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RESEARCH LETTER

Relative effects of genetically proxied glucagon-like peptide-1 receptor agonism on muscle and fat mass: A Mendelian randomization study

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1 | BACKGROUND/CONTEXT

Glucagon-like peptide-1 receptor (GLP1R) agonists are second-line pharmaceutical agents primarily indicated for adults with type 2 diabetes mellitus. Their use is expanding globally as pharmacological interventions for weight reduction.[1] However, there remains uncertainty regarding whether the weight reduction primarily results from body fat or lean mass reduction.[2] Conventional epidemiological study designs have inherent limitations, including residual confounding by indication. Mendelian randomization, a design less vulnerable to confounding due to the random allocation of genetics at conception, is increasingly used to investigate side effects of medications across diverse populations.[3] We conducted a drug-target Mendelian randomization study to investigate whether genetically proxied GLP1R agonism reduces muscle and fat mass, leveraging large-scale summary statistics from genome-wide association studies (GWAS).

2 | METHODS

This is a drug-target Mendelian randomization design, which has three assumptions. First, the genetic instruments selected within the target gene of GLP1R agonist should effectively proxy GLP1R agonism (Relevance). Second, there should be no gene-outcome confounders (Independence). Third, any genetic association with the outcome must operate via its relation with the exposure (Exclusion restriction) (Figure 1). The study was reported according to the STROBE-MR checklist (Supplemental Material).[4]

2.1 | Instruments for genetically proxied GLP1R agonism

Recent genetic studies suggested that GLP1R agonism may influence body weight and type 2 diabetes mellitus via different mechanisms.[5] We identified instruments for genetically proxied GLP1R agonism based on their statistical significance with body mass index (BMI, n: 806834),[6] defining *GLP1R* gene region as ±100kbp of the *GLP1R* gene (Chr6: 39016557–39 059 079, GRCh37/hg19, from NCBI). Given the correlated nature of the variants, we only included the index variant of GLP1R agonism (the variant with lowest p-value for BMI) in the main analyses. Additionally, we employed rs1042044, a missense variant and one of the lead signals related to BMI at *GLP1R* for genetic proxying of GLP1R agonism as sensitivity analyses.[7]

2.2 | Genetic associations with the outcomes

Genetic associations of body compositions were obtained from several relevant GWAS involving individuals of European ancestry. For muscle mass, we included appendicular lean mass (ALM) (standard deviation (SD), $n = 450\,243$), whole body fat-free mass (SD,

Gill Dipender and Au Yeung Shiu Lun are the joint senior authors.

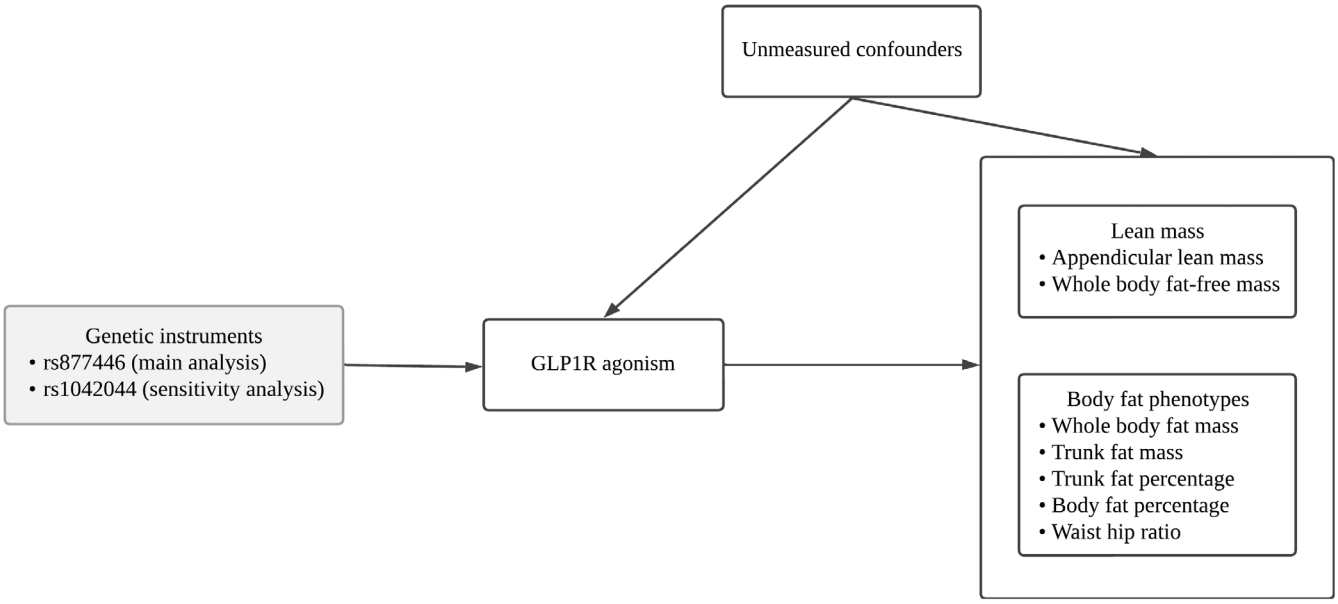

FIGURE 1 Schematic diagram of this drug-target Mendelian randomization design. *GLP1R—glucagon-like peptide-1 receptor.

