	0.15	0.44	−0.66 (−2.09, 0.66)	0.30	0.002	0.19	0.11 (−0.11, 0.44)	0.32	$<2\times10^{-5}$	0.11 (−0.11, 0.33)	0.44
		Lenient	86	−0.00 (−0.22, 0.22)	0.89	0.30	−1.76 (−3.41, −0.22)	0.03*	0.004	0.03*	−0.00 (−0.33, 0.22)	0.73	0.01[c]		
		Strict	7	0.11 (−0.77, 0.88)	0.88	0	6.27 (−0.77, 13.31)	0.14	−0.013	0.14	0.22 (−0.88, 1.21)	0.70	0.71		
	Fasting glucose	All	115	0.05 (0.01, 0.09)	0.02*	0.50	−0.27 (−0.50, −0.04)	0.02*	0.007	0.01*	0.04 (−0.00, 0.08)	0.08	$<5\times10^{-5}$	0.06 (0.02, 0.09)	0.001**
		Lenient	85	0.04 (−0.00, 0.08)	0.09	0.33	−0.28 (−0.54, −0.03)	0.03*	0.007	0.01*	0.01 (−0.04, 0.06)	0.68	<0.01	0.04 (0.00, 0.08)	0.04*
		Strict	7	0.10 (−0.02, 0.23)	0.10	0.00	−0.32 (−1.26, 0.62)	0.53	0.011	0.41	0.06 (−0.09, 0.21)	0.44	0.63		
	Fasting insulin	All	115	0.02 (−0.01, 0.06)	0.21	0.34	−0.13 (−0.34, 0.08)	0.23	0.004	0.15	0.02 (−0.03, 0.06)	0.47	1×10^{-5}	0.02 (−0.01, 0.06)	0.18
		Lenient	85	0.01 (−0.03, 0.05)	0.71	0.30	−0.32 (−0.57, −0.07)	0.01*	0.008	0.01*	0.01 (−0.04, 0.06)	0.75	<0.01	0.02 (−0.02, 0.05)	0.42
		Strict	7	0.01 (−0.15, 0.17)	0.89	0.20	−0.62 (−1.84, 0.59)	0.36	0.016	0.35	−0.02 (−0.18, 0.14)	0.80	0.16		
	HOMA-B	All	112	−0.00 (−0.04, 0.04)	0.92	0.31	−0.05 (−0.27, 0.17)	0.65	0.001	0.66	−0.01 (−0.06, 0.04)	0.65	6×10^{-4}	0.00 (−0.03, 0.04)	0.86
		Lenient	83	−0.01 (−0.05, 0.03)	0.69	0.24	−0.10 (−0.37, 0.16)	0.44	0.003	0.48	−0.01 (−0.06, 0.04)	0.74	0.02[c]		
		Strict	6	−0.08 (−0.26, 0.09)	0.34	0.00	−0.95 (−2.10, 0.20)	0.18	0.021	0.21	−0.09 (−0.26, 0.09)	0.32	0.18		
	HOMA-IR	All	112	0.02 (−0.02, 0.06)	0.30	0.18	−0.25 (−0.48, −0.01)	0.04*	0.006	0.02*	0.02 (−0.04, 0.08)	0.48	0.04	0.03 (−0.01, 0.07)	0.17
		Lenient	83	0.00 (−0.05, 0.05)	0.93	0.22	−0.37 (−0.68, −0.07)	0.02*	0.009	0.02*	0.01 (−0.05, 0.08)	0.70	0.035	0.01 (−0.04, 0.06)	0.67
		Strict	6	0.05 (−0.13, 0.23)	0.60	0	−1.08 (−2.31, 0.14)	0.16	0.28	0.14	0.10 (−0.11, 0.30)	0.37	0.33		
Grip strength	Diabetes	All	100	0.72 (0.51, 1.01)	0.06	0.87	0.08 (0.02, 0.32)	0.001**	0.027	0.002**	0.87 (0.69, 1.09)	0.22	$<2\times10^{-5}$	0.72 (0.58, 0.88)	0.002**
		Lenient	74	0.88 (0.68, 1.13)	0.32	0.68	0.22 (0.08, 0.63)	0.01*	0.017	0.01*	0.88 (0.69, 1.13)	0.32	$<2\times10^{-5}$	0.77 (0.62, 0.95)	0.02*
		Strict	27	0.74 (0.55, 1.01)	0.05	0.38	0.62 (0.15, 2.59)	0.52	0.002	0.81	0.88 (0.63, 1.24)	0.47	0.02[c]		
	HbA₁c (% units)	All	39	−0.03 (−0.10, 0.03)	0.31	0.14	0.24 (−0.20, 0.69)	0.29	−0.003	0.23	0.00 (−0.08, 0.09)	0.95	0.13		

