Journal of Multidisciplinary Healthcare

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

No Genetic Causal Relationship Between HIV Infection and Insulin Resistance, Diabetes: A Bidirectional Mendelian Randomization Analysis

Pengfei Liu[1], Qiurong Zeng[2]

[1]Department of Clinical Medicine, North Sichuan Medical College, Nanchong, Sichuan, People's Republic of China; [2]Department of Laboratory Medicine, North Sichuan Medical College, Nanchong, Sichuan, People's Republic of China

Correspondence: Pengfei Liu, Email lpfei01@163.com

Background: The causal relationship between HIV infection and insulin resistance, as well as diabetes mellitus, remains uncertain. This study explores these associations using genome-wide association study data and Mendelian randomization techniques.

Methods: We performed bidirectional, two-sample Mendelian randomization analyses to evaluate the causal links between HIV infection and insulin resistance, as well as type 1 diabetes, type 2 diabetes, and gestational diabetes. Additionally, we assessed the relationship between HIV infection and glycated hemoglobin. Five Mendelian randomization methods were employed: inverse variance weighting, MR-Egger, weighted median, weighted mode, and simple mode. Cochran's Q test was used to assess heterogeneity, while the MR-Egger intercept test evaluated horizontal pleiotropy. Sensitivity was evaluated using the leave-one-out method.

Results: No causal effects were found between HIV infection and insulin resistance, type 1 diabetes, type 2 diabetes, gestational diabetes, or HbA1c levels. IVW analysis and other Mendelian randomization methods consistently yielded null results (all $p > 0.05$). Reverse Mendelian randomization analyses supported these null findings. Sensitivity analyses confirmed the robustness of our results, with no significant heterogeneity or pleiotropy detected.

Conclusion: This Mendelian randomization study found no significant causal links between HIV infection and insulin resistance or diabetes mellitus. The null association with glycated hemoglobin further supports these findings. These results provide insights into the pathogenesis of insulin resistance and diabetes in individuals living with HIV, highlighting the need for further exploration of potential mediating factors, such as antiretroviral therapy, inflammation, and obesity.

Keywords: HIV infection, insulin resistance, diabetes, Mendelian randomization study, mediating factors

Introduction

Human immunodeficiency virus (HIV) is a retrovirus that primarily infects activated CD4+ T lymphocytes,[1] leading to a decrease in the number of host CD4+ T cells, which, in turn, causes immunodeficiency and may eventually progress to acquired immunodeficiency syndrome (AIDS).[2] According to statistics from the United Nations Joint Programme on HIV/AIDS, since the onset of the AIDS epidemic, 85.6 million people worldwide have been infected with HIV, and 40.4 million have died from AIDS-related diseases. While the global number of AIDS-related deaths has decreased by 51% since 2010, by 2023, 39 million people are still living with HIV, and 630,000 people have died from AIDS-related illnesses.[3] These data indicate that HIV/AIDS and its related diseases continue to be severe global public health challenges.

Despite the decline in mortality among HIV-infected people, their life expectancy is still lower than that of the general population, which is associated with an increased risk of contracting noncommunicable diseases (NCDs), such as diabetes mellitus, insulin resistance (IR), cardiovascular diseases, both AIDS-related and non-AIDS-related malignancies, metabolic syndrome, and others.[4] These factors contributing to increased risk include traditional risk factors (such as smoking, alcohol abuse, and drug misuse). In addition, HIV-specific factors (such as the toxicity of antiretroviral therapy, persistent high levels

Received: 12 June 2025
Accepted: 18 September 2025
Published: 30 September 2025

of inflammation, and immune activation).[5,6] However, the specific causal relationship between HIV infection and noncommunicable diseases remains unclear.

The physiological definition of IR is that the body requires relatively high levels of circulating insulin to effectively exert glucose-lowering effects on target cells.[7] A 2017 cross-sectional study in Cameroon, sub-Saharan Africa, reported that the prevalence of IR among HIV-infected individuals was as high as 47.3%.[8] Studies have shown that IR in individuals with HIV is not only linked to factors such as antiretroviral therapy(ART), the gut microbiota, and immune activation but may also be directly associated with HIV infection itself.[9,10] As a result, the causal relationship between HIV infection and IR remains unclear.

Diabetes is a group of metabolic diseases characterized by defects in insulin secretion, defects in insulin action, or both, leading to chronic hyperglycemia. Depending on the cause, diabetes can be divided into four categories: type 1 diabetes (T1D), type 2 diabetes (T2D), other specific types of diabetes, and gestational diabetes (GDM). T1D is caused by the destruction of β-cells, which primarily leads to absolute insulin deficiency. T2D ranges from predominantly IR with relative insulin deficiency to predominantly an insulin secretory defect with IR. Other specific types of diabetes include genetic defects in beta cells, genetic defects in insulin action, exocrine diseases of the pancreas, etc. GDM is defined as any degree of impaired glucose tolerance that develops or is first identified during pregnancy. The main diagnostic indicator for diabetes is glycated hemoglobin (GHbA1c), which is also an important chronic blood glucose marker.[11] A global meta-analysis conducted in 2020 revealed that the prevalence of diabetes among HIV-infected individuals ranged from 1.3% to 26%, with an incidence rate ranging from 2.9% to 12.8%.[12] Additionally, studies in low- and middle-income countries have reported that the incidence of diabetes among HIV-infected individuals ranges from 1.3% to 18%.[13] These data indicate that HIV infection may increase the risk of diabetes,[14,15] but the causal relationship between HIV and diabetes remains unclear.

Instrumental variables (IVs) are variables that are associated with the exposure under study but are not influenced by confounders. They affect the outcome solely through their relationship with risk factors. While any variable that meets these criteria can serve as an instrumental variable, genetic variants are often considered reasonable choices because of their unique genetic characteristics.[16] Mendelian randomization (MR) uses genetic variation, such as single nucleotide polymorphisms (SNPs), as instrumental variables to assess whether observational associations between exposure factors and outcomes are causal. This approach effectively avoids reverse causality bias and confounding—issues commonly encountered in traditional studies[16–19]—and provides a level of evidence that is regarded as just below that of randomized controlled trials (RCTs).[16]

This study aims to investigate whether HIV infection is causally associated with metabolic diseases via an MR approach, integrating the most recent data on HIV infection with data on IR, D1M, D2M, and GDM. Additionally, the relationship between HIV infection and GHbA1c will be analyzed to further support and validate these causal associations.

Methods

Study Design

This study utilized two-sample bidirectional MR analysis to evaluate the causal relationships between HIV infection and IR and diabetes. This study strictly followed the basic principles outlined in the Guidelines for the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization (STROBE-MR).[20] In this study, SNPs were used as IVs, requiring the following three core assumptions: (1) Correlation assumption: a significant correlation exists between the IVs and the exposure factors; (2) Independence assumption: the IVs is not associated with any potential confounding factors; (3) Exclusivity assumption: the IVs affects the outcome solely through the exposure factors, without influence from other factors. The study design is shown in Figure 1.

Data Sources

All data used in this study were obtained from the IEU Open GWAS database and Finnish databases. To ensure population homogeneity, datasets for both exposures and outcomes were selected exclusively from individuals of European ancestry.