$n = 454\,850$) and trunk fat-free mass (SD, $n = 454\,508$) from a recent GWAS meta-analysis and the UK Biobank.[8,9] For fat-related measures, we included whole body fat mass (SD, $n = 454\,137$), trunk fat mass (SD, $n = 454\,588$), trunk fat percentage (SD, $n = 454\,613$), body fat percentage (SD, $n = 454\,633$) from the UK Biobank[9] and waist-to-hip ratio (WHR) (SD, $n = 697\,734$) from the GIANT consortium.[6] Supplementary Table 1 showed the details of the included GWAS in this study.

2.3 | Statistical analyses

We approximated the F statistic as the strength of instrument, with larger F statistic indicating a lower risk of weak instrument bias. We used Wald ratio to assess the association of genetically proxied GLP1R agonism with the outcomes concerned. No additional sensitivity analyses were implemented, as any variants (if present) were from the same gene region and hence would be similarly vulnerable to pleiotropy, although likely vertical (unbiased).

All statistical analyses were performed using R version 4.4.1 with R packages '*TwoSampleMR*' (version 0.6.8) and '*forestplot*' (version 3.1.3). Ethics approval was not required, given this study only used publicly available data.

3 | RESULTS

Supplementary Table 2 showed the information about the instruments. The index variant in *GLP1R* was rs877446, which showed a strong association with BMI (p-value: 2.9E-07, F statistic: 27). The commonly used variant, rs1042044, also demonstrated a strong association with BMI (p-value: 2.8E-06, F statistic: 23). These indicated low evidence for weak instrument bias. However, these two variants were in high linkage disequilibrium (r^2: 0.89).

As shown in Figure 2A, genetically proxied GLP1R agonism, using rs877446, was associated with reduction in both whole body fat-free mass (β: −0.56 per standard deviation (SD) of BMI reduction, 95% confidence interval (CI): −0.84 to −0.28) and trunk fat-free mass (β: −0.46 per SD, 95% CI: −0.74 to −0.18), but not significantly with ALM (β: −0.40 per SD, 95% CI: −0.82 to 0.03). For fat-related phenotypes, genetically proxied GLP1R agonism was associated with lower whole body fat mass (β: −0.83 per SD, 95% CI: −1.27 to −0.39), trunk fat mass (β: −0.92 per SD, 95% CI: −1.37 to −0.46), trunk fat percentage (β: −0.68 per SD, 95% CI: −1.10 to −0.27) and body fat percentage (β: −0.53 per SD, 95% CI: −0.88 to −0.19).

Sensitivity analyses using rs1042044 yielded similar findings (Figure 2B), although associations with ALM and WHR were stronger compared with the main analyses.

4 | CONCLUSIONS

To the best of our knowledge, this is the largest Mendelian randomization study assessing the relative effects of genetically proxied GLP1R agonism on muscle and fat mass. Consistent with previous randomized controlled trials (RCTs), our findings indicate that genetically proxied GLP1R agonism is associated with a reduction in BMI. Importantly, this reduction appears to be predominantly due to a loss of fat mass rather than lean mass, as evidenced by the reduction in body fat percentage. As such, our study provides genetic evidence against recent concerns that GLP1R agonists induce weight loss primarily through reductions in muscle mass.[2]

Currently, there is limited evidence to support that GLPR agonism directly leads to physical frailty or sarcopenia.[10] Our study is