Table 1 (continued)

Exposures	Outcomes	SNP selection[a]	No. of SNPs	Inverse variance weighting with multiplicative random effects		MR-Egger					Weighted median		MR-PRESSO		
				Estimates (95% CI)	p	I^{2b}	Estimates (95% CI)	p	Intercept	Intercept p	Estimates (95% CI)	p	Global test p	Estimates (95% CI)	p
		Lenient	28	−0.00 (−0.08, 0.07)	0.93	0.18	0.40 (−0.12, 0.91)	0.14	−0.005	0.14	0.03 (−0.06, 0.12)	0.50	0.15		
		Strict	12	−0.05 (−0.16, 0.06)	0.38	0	0.43 (−0.36, 1.22)	0.31	−0.005	0.26	−0.07 (−0.22, 0.08)	0.37	0.40		
	HbA$_{1c}$ (mmol/mol)	All	39	−0.33 (−1.10, 0.33)	0.31	0.14	2.64 (−2.2, 7.59)	0.29	−0.003	0.23	0.00 (−0.88, 0.99)	0.95	0.13		
		Lenient	28	−0.00 (−0.88, 0.77)	0.93	0.18	4.4 (−1.32, 10.01)	0.14	−0.005	0.14	0.33 (−0.66, 1.32)	0.50	0.15		
		Strict	12	−0.55 (−1.76, 0.66)	0.38	0	4.73 (−3.96, 13.42)	0.31	−0.005	0.26	−0.77 (−2.42, 0.88)	0.37	0.40		
	Fasting glucose	All	45	−0.07 (−0.17, 0.04)	0.23	0.25	0.17 (−0.55, 0.89)	0.65	−0.003	0.52	−0.04 (−0.18, 0.11)	0.61	0.045[c]		
		Lenient	29	−0.05 (−0.18, 0.07)	0.39	0.06	0.18 (−0.63, 0.98)	0.67	−0.003	0.57	−0.04 (−0.21, 0.14)	0.69	0.28		
		Strict	15	−0.04 (−0.21, 0.12)	0.60	0.00	0.13 (−0.80, 1.06)	0.79	−0.002	0.72	−0.03 (−0.25, 0.20)	0.81	0.48		
	Fasting insulin	All	45	−0.05 (−0.16, 0.06)	0.36	0.23	0.16 (−0.57, 0.88)	0.68	−0.002	0.57	0.01 (−0.14, 0.15)	0.94	0.06		
		Lenient	29	−0.00 (−0.14, 0.13)	0.95	0.21	0.36 (−0.53, 1.26)	0.43	−0.004	0.42	0.05 (−0.13, 0.23)	0.58	0.10		
		Strict	15	−0.05 (−0.25, 0.15)	0.64	0.23	0.92 (−0.12, 1.96)	0.11	−0.11	0.09	−0.06 (−0.31, 0.19)	0.64	0.11		
	HOMA-B	All	42	−0.14 (−0.24, −0.03)	0.01*	0.11	−0.39 (−1.10, 0.33)	0.30	0.003	0.49	−0.16 (−0.31, −0.02)	0.02*	0.22		
		Lenient	27	−0.07 (−0.21, 0.06)	0.30	0.11	−0.19 (−1.09, 0.71)	0.68	0.001	0.80	−0.09 (−0.27, 0.10)	0.37	0.22		
		Strict	14	−0.22 (−0.39, −0.04)	0.01*	0.65	0.12 (−0.85, 1.09)	0.82	0.001	0.82	−0.32 (−0.56, −0.07)	0.01*	0.75		
	HOMA-IR	All	42	−0.09 (−0.22, 0.03)	0.13	0.01	−0.19 (−1.02, 0.64)	0.66	0.001	0.82	−0.10 (−0.27, 0.07)	0.23	0.38		
		Lenient	27	−0.05 (−0.22, 0.12)	0.53	0.14	−0.32 (−1.42, 0.77)	0.57	0.003	0.63	−0.02 (−0.24, 0.20)	0.84	0.19		
		Strict	14	−0.20 (−0.43, 0.02)	0.07	0.00	−0.16 (−1.44, 1.11)	0.81	−0.000	0.95	−0.22 (−0.53, 0.09)	0.16	0.37		