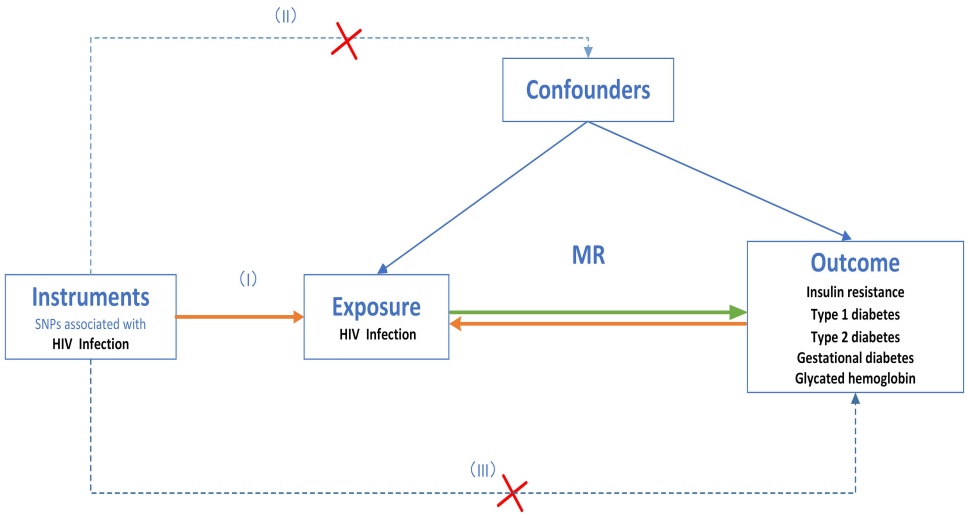

Figure 1 Study design. (I) Correlation assumption: IVs are related to the exposure. (II) Independence assumption: IVs are independent of confounders. (III) Exclusivity assumption: IVs affect the outcome only through the exposures.
Abbreviation: MR, Mendelian randomization.

The datasets on HIV infection and comorbidity with other diseases are derived from Finnish databases and consist of the following two groups: finn-b-AB1_HIV, which addresses infectious and parasitic diseases caused by HIV, and finn-b-AB1_OTHER_CONDITIONS, which covers other conditions caused by HIV. Given that this study aimed to explore the relationship between HIV infection and noncommunicable diseases such as IR and diabetes, the finn-b-AB1_OTHER_CONDITIONS dataset was selected.

The specific datasets used in this study were as follows: HIV infection (Finn-b-AB1A-OTHER-CONDITIONS: 333 cases and 218,435 controls), IR (Ebi-a-GCST005179: 37,037 participants), T1D (Ebi-a-GCST90014023: 520,580 participants, including 18,942 cases and 501,638 controls), T2D (Ebi-a-GCST006867: 655,666 participants, including 61,714 cases and 1178 controls), GDM (Finn-b-GEST_DIABETES: 5687 cases and 117,892 controls), and GHbA1c (Ebi-a-GCST005179: 344,182 participants). Data on other specific types of diabetes mellitus were not analyzed because of the current lack of data and their low prevalence. (Detailed information on the GWAS data used in this study can be found in Table S1).

Selection of Genetic Instruments

In this study, instrumental variables were rigorously screened via pooled GWAS data to ensure that they satisfied the core assumptions of MR analysis. First, the selected SNPs had to be significantly correlated with the exposure factors, with p values at the genome-wide significance level being less than 5×10^{-8}. Second, to minimize potential bias from linkage disequilibrium, we applied an $R^2 < 0.001$ threshold and a clustering window of >10,000 kb for SNPs aggregation. Next, each SNP was manually examined via the PhenoScape database (PhenoScanner)[21] and the LDtrait tool[22] to exclude genetic variants associated with potential confounders.

In addition, to prevent the influence of weak instrumental variables on causal inference, we calculated the strength of all remaining SNPs as instrumental variables by assessing the F statistic, which is defined as:

$$F = \frac{R^2(N-2)}{1-R^2}$$

where R^2 represents the proportion of variance in HIV infection explained by each instrument and where N is the GWAS sample size for HIV infection.[23]

https://doi.org/10.2147/JMDH.S546669

The R^2 value was calculated via the following formula:

$$R^2 = \frac{2 \times \ EAF \times (1 - EAF) \times \beta^2}{2 \times \ EAF \times (1 - EAF) \times \beta^2 + 2 \times \ EAF \times (1 - EAF) \times N \times \ SE(\beta)^2}$$

Here, EAF refers to the effect allele frequency, β is the estimated genetic effect on HIV infection, and SE (β) denotes the standard error of the effect.[23] F statistics greater than 10 are considered indicative of strong instrumental variables and are deemed appropriate for MR analyses.[24]

Finally, the exposure and outcome datasets were harmonized to exclude palindromic and ambiguous SNPs with incongruent alleles, ensuring allelic consistency. The filtered SNPs were then used in two-sample MR analyses to provide robust evidence of genetic causation.

Statistical Analysis

In conducting forward MR analyses, where HIV infection was treated as the exposure factor, we began by identifying SNPs that reached genome-wide significance ($P < 5 \times 10^{-8}$) to serve as IVs. Given the limited number of SNPs identified, we adjusted the threshold to $P < 5 \times 10^{-5}$. For the inverse MR analysis, however, we adhered to the genome-wide significance threshold ($P < 5 \times 10^{-8}$) when selecting SNPs to serve as IVs.

To evaluate the causal relationships between HIV infection and IR, diabetes mellitus, and GHbA1c, we applied various MR analytical methods, including inverse variance weighting (IVW), MR–Egger regression, weighted median, simple mode, and weighted mode. The IVW method was used as the primary analytical approach, as it delivers the most accurate results without requiring the assumption of horizontal pleiotropy validity.[25] We subsequently performed a series of sensitivity analyses. To detect heterogeneity in the SNP effects of the instrumental variables, we applied Cochran's Q test, with $P < 0.05$ indicating significant heterogeneity.[26] We applied the MR–Egger intercept test to assess the potential presence of horizontal pleiotropy. Additionally, we utilized the MR-PRESSO method to identify and exclude SNP outliers with potential pleiotropic effects, ensuring that the final estimates aligned with the results of the IVW method.[27] To further evaluate robustness, we conducted a leave-one-out sensitivity analysis to assess the influence of each individual SNP on causal inference.[28]

Statistical analyses were conducted via R software (version 4.4.0), leveraging the "TwoSampleMR" (version 0.6.1) and "ggplot2" (version 3.5.1) packages for data processing and visualization. All presented P values were two-tailed (all presented P values were two tailed), where P values between 0.01 and 0.05 were considered suggestive causal inferences. In this analysis, MR results were reported as odds ratios (ORs) with 95% confidence intervals (CIs), where the ORs represented the relationship between a per-unit change in exposure factors and the risk of the outcome.

Results

Result 1: Positive Relationship Between HIV Infection and Insulin Resistance and Diabetes Mellitus

On the basis of the assumptions of MR analysis, this study examines HIV infection as an exposure to assess its causal relationships with IR, T1D, T2D, and GDM. IVs that are strongly correlated with these outcomes were selected: specifically, 6 for IR, 33 for T1D, 6 for T2D, and 34 for GDM (Tables S2.1–S2.4 for detailed IVs).