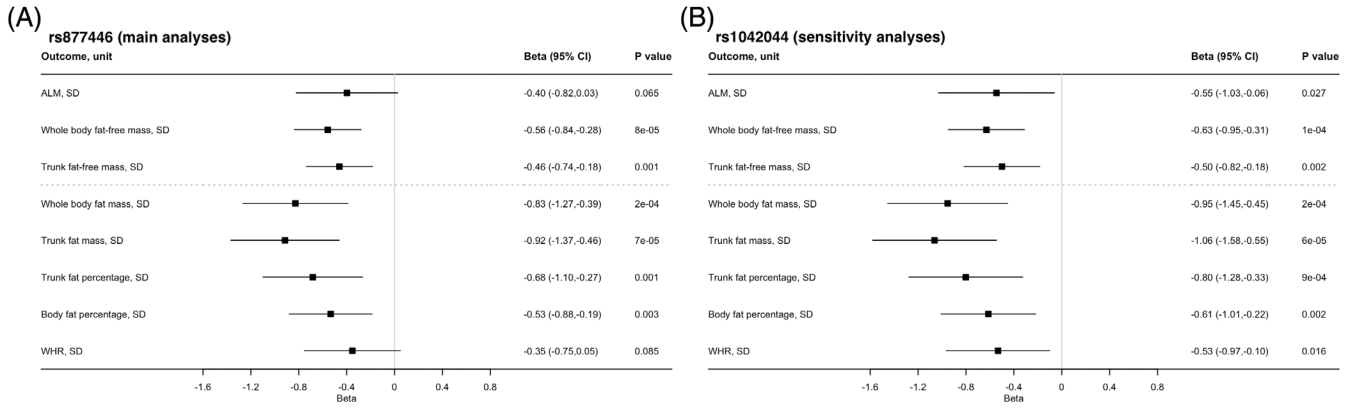

FIGURE 2 Association of genetically proxied glucagon-like peptide-1 receptor agonism (per standard deviation reduction in body mass index) with fat and muscle mass phenotypes using drug-target Mendelian randomization using (A) rs877446 and (B) rs1042044. ALM—appendicular lean mass; BMI—body mass index; SD—standard deviation; 95% CI—95% confidence interval.

consistent with a meta-analysis showing that GLP1R agonist users and controls had comparable decreases in lean mass percentage, but GLP1R agonist users had greater decreases in fat mass.[11] Nevertheless, reduction in muscle mass does not necessarily imply reduced physical functioning, in regard to comments elsewhere that GLP1R agonist use was associated with patient's mobility and physical functioning.[10]

Despite the strengths of Mendelian randomization, which is less vulnerable to residual confounding, several limitations remained. First, Mendelian randomization relies on specific assumptions. We selected instruments based on BMI, which is more likely to capture the mechanisms underlying the weight reduction effects of GLP1R agonism, making it a more valid approach compared with using type 2 diabetes mellitus or glycated haemoglobin.[5] Although there was considerable overlap due to the inclusion of the UK Biobank in both exposure and outcome data sources, our large F statistics mitigate potential biases from weak instrument effects. Additionally, relying on one SNP reduces the statistical power to detect causal relationships, but our analyses showed the expected associations for several outcomes. Using single variant prevented us from implementing standard sensitivity analyses, although arguably any pleiotropic effects are likely a reflection of vertical pleiotropy and thus would not bias our analyses.[12] Second, our study represented lifelong effects of genetically proxied GLP1R agonism and cannot address any acute changes in body composition that may occur upon initiation of GLP1R agonists in clinical settings. Furthermore, the degree of change in BMI arising from GLP1R agonism was different between pharmacological intervention and genetic variation and hence has implications regarding the effect sizes, but less likely for direction. Lastly, our study was restricted to general European population, and further investigations are warranted to determine their applicability to other populations, including different ethnicities (e.g. Asians), demographic characteristics (e.g. adolescents where the U.S. Food and Drug Administration approved the use of this drug for weight management aged 12+) and frailty status.[13]

In conclusion, our study provides genetic evidence that GLP1R agonism reduces weight, with more body fat loss than muscles loss. These findings warrant further verifications through RCTs.

AUTHOR CONTRIBUTIONS

SLAY designed the study, with the help from DG. YL conducted the analyses, with feedback from SLAY and DG. SLAY and YL wrote the first draft of the manuscript with critical feedback and revisions from SL, YFW, CLC and DG. All authors gave final approval of the version to be published. SLAY and YL had primary responsibility for final content.

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Data related to BMI and WHR were provided by investigators from the GIANT Consortium. Summary statistics of ALM are available in the GWAS Catalog (Study accession: GCST90000025). Summary statistics of body compositions were obtained from GWAS pipeline using PHESANT-derived variables from the UK Biobank, which were all extracted from the IEU GWAS database (https://gwas.mrcieu.ac.uk/).

CONFLICT OF INTEREST STATEMENT

SLAY received honorarium from Standard BioTools for scientific presentations of proteomic studies, which are not related to this study. DG works with academia, investors, pharma and biotech in using genetic data to inform drug development and has financial interests in several biotech companies. Other authors declared no other conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16171.

DATA AVAILABILITY STATEMENT

All data used in this study can be found in the Supplemental Table, and the URLs described in the Acknowldegement.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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