Estimates with 95% CI for diabetes are expressed as OR; in % units (mmol/mol) for HbA$_{1c}$, in mmol/l for fasting glucose, and in log$_e$(pmol/l) for fasting insulin; per 1SD increase in lean mass/grip strength

HbA$_{1c}$ (mmol/mol) was estimated by multiplying HbA$_{1c}$ (% units) by 11

MR-PRESSO analysis was only carried out for associations with a significant global test p value ($p < 0.05$)

[a] 'All' represents analyses without removing pleiotropic SNPs; 'Lenient' represents analyses after removing pleiotropic SNPs using a lenient approach; 'Strict' represents analyses after removing pleiotropic SNPs using a strict approach

[b] I^2 of Wald estimate

[c] MR-PRESSO could not identify a significant outlier

[d] Not enough SNPs for MR-PRESSO analysis

*$p<0.05$, **$p<0.01$

Table 2 Assessment of differences by sex, p values for tests of interaction

Exposures	Outcomes	SNP selection[a]	Inverse variance weighting p for sex difference	MR-Egger p for sex difference	Weighted median p for sex difference	MR-PRESSO p for sex difference
Effect of lean mass on diabetes and glycaemic traits						
Lean mass	Diabetes	All	0.84	0.53	0.77	0.87
		Lenient	0.50	0.03	0.05	0.37
		Strict	0.47	0.67	0.01	0.93
	HbA$_{1c}$	All	0.20	0.10	0.56	0.05
		Lenient	0.37	0.004	0.35	
		Strict	0.81	0.20	0.88	
	Fasting glucose	All	0.51	0.08	0.52	0.76
		Lenient	0.71	0.16	0.61	
		Strict	0.44	0.94	0.56	
	Fasting insulin	All	0.26	0.78	0.33	
		Lenient	0.93	0.10	0.70	
		Strict	0.78	0.30	1.00	
	HOMA-B	All	0.79	0.82	0.64	
		Lenient	0.40	0.51	0.68	
		Strict	0.48	0.05	0.80	
	HOMA-IR	All	0.28	0.004	0.33	
		Lenient	0.12	0.002	0.74	
		Strict	0.23	0.05	0.16	
Effect of diabetes and glycaemic traits on lean mass						
Diabetes	Lean mass	All	0.53	0.69	0.27	0.06
		Removed	0.03	0.09	0.61	0.32
HbA$_{1c}$		All	0.66	0.99	0.29	0.36
		Removed	0.25	0.58	0.29	0.22
Fasting glucose		All	0.55	0.88	0.73	0.71
		Removed	0.08	0.90	0.08	0.03
Fasting insulin		All	0.73	0.93	0.96	0.02
		Removed	0.84			
HOMA-B		All	0.48	0.07	0.45	0.35

MR-PRESSO analysis was only carried out for associations with a significant global test p value ($p < 0.05$) in Table 1. Associations without an MR-PRESSO estimate were not tested for differences by sex

Bonferroni corrected significance level (0.05/41 = 0.001) was used to correct for multiple comparisons

[a] 'All' represents analyses without removing pleiotropic SNPs; 'Lenient' represents analyses after removing pleiotropic SNPs using a lenient approach; 'Strict' represents analyses after removing pleiotropic SNPs using a strict approach; 'Removed' represents analyses after removing pleiotropic SNPs

pleiotropy definition and MR-PRESSO, but not using the strict definition although the estimate was similar. I^2 was lower after removing pleiotropic SNPs (Table 1).