Analysis via the IVW method did not reveal significant causal relationships. The results were as follows: IR (OR = 1.004, 95% CI [0.991, 1.018], p = 0.525), T1D (OR = 1.009, 95% CI [0.900, 1.027], p = 0.359), T2D (OR = 0.994, 95% CI [0.969, 1.021], p = 0.671), and GDM (OR = 1.006, 95% CI [0.988, 1.025], p = 0.489) (Figure 2A–D).

Scatter plot analyses demonstrated that the results obtained from the MR–Egger, weighted median, simple mode, and weighted mode methods were consistent with those of the IVW method, further reinforcing the robustness of the findings (Figure 3A–D).

Cochran's Q test results indicated that the p values for both the IVW and MR–Egger methods exceeded 0.05, suggesting that there was no significant heterogeneity among the instrumental variables (Tables S3.1–S3.4 for

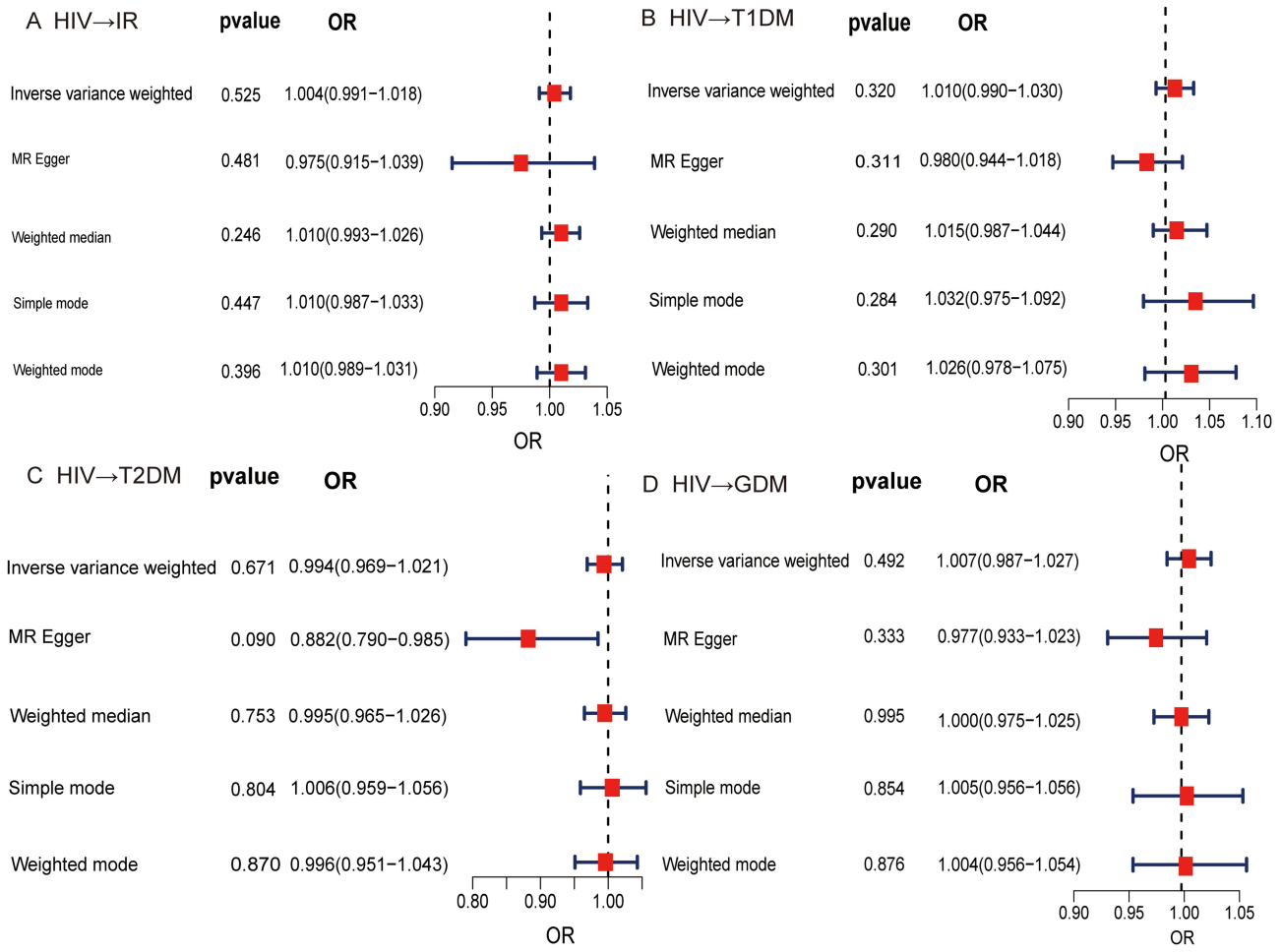

Figure 2 Results of MR analysis of the effects of HIV infection on insulin resistance and diabetes mellitus. (**A**) Shows the results of MR analysis of HIV infection and IR; (**B**) Shows the results of MR analysis of HIV infection and T1D; (**C**) Shows the results of analysis of HIV infection and T2D; (**D**) Shows the results of analysis of HIV infection and GDM.

heterogeneity). Furthermore, MR-PRESSO indicated no significant outlier SNPs (Tables S4.1–S4.4), and MR–Egger regression detected no evidence of horizontal pleiotropy (Tables S5.1–S5.4 for Pleiotropy).

Funnel plot analysis revealed that the causal effects were symmetrically distributed, supporting the robustness of MR–Egger regression (Figure S1 for the funnel plots). Additionally, sensitivity analysis via forest plots and the leave-one-out method further confirmed that excluding each SNP individually did not significantly alter the results, suggesting that the analysis is robust and reliable, with no single SNP having a significant effect on the causal relationships among HIV infection, IR, and diabetes (Figures S2 and S3 for the forest and leave-one-out plots).

Result 2: Inverse Associations of HIV Infection with Insulin Resistance and Diabetes Mellitus

Similarly, we analyzed the effects of IR and diabetes as exposure factors on HIV infection. A total of 47, 72, 114, and 17 highly correlated IVs were selected for analysis (Tables S2.5–S2.8 for detailed IVs). In the analysis of T1D, the instrumental variable rs1008438 was excluded because of its association with the HIV gp41 C34 peptide.