Influence of genetically predicted diabetes risk and glycaemic traits on lean mass and grip strength

We obtained 141 SNPs for diabetes, 35 for HbA$_{1c}$, 30 for fasting glucose, 14 for fasting insulin and five for HOMA-B, after removing correlated SNPs. HOMA-IR was excluded from the analyses because there were no genome-wide significant SNPs. All the above SNPs had F statistics larger than 10 with overall F statistics of 70.8 for diabetes, 154.9 for HbA$_{1c}$, 118.1 for fasting glucose, 42.6 for fasting insulin and 46.4 for HOMA-B. Attributes of these SNPs are shown in ESM Table 5. Among the included SNPs, 68, 12, 14 and 12 SNPs were considered to be pleiotropic SNPs for diabetes, HbA$_{1c}$, fasting glucose and fasting insulin, respectively, as they may be directly or indirectly related to the outcomes (lean mass/grip strength) after searching on Phenoscanner and/or the GWAS Catalog. No pleiotropic SNPs were identified for HOMA-B.

Table 3   Association of diabetes, HbA$_{1c}$, fasting glucose and fasting insulin with male lean mass, female lean mass and grip strength using Mendelian randomisation

Exposures	Outcomes	SNP selection[a]	No. of SNPs	Inverse variance weighting with multiplicative random effects			MR-Egger				Weighted median		MR-PRESSO		
				β (95% CI)	p	I²[b]	β (95% CI)	p	Intercept	Intercept p	β (95% CI)	p	Global test p	β (95% CI)	p
Diabetes	Male lean mass	All	141	0.03 (−0.01, 0.07)	0.12	0.94	−0.08 (−0.16, 0.01)	0.08	0.008	0.01*	−0.02 (−0.04, 0.00)	0.06	<2×10⁻⁵	−0.00 (−0.02, 0.02)	0.80
		Removed	73	−0.03 (−0.05, −0.01)	0.01*	0.51	−0.08 (−0.15, −0.01)	0.03*	0.003	0.14	−0.02 (−0.04, 0.01)	0.13	<2×10⁻⁵	−0.02 (−0.04, −0.00)	0.04*
HbA$_{1c}$ (% units)		All	35	0.06 (−0.20, 0.31)	0.66	0.96	−0.08 (−0.55, 0.40)	0.75	0.002	0.40	0.09 (−0.03, 0.20)	0.13	<2×10⁻⁵	0.04 (−0.05, 0.14)	0.38
		Removed	23	0.00 (−0.10, 0.10)	0.99	0.36	0.03 (−0.15, 0.20)	0.75	−0.001	0.70	0.08 (−0.04, 0.20)	0.18	0.04	0.03 (−0.05, 0.11)	0.43
HbA$_{1c}$ (mmol/mol)		All	35	0.01 (−0.02, 0.03)	0.66	0.96	−0.01 (−0.05, 0.04)	0.75	0.002	0.40	0.01 (−0.00, 0.02)	0.13	<2×10⁻⁵	0.00 (−0.00, 0.01)	0.38
		Removed	23	0.00 (−0.01, 0.01)	0.99	0.36	0.00 (−0.01, 0.02)	0.75	−0.001	0.70	0.01 (−0.00, 0.02)	0.18	0.04	0.00 (−0.00, 0.01)	0.43
Fasting glucose		All	30	0.03 (−0.11, 0.18)	0.65	0.89	0.07 (−0.20, 0.34)	0.60	−0.001	0.74	0.09 (0.02, 0.17)	0.02*	<2×10⁻⁵	0.06 (−0.02, 0.14)	0.18
		Removed	16	−0.15 (−0.32, 0.02)	0.80	0.76	−0.42 (−0.79, −0.06)	0.04*	0.008	0.12	−0.11 (−0.24, 0.02)	0.10	<2×10⁻⁵	−0.14 (−0.29, 0.01)	0.10
Fasting insulin		All	14	0.76 (0.16, 1.36)	0.01*	0.96	2.55 (−0.88, 5.98)	0.17	−0.031	0.32	0.23 (−0.01, 0.47)	0.06	<2×10⁻⁵	0.69 (0.39, 0.99)	0.004**
		Removed	2[c]	−0.19 (−0.89, 0.51)	0.59											
HOMA-B		All	5	0.02 (−0.30, 0.34)	0.92	0.84	−1.97 (−3.47, −0.46)	0.01*	0.051	0.08	−0.09 (−0.26, 0.07)	0.25	<0.001	−0.10 (−0.30, 0.11)	0.43
Diabetes	Female lean mass	All	141	0.04 (0.01, 0.08)	0.02*	0.94	−0.06 (−0.14, 0.02)	0.15	0.008	0.01*	−0.01 (−0.03, 0.01)	0.47	<2×10⁻⁵	0.02 (−0.00, 0.03)	0.12
		Removed	73	−0.00 (−0.03, 0.02)	0.93	0.67	−0.01 (−0.09, 0.07)	0.78	0.001	0.79	−0.03 (−0.05, 0.00)	0.06	<2×10⁻⁵	−0.01 (−0.03, 0.01)	0.32
HbA$_{1c}$ (% units)		All	35	0.11 (−0.13, 0.36)	0.36	0.93	−0.08 (−0.52, 0.37)	0.74	0.004	0.33	0.15 (0.04, 0.25)	0.01*	<2×10⁻⁵	0.09 (−0.01, 0.20)	0.10
		Removed	23	0.07 (−0.05, 0.19)	0.27	0.59	0.09 (−0.13, 0.30)	0.44	−0.000	0.84	0.14 (0.03, 0.26)	0.01*	2×10⁻⁵	0.09 (−0.01, 0.20)	0.10
HbA$_{1c}$ (mmol/mol)		All	35	0.01 (−0.01, 0.03)	0.36	0.93	−0.01 (−0.05, 0.03)	0.74	0.004	0.33	0.01 (0.00, 0.02)	0.01*	<2×10⁻⁵	0.01 (−0.00, 0.02)	0.10
		Removed	23	0.01 (−0.00, 0.02)	0.27	0.59	0.01 (−0.01, 0.03)	0.44	−0.000	0.84	0.01 (0.00, 0.02)	0.01*	2×10⁻⁵	0.01 (−0.00, 0.02)	0.10
Fasting glucose		All	30	0.08 (−0.05, 0.20)	0.24	0.87	0.09 (−0.14, 0.33)	0.45	−0.001	0.87	0.11 (0.03, 0.18)	0.004**	<2×10⁻⁵	0.07 (−0.02, 0.16)	0.12
		Removed	16	0.00 (−0.14, 0.15)	0.96	0.68	−0.40 (−0.65, −0.16)	0.01*	0.011	0.003**	0.02 (−0.12, 0.15)	0.83	<2×10⁻⁵	0.04 (−0.10, 0.17)	0.61
Fasting insulin		All	14	0.66 (0.12, 1.19)	0.02*	0.95	2.40 (−0.63, 5.44)	0.15	−0.030	0.27	0.22 (0.02, 0.42)	0.03*	<2×10⁻⁵	0.32 (0.15, 0.49)	0.01*
		Removed	2[c]	−0.07 (−0.84, 0.70)	0.86											
HOMA-B		All	5	−0.10 (−0.33, 0.13)	0.39	0.73	0.07 (−1.85, 1.99)	0.95	−0.004	0.87	−0.17 (−0.32, −0.11)	0.04*	0.01	−0.19 (−0.27, −0.11)	0.02*
Diabetes	Grip strength	All	141	−0.01 (−0.02, 0.00)	0.07	0.78	−0.02 (−0.04, 0.00)	0.13	0.001	0.42	−0.01 (−0.02, −0.00)	0.048*	<2×10⁻⁵	−0.01 (−0.02, −0.00)	0.02*
		Removed	73	−0.01 (−0.02, −0.00)	0.02*	0.57	−0.01 (−0.05, 0.03)	0.67	−0.000	0.76	−0.02 (−0.03, −0.00)	0.01*	<2×10⁻⁵	−0.01 (−0.02, −0.00)	0.01*
HbA$_{1c}$ (% units)		All	35	−0.01 (−0.09, 0.06)	0.68	0.77	−0.04 (−0.17, 0.09)	0.54	0.001	0.63	−0.01 (−0.06, 0.04)	0.64	<2×10⁻⁵	0.01 (−0.04, 0.06)	0.70
		Removed	23	−0.02 (−0.09, 0.05)	0.56	0.69	−0.07 (−0.19, 0.06)	0.30	0.001	0.38	−0.02 (−0.08, 0.03)	0.37	<2×10⁻⁵	−0.00 (−0.06, 0.05)	0.87
HbA$_{1c}$ (mmol/mol)		All	35	−0.00 (−0.01, 0.01)	0.68	0.77	−0.00 (−0.02, 0.01)	0.54	0.001	0.63	−0.00 (−0.01, 0.00)	0.64	<2×10⁻⁵	0.00 (−0.00, 0.01)	0.70
		Removed	23	−0.00 (−0.01, 0.00)	0.56	0.69	−0.01 (−0.02, 0.01)	0.30	0.001	0.38	−0.00 (−0.01, 0.00)	0.37	<2×10⁻⁵	−0.00 (−0.01, 0.00)	0.87
Fasting glucose		All	30	0.02 (−0.03, 0.07)	0.38	0.74	−0.00 (−0.09, 0.08)	0.98	0.001	0.55	0.01 (−0.02, 0.05)	0.41	<2×10⁻⁵	0.01 (−0.02, 0.04)	0.60
		Removed	16	0.01 (−0.06, 0.09)	0.73	0.70	−0.14 (−0.30, 0.01)	0.09	0.004	0.046*	−0.03 (−0.09, 0.03)	0.27	<2×10⁻⁵	−0.01 (−0.06, 0.04)	0.73
Fasting insulin		All	14	0.10 (−0.04, 0.23)	0.16	0.82	0.28 (−0.53, 1.09)	0.51	−0.003	0.66	0.12 (0.03, 0.21)	0.01*	<2×10⁻⁵	0.12 (0.02, 0.21)	0.03*
		Removed	2[c]	−0.02 (−0.30, 0.25)	0.86											
HOMA-B		All	5	0.06 (−0.16, 0.29)	0.58	0.70	−0.70 (−2.43, 1.02)	0.48	0.020	0.44	0.04 (−0.13, 0.22)	0.62	0.01	−0.02 (−0.21, 0.17)	0.87