The results of the IVW analysis revealed no significant causal associations. Specifically, the results were as follows: for IR: OR = 0.787 (95% CI [0.293, 2.109]), p = 0.633; for T1D: OR = 1.038 (95% CI [0.946, 1.139]), p = 0.43; for T2D: OR = 0.993 (95% CI [0.815, 1.211]), p = 0.948; for GDM: OR = 1.197 (95% CI [0.896, 1.600]), p = 0.224 (Figure 4A–D).

https://doi.org/10.2147/JMDH.S546669

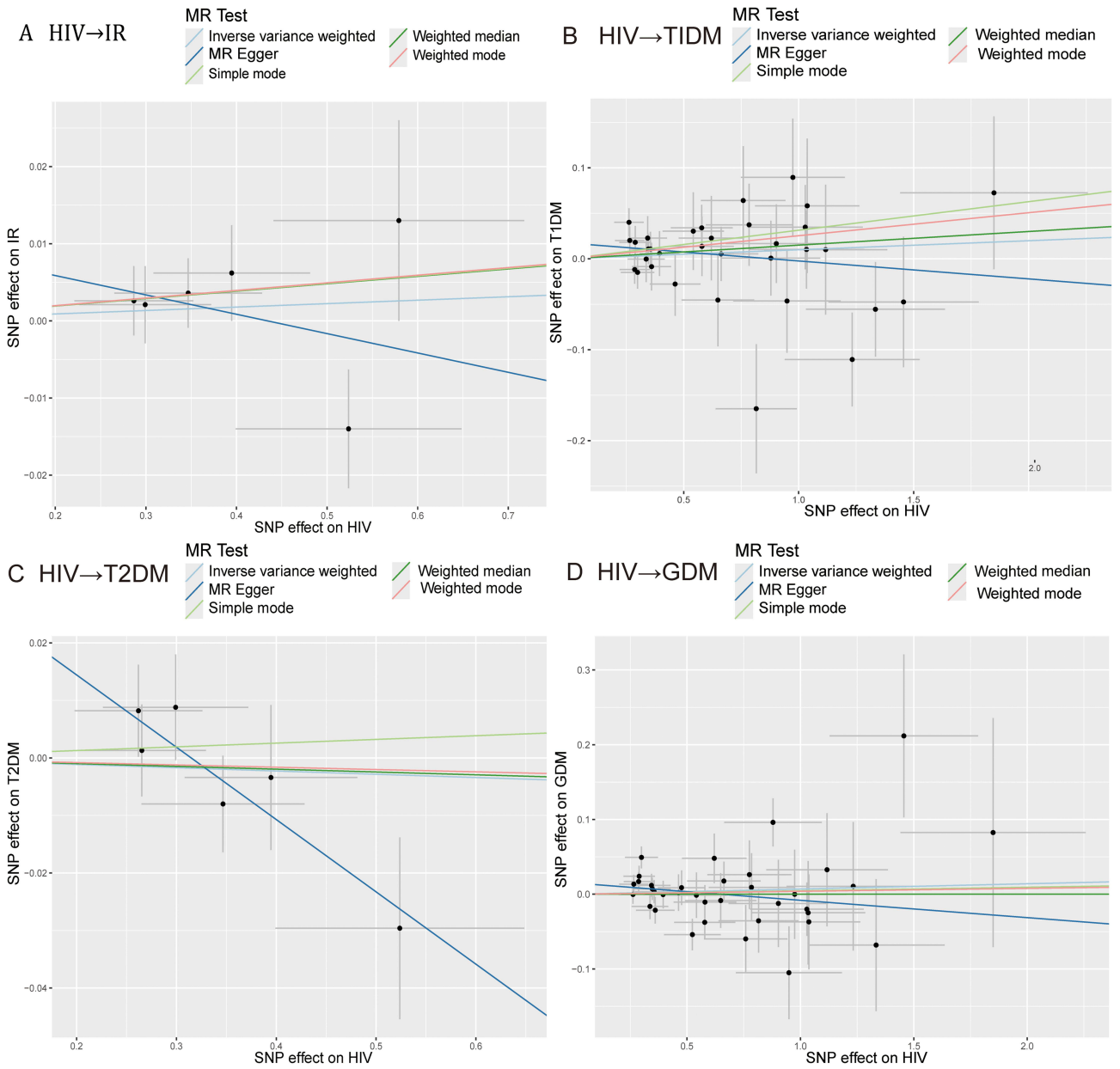

Figure 3 Scatter plots of MR analysis of the effects of HIV infection on insulin resistance and diabetes mellitus. (**A**) Shows the scatter plot of MR analysis of HIV infection with IR; (**B**) Shows the scatter plot of MR analysis of HIV infection with T1D; (**C**) Shows the scatter plot of MR analysis of HIV infection with T2D; (**D**) Shows the scatter plot of MR analysis of HIV infection with GDM.

The scatter plots confirmed that the ORs derived from the MR–Egger, weighted median, simple mode, and weighted mode methods were consistent with those from the IVW method, further validating the robustness of the results (Figure 5A–D).

Cochran's Q test revealed that the p values for both the IVW and MR–Egger analyses were greater than 0.05, indicating that there was no significant heterogeneity among the IVs (Tables S3.5–S3.8 for heterogeneity). Furthermore, MR-PRESSO indicated no significant outlier SNPs (Tables S4.5–S4.8), and MR–Egger regression detected no evidence of horizontal pleiotropy (Tables S5.5–S5.8 for Pleiotropy).

Funnel plot analysis demonstrated that the causal effects were symmetrically distributed, further supporting the findings of the MR–Egger regression (Figure S4 for the funnel plots). Sensitivity analysis, including forest plots and