β with 95% CI in terms of SD change in lean mass/grip strength; per log odds of diabetes, in % units (mmol/mol) for HbA$_{1c}$, mmol/l for fasting glucose and log$_e$(pmol/l) for fasting insulin

HbA$_{1c}$ (mmol/mol) was estimated by multiplying HbA$_{1c}$ (% units) by 11

[a] 'All' represents analyses without removing pleiotropic SNPs; 'Removed' represents analyses after removing pleiotropic SNPs

[b] I² of Wald estimate

[c] Not enough SNPs for sensitivity analyses

*p<0.05, **p<0.01

ESM Table 6 shows the phenotypes related to the potentially pleiotropic SNPs.

Table 3 shows that diabetes was inversely and significantly associated with male lean mass and grip strength after removing pleiotropic SNPs as well as being robust to sensitivity analysis using MR-PRESSO. HbA$_{1c}$, fasting glucose and HOMA-B were not significantly associated with grip strength in any analyses or to lean mass in most analyses, especially after removing pleiotropic SNPs or outliers. Fasting insulin was positively and significantly associated with male and female lean mass and possibly with grip strength before removing pleiotropic SNPs but no significant association was found after removing pleiotropic SNPs. No significant difference by sex was found.

Power calculations showed at least 80% power to detect an OR of 0.94 and 0.81 per 1 SD of lean mass and grip strength, respectively. Results from power calculations are shown in ESM Table 7.

Discussion

Consistent with the randomised controlled trials in people with metabolic diseases [6], we found some evidence that grip strength (an indicator of muscle strength) and lean mass could be associated with diabetes in the general population. Conversely, diabetes could be associated with lower whole body lean mass and lower grip strength while glycaemic traits generally showed no association. To our knowledge, this is the first Mendelian randomisation study using the most recent GWAS to assess the bi-directional relations between muscle mass and grip strength on the one hand and diabetes and glycaemic traits on the other hand.

Our results suggest that female lean mass was related to diabetes while male lean mass was not, although the estimates were directionally similar with no strong evidence of sex-specific effects. We also cannot rule out that grip strength may be inversely associated with diabetes consistent with previous studies on grip strength [11, 39]. An inverse association of diabetes with lean mass and grip strength is consistent with previous studies suggesting that diabetes may directly affect skeletal muscle [40, 41]. By contrast, fasting insulin also showed a possible positive association with lean mass, consistent with its role as a growth promoter. However, given the lack of robustness to sensitivity analyses this result requires replication.