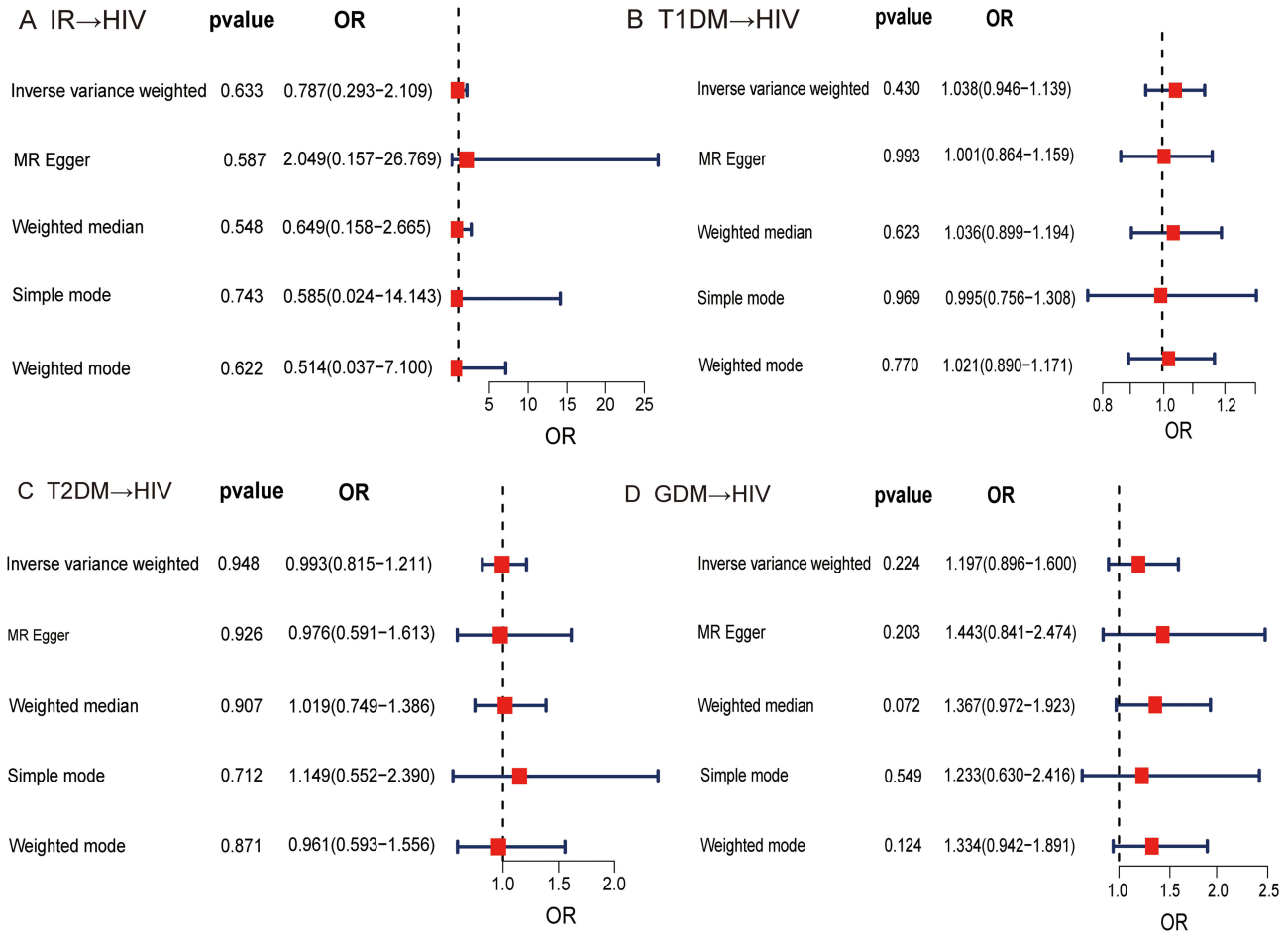

Figure 4 Results of MR analysis of the effects of insulin resistance and diabetes mellitus on HIV infection. (**A**) Shows the results of MR analysis of IR and HIV infection; (**B**) Shows the results of MR analysis of T1D and HIV infection; (**C**) Shows the results of MR analysis of T2D and HIV infection; and (**D**) Shows the results of MR analysis of GDM and HIV infection.

leave-one-out analysis, further confirmed that excluding individual SNPs did not significantly alter the IVW analysis results, indicating the robustness of the findings (Figures S5 and S6 for the forest and leave-one-out plots).

Result 3: HIV and Glycated Hemoglobin MR Analysis

The study also examined the causal relationship between HIV infection (exposure) and GHbA1c (outcome). We selected 34 IVs highly correlated with GHbA1c for analysis (Table S2.9 for detailed IVs). The analysis of a European cohort revealed no significant causal relationship between HIV infection and GHbA1c via the IVW method (OR = 1.001, 95% CI [0.998, 1.004], p = 0.554; Figure 6A). Scatter plots confirmed that the results of the MR–Egger, weighted median, simple mode, and weighted mode methods were consistent with those of the IVW method, further validating the robustness of the findings (Figure 6B).

Cochran's Q test indicated no significant heterogeneity between individual SNPs, with p values greater than 0.05 for both the IVW and MR–Egger methods (Table S3.9 for heterogeneity). MR-PRESSO detected no significant outlier SNPs (Table S4.9), and MR-Egger regression detected no evidence of horizontal pleiotropy (Table S5.9). Funnel plot analysis revealed a symmetrical distribution of causal effects, supporting the robustness of the MR–Egger regression results (Figure S7A for the funnel plots). Sensitivity analyses, including forest plots and leave-one-out analysis, revealed that excluding individual SNPs did not significantly affect the IVW results, confirming the robustness and reliability of the findings (Figure S7B and C for the forest and leave-one-out plots).

https://doi.org/10.2147/JMDH.S546669

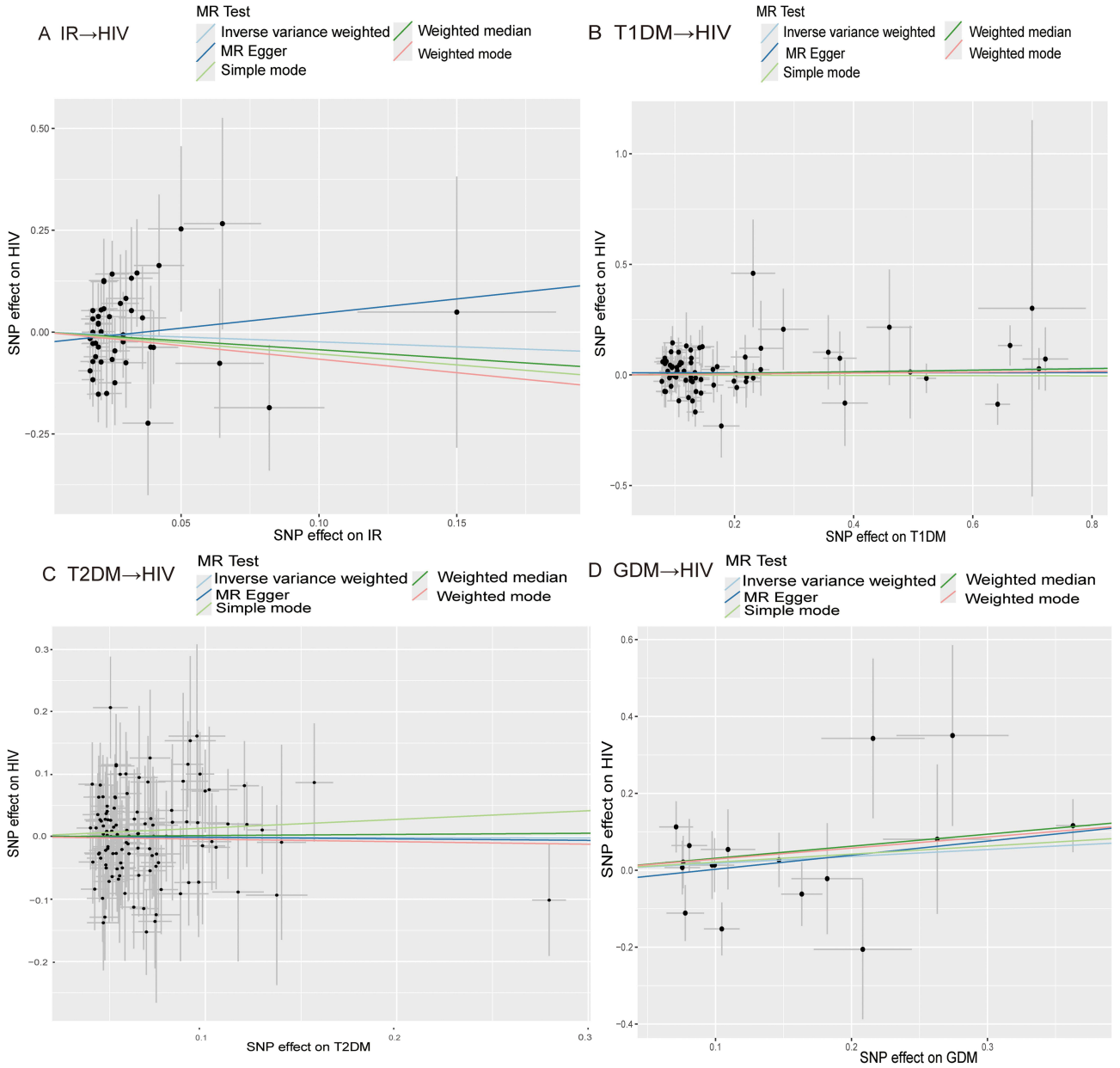

Figure 5 Scatter plots of MR analysis for insulin resistance and diabetes mellitus in HIV infection. (**A**) Shows the scatter plot of MR analysis of IR with HIV infection; (**B**) Shows the scatter plot of MR analysis of T1D with HIV infection; (**C**) Shows the scatter plot of MR analysis of T2D with HIV infection; (**D**) Shows the scatter plot of MR analysis of GDM with HIV infection.

For further analysis, GHbA1c was treated as the exposure factor, and HIV infection was treated as the outcome variable. A total of 276 IVs highly correlated with GHbA1c were selected for MR analysis (Table S2.10 for detailed IVs). In the European population, the IVW method revealed no significant causal relationship between GHbA1c and HIV infection (OR = 0.948, 95% CI [0.672, 1.338], p = 0.761; Figure 6C). Scatter plots confirmed that the results of the MR–Egger, weighted median, simple mode, and weighted mode methods were consistent with those of the IVW method, further validating the robustness of the findings (Figure 6D).

According to Cochran's Q test, the p values for both IVW and MR–Egger were greater than 0.05, indicating no significant heterogeneity among the instrumental variables (Table S3.10 for heterogeneity). MR-PRESSO indicated no significant outlier SNPs (Table S4.10), and MR–Egger regression detected no evidence of horizontal pleiotropy (Table S5.10). Funnel plot

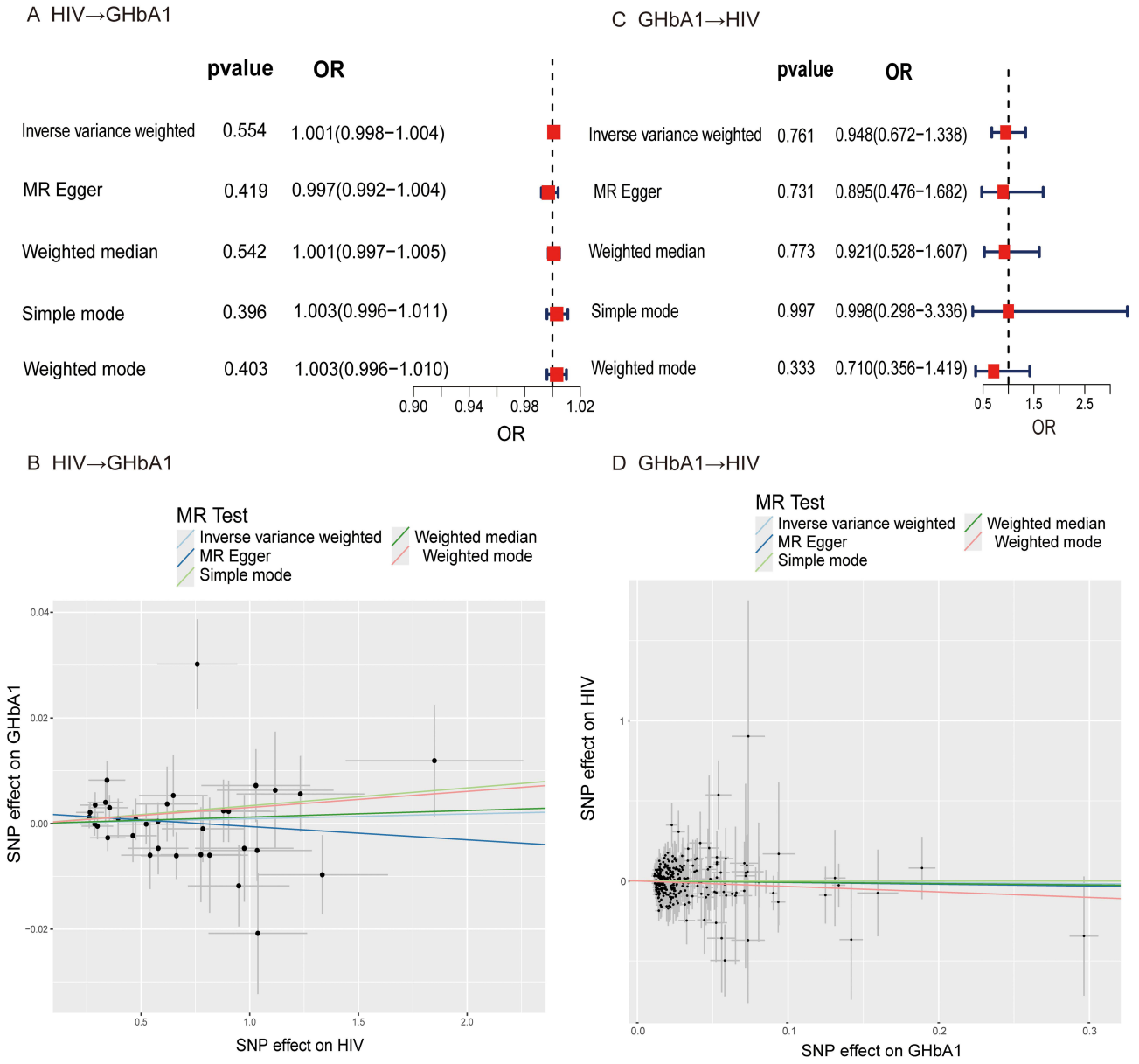

Figure 6 Bidirectional scatter plots and results of MR analysis of the effects of HIV infection on glycated hemoglobin. (**A**) Shows the scatter plot of MR analysis between HIV infection and glycated hemoglobin; (**B**) Shows the MR analysis results between HIV infection and glycated hemoglobin; (**C**) Shows the scatter plot of MR analysis between glycated hemoglobin and HIV infection; (**D**) Shows the MR analysis results between glycated hemoglobin and HIV infection.

analysis further supported the robustness of MR–Egger regression (Figure S8A for the funnel plots), and sensitivity analysis confirmed that no single SNP significantly affected the IVW results (Figure S8B and C for the forest and leave-one-out plots).

Discussion

This study systematically investigated the causal relationships between HIV infection and IR and diabetes mellitus through a two-sample MR approach on the basis of data from the GWAS database. The relationships between GHbA1c, a key biomarker of diabetes, and HIV infection were subsequently analyzed to validate the previous findings, yielding consistent conclusions. The study revealed no statistically significant causal relationships between HIV infection and IR and diabetes. Multiple sensitivity analyses were conducted to ensure the robustness of the results, further reinforcing the reliability of the findings.

Our study found no direct causal effect of HIV infection on IR. This result is consistent with existing research suggesting that the increased IR observed among people living with HIV is mainly driven by traditional risk factors (such as age and obesity) and HIV-related factors—particularly ART—rather than HIV itself.[5,6] Notably, ART, the cornerstone of lifelong HIV treatment, exerts complex and wide-ranging effects on metabolism. For example, protease inhibitors (PIs), such as lopinavir, ritonavir and nelfinavir, can directly interfere with the function of GLUT4 transporters, thereby reducing glucose uptake in adipocytes and muscle cells.[29–31] Some PIs may also inhibit adipocyte differentiation[32] and modulate the expression and localization of sterol regulatory element-binding protein 1, which in turn affects the expression of lipogenic factors[33,34] and triglyceride storage. These changes may contribute to abnormal lipid accumulation and disrupted signaling in insulin target tissues.[35] PIs have also been shown to induce endoplasmic reticulum stress and activate inflammatory pathways, such as the NF-κB–IKK cascade, further worsening IR.[36,37] Nucleoside reverse transcriptase inhibitors (NRTIs), such as stavudine, may contribute to the progression of IR by inducing mitochondrial DNA damage and impairing energy metabolism.[38,39] In recent years, epigenetic modifications have also been recognized as potential mechanisms involved in this process.[40] Collectively, these findings suggest that HIV infection may influence insulin sensitivity indirectly through multiple mediating pathways rather than acting as a direct causative factor. This is in line with our MR results. However, some observational studies have reported contradictory findings, likely due to confounding factors—such as ART exposure—that are difficult to fully control for.[41,42] For example, a 2019 cross-sectional study in Uganda involving perinatally HIV-infected children reported an association between HIV infection and IR,[43] and a 2023 prospective study reached similar conclusions.[44]

Additionally, our study found no significant causal association between HIV infection and either T1D or T2D, although epidemiological evidence suggests a higher risk of T2D in people with HIV compared to the general population.[45–48] This elevated risk is thought to result primarily from traditional factors (eg, age, obesity, baseline IR, dyslipidemia) and HIV-related factors (eg, specific ART drugs, HCV coinfection) rather than HIV itself. For instance, a US-based prospective study identified age, HCV coinfection and prolonged ART as key risk factors, with little contribution from HIV per se.[49] Another study, with a median follow-up of over seven years, found that T2D incidence was significantly associated with baseline IR, hypertriglyceridemia, central obesity and statin therapy, but not with HIV-related variables.[50] Mechanistic studies support these findings as well.[51] The metabolic side effects of HIV medications are known to play a critical role in T2D development. PIs, like indinavir and ritonavir, impair peripheral glucose uptake by disrupting GLUT4 function. They may also suppress peroxisome proliferator-activated receptor activity by interfering with cellular retinoic acid-binding protein 1, leading to adipocyte inflammation and free fatty acid release, which negatively affect insulin secretion and sensitivity.[52,53] Moreover, nelfinavir and indinavir can directly damage pancreatic β-cells, resulting in impaired insulin secretion.[54,55] Long-term use of NRTIs (eg, stavudine, zidovudine) has been linked to mitochondrial DNA damage, energy metabolism dysfunction and insulin resistance.[56] Integrase inhibitors may contribute to diabetes through mechanisms such as magnesium depletion.[57] These mediators support the conclusion that HIV infection is not a direct cause of T2D but exerts indirect effects through complex mechanisms—particularly ART-related pathways—consistent with our causal inference findings.

Finally, we found no statistically significant causal association between HIV infection and GDM. Although some studies (eg, a 2023 South African cohort study) have reported an elevated risk of glucose metabolism abnormalities in HIV-positive pregnant women,[58] these findings do not contradict our results. Meta-analyses published in 2017 and 2023, both globally and in the UK/Ireland, also found no significant association between HIV and GDM,[59,60] further supporting the notion that HIV infection itself is not a direct trigger of GDM. Existing evidence suggests that the increased GDM risk among HIV-positive pregnant women may result from multiple mediating factors, including impaired placental function due to HIV infection, ART exposure, hormonal imbalances, metabolic disruptions and abnormal regulation of growth factors—with ART playing a particularly prominent role.[61] ART may interfere with placental endocrine function, for example by reducing progesterone[62] and leptin (which has anti-diabetic properties),[63] increasing cortisol levels[64] and disrupting the placental growth hormone–insulin-like growth factor-1 (GH–IGF-1) axis,[65,66] thereby contributing to impaired glucose metabolism. Therefore, HIV may indirectly promote the development of GDM via multiple intermediary pathways rather than acting as a direct cause.

Although this study did not identify a significant causal relationship between HIV infection and IR or diabetes, the findings hold important implications for public health policy. Close attention should be given to risk factors linked to IR and diabetes in HIV-infected patients, such as antiretroviral therapy, coinfections, and lifestyle factors, as part of their

treatment and disease management. Therefore, it is crucial to develop more precise, personalized public health policies aimed at improving these patients' quality of life and extending their life expectancy.

The present study has several strengths, most notably its use of a rigorous MR design, which effectively minimized the impact of confounding factors and reduced the likelihood of reverse causality. Additionally, the instrumental variables selected were strongly associated with the exposure factors of interest and were not in linkage disequilibrium. In our analyses, the F statistics of the instrumental variables were all well above 10, demonstrating the strong validity of the genetic instruments. Horizontal pleiotropy poses a significant challenge for MR studies, as genetic variations can influence results through pathways unrelated to the target exposure factors. To address this, several sensitivity analyses were conducted to minimize the effects of heterogeneity and pleiotropy, ensuring the robustness of our findings. The results of the MR–Egger intercept test did not show horizontal pleiotropy, which further confirms the reliability of our results. In addition, the results were further validated in this study via MR analysis of GHbA1c, and all this evidence supports the reliability of our findings. Finally, the sample size was large enough, enabling us to obtain more accurate results.

While this study provides valuable insights, it also has several limitations. The findings are primarily based on GWAS data, which predominantly focus on individuals of European ancestry, making it uncertain whether the results can be generalized to other ethnic groups. Given the limited data on the associations between HIV infection and IR and diabetes in other populations, further validation in diverse cohorts would be highly valuable. Additionally, although this study suggests that there is no causal relationship between these factors, the underlying mechanisms through which HIV-infected individuals develop comorbid IR and diabetes warrant further investigation.

Conclusion

This study revealed no significant causal relationships between HIV infection and IR or diabetes. These findings provide valuable insights for clinical practice, suggesting that while metabolic health is a critical aspect of managing HIV-infected individuals, HIV infection itself should not be considered a direct cause of IR and diabetes. Further research is needed to investigate potential mediators or underlying mechanisms—such as ART, obesity, and chronic inflammation—that may contribute to the development of IR and diabetes in this population. Clinicians should consider these factors when developing personalized treatment strategies to optimize patient management and outcomes.

Abbreviations

AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; GDM, gestational diabetes; GHbA1c, glycated hemoglobin; HIV, human immunodeficiency virus; IR, insulin resistance; IV, instrumental variable; IVW, inverse variance weighting; MR, Mendelian randomization; NCD, noncommunicable disease; NRTIs, nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; RCT, randomized controlled trial; SNP, single nucleotide polymorphism; T1D, type 1 diabetes; T2D, type 2 diabetes.

Data Sharing Statement

The original data used are publicly available at https://gwas.mrcieu.ac.uk/. and https://www.finngen.fi/en. The original contributions presented in the This study is included in the article, and further inquiries can be directed to the corresponding author.

Ethics Approval Statement

The genetic data used in this study were sourced from publicly available genome-wide association study databases. All data are legally obtained and consist of anonymized summary statistics. The original studies received ethical approval from the respective institutions and obtained informed consent from participants. In accordance with Article 32, Sections (1) (use of legally obtained public data) and (2) (use of anonymized data) of the "Ethical Review Measures for Life Science and Medical Research Involving Humans" (Guo Wei Ke Jiao Fa (2023) No. 4) issued by the National Health Commission of China, this study does not involve harm to human participants, sensitive personal information, and commercial interests. Therefore, it meets the statutory criteria for exemption from ethical review. Based on these regulations, this study does not require review by an institutional ethics committee.

Consent for Publication

All authors have approved the submitted final version and are to be personally accountable for their contributions.

Acknowledgments

Thanks to North Sichuan Medical College and its affiliated hospital for providing academic support and research resources, which greatly contributed to the successful completion of this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was not supported by any funding.

Disclosure

The authors declare no competing interests in this work.

References

1. Chan DC, Kim PS. HIV entry and its inhibition. *Cell*. 1998;93(4):681–684. doi:10.1016/S0092-8674(00)81430-0
2. Bekker LG, Beyrer C, Mgodi N, et al. HIV infection. *Nat Rev Dis Primers*. 2023;9(1):42. doi:10.1038/s41572-023-00452-3
3. UNAIDS. Global HIV & AIDS statistics—fact sheet. Available from: https://www.unaids.org/en/resources/fact-sheet. Accessed July 22, 2024.
4. Kiplagat J, Tran DN, Barber T, et al. How health systems can adapt to a population aging with HIV and comorbid disease. *Lancet HIV*. 2022;9(4):e281–e292. doi:10.1016/S2352-3018(22)00009-1
5. Ghosn J, Taiwo B, Seedat S, et al. HIV. *Lancet*. 2018;392(10148):685–697. doi:10.1016/S0140-6736(18)31311-4
6. Croxford S, Kitching A, Desai S, et al. Mortality and causes of death in people diagnosed with HIV in the era of highly active antiretroviral therapy compared with the general population: an analysis of a national observational cohort. *Lancet Public Health*. 2017;2(1):e35–e46. doi:10.1016/S2468-2667(16)30020-2
7. Petersen MC, Shulman GI. Mechanisms of insulin action and insulin resistance. *Physiol Rev*. 2018;98(4):2133–2223. doi:10.1152/physrev.00063.2017
8. Noumegni SRN, Nansseu JR, Ama VJM, et al. Insulin resistance and associated factors among HIV-infected patients in sub-Saharan Africa: a cross-sectional study from Cameroon. *Lipids Health Dis*. 2017;16(1):148. doi:10.1186/s12944-017-0543-1
9. Pedro MN, Rocha GZ, Guadagnini D, et al. Insulin resistance in HIV-patients: causes and consequences. *Front Endocrinol*. 2018;9:514. doi:10.3389/fendo.2018.00514
10. Harbuwono DS, Nenfiati, Tahapary DL, et al. Defining the optimum HOMA-IR cutoff value for insulin resistance among ARV-treated HIV patients in Indonesia. *Diabetes Metab Syndr*. 2023;17(2):102719. doi:10.1016/j.dsx.2023.102719
11. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2014;37(suppl 1):S81–S90. doi:10.2337/dc14-S081
12. Daultrey H, Youseff E, Wright J, et al. The investigation of diabetes in people living with HIV: a systematic review. *Diabet Med*. 2021;38(4):e14454. doi:10.1111/dme.14454
13. Patel P, Rose CE, Collins PY, et al. Noncommunicable diseases among HIV-infected persons in low-income and middle-income countries: a systematic review and meta-analysis. *AIDS*. 2018;32(suppl 1):S5–S20. doi:10.1097/QAD.0000000000001888
14. Jeremiah K, Filteau S, Faurholt-Jepsen D, et al. Diabetes prevalence by HbA1c and oral glucose tolerance test among HIV-infected and uninfected Tanzanian adults. *PLoS One*. 2020;15(4):e0230723. doi:10.1371/journal.pone.0230723
15. Hernandez-Romieu AC, Garg S, Rosenberg ES, et al. Is diabetes prevalence higher among HIV-infected individuals compared with the general population? Evidence from MMP and NHANES 2009–2010. *BMJ Open Diabetes Res Care*. 2017;5(1):e000304. doi:10.1136/bmjdrc-2016-000304
16. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomization studies: a guide, glossary, and checklist for clinicians. *BMJ*. 2018;362:k601. doi:10.1136/bmj.k601
17. Emdin CA, Khera AV, Kathiresan S. Mendelian randomization. *JAMA*. 2017;318(19):1925–1926. doi:10.1001/jama.2017.17219
18. Davey Smith G, Ebrahim S. Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol*. 2003;32(1):1–22. doi:10.1093/ije/dyg070
19. Evans DM, Davey Smith G. Mendelian randomization: new applications in the coming age of hypothesis-free causality. *Annu Rev Genomics Hum Genet*. 2015;16:327–350. doi:10.1146/annurev-genom-090314-050016
20. Skrivankova VW, Richmond RC, Woolf BAR, et al. Strengthening the reporting of observational studies in epidemiology using Mendelian randomization: the STROBE-MR statement. *JAMA*. 2021;326(16):1614–1621. doi:10.1001/jama.2021.18236
21. Kamat MA, Blackshaw JA, Young R, et al. PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations. *Bioinformatics*. 2019;35(22):4851–4853. doi:10.1093/bioinformatics/btz469

22. Brion MJ, Shakhbazov K, Visscher PM. Calculating statistical power in Mendelian randomization studies. *Int J Epidemiol*. 2013;42(5):1497–1501. doi:10.1093/ije/dyt179
23. Papadimitriou N, Dimou N, Tsilidis KK, et al. Physical activity and risks of breast and colorectal cancer: a Mendelian randomization analysis. *Nat Commun*. 2020;11(1):597. doi:10.1038/s41467-020-14389-8
24. Hemani G, Bowden J, Davey Smith G. Evaluating the potential role of pleiotropy in Mendelian randomization studies. *Hum Mol Genet*. 2018;27 (R2):R195–R208. doi:10.1093/hmg/ddy163
25. Greco MF, Minelli C, Sheehan NA, Thompson JR. Detecting pleiotropy in Mendelian randomization studies with summary data and a continuous outcome. *Stat Med*. 2015;34(21):2926–2940. doi:10.1002/sim.6522
26. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet*. 2018;50(5):693–698. doi:10.1038/s41588-018-0099-7
27. Burgess S, Bowden J, Fall T, et al. Sensitivity analyses for robust causal inference from Mendelian randomization analyses with multiple genetic variants. *Epidemiology*. 2017;28(1):30–42. doi:10.1097/EDE.0000000000000559
28. Hemani G, Tilling K, Davey Smith G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. *PLoS Genet*. 2017;13(11):e1007081. doi:10.1371/journal.pgen.1007081
29. Hruz PW. Molecular mechanisms for insulin resistance in treated HIV infection. *Best Pract Res Clin Endocrinol Metab*. 2011;25(3):459–468. doi:10.1016/j.beem.2010.10.017
30. Murata H, Hruz PW, Mueckler M. The mechanism of insulin resistance caused by HIV protease inhibitor therapy. *J Biol Chem*. 2000;275 (27):20251–20254. doi:10.1074/jbc.C000228200
31. Koster JC, Remedi MS, Qiu H, et al. HIV protease inhibitors acutely impair glucose-stimulated insulin release. *Diabetes*. 2003;52(7):1695–1700. doi:10.2337/diabetes.