A possible mechanism for the inverse association of grip strength (and possibly lean mass) with diabetes could be an increase in insulin action and lowering of blood glucose among people with higher muscle strength, which may help to reduce the risk of diabetes [42, 43]. However, lean mass and grip strength were not shown to benefit glycaemic traits in our analyses. Further investigation of the effect of muscle strength on postprandial glucose and insulin activity could provide more insight into any possible mechanism. The inverse association may also be a possible cause of the low obesity but high diabetes rate in Asian populations compared with Western populations, as Asian individuals usually have a lower muscle mass, thus lower muscle strength [44, 45].

The association of lower muscle mass with diabetes has also been discussed in previous studies where the optimal form of exercise for reducing diabetes is in question [46]. Our results may suggest increasing both muscle mass and strength could be associated with lower risk of diabetes. Therefore, promotion of both muscle mass and strength building may be possible interventions for reducing diabetes risk.

The choice of genetic predictors is also an important point to note. In contrast to a recent study that assessed the effect of grip strength on frailty indices [18], we have chosen absolute, rather than relative, grip strength because relative grip strength (grip strength/body weight) takes account of weight, which represents lean mass, bone mass and fat mass, making the estimates more a measure of overall muscle fitness than muscle strength alone. Moreover, a change in relative grip strength may not only represent a change in grip strength but also a change in body fat mass. As such, absolute grip strength may be a better proxy for examining the effect of muscle strength alone.

Although we used a bi-directional Mendelian randomisation design, which is more resistant to confounding, and used publicly available GWAS data to reduce the likelihood of underpowered analyses, there are some limitations, primarily concerning the assumptions of Mendelian randomisation. First, the SNPs are assumed to be strongly associated with the exposure, as indicated by a high F statistic and SNPs reaching genome-wide significance in the most recent GWAS. Second, the SNPs are assumed to be independent of confounders of the exposure–outcome relation, as has been empirically shown elsewhere [47]. Third, the SNPs are assumed to affect the outcomes through the exposure of interest only, i.e. the exclusion restriction assumption. To identify these potential pleiotropic effects, we checked for associated phenotypes of the SNPs using both the GWAS Catalog and Phenoscanner, and we obtained estimates without these potentially invalid SNPs. In addition, it is difficult to determine all pleiotropic SNPs as the complex relationship between some phenotypes might not be well understood; therefore the results should be interpreted with caution. Specifically, it is unclear which aspects of body size and composition, such as height, act on diabetes via mechanisms other than fat mass, muscle mass and muscle quality, i.e. grip strength. In this way, strictly removing genetic variants because of potential pleiotropy may also have removed a true effect. Fourth, population stratification might affect the estimates. However, the SNP-exposure and SNP-outcome association were mainly obtained from European individuals with genomic control, which should have minimised this possibility.

Fifth, our results were mainly based on people of European ancestry and may not extend to other populations. However, we would expect the causal effects of grip strength and lean mass to be similar across all populations, although they might be more relevant in some specific populations. Sixth, we cannot determine the clinical significance of the results because Mendelian randomisation should be interpreted as testing for causation rather than indicating the size of any causal effect. Although a small effect size may not be clinically significant, the effect on population health may still be important. Seventh, the effect of SNPs on phenotype may be compensated for during development, i.e. canalisation [7]; however, whether such canalisation effects exist is unknown. Eighth, our study may be inadequately powered to detect differences by sex. Finally, we rely on the integrity of the underlying GWAS, particularly those based on case–control studies, whose design may not include consideration of selection bias by prior death [48, 49]. Such selection bias is most likely to occur for exposures that cause premature death and diseases that occur at older ages, and so may not be particularly relevant here.

Conclusion

Our study suggests that muscle mass and strength may have some favourable effects on diabetes. Conversely, diabetes may be related to reduced muscle mass and grip strength. Because muscle building has the advantage of being a potentially attractive target, interventions on muscle strength building, such as resistance training, could be further investigated as possible diabetes-preventive measures.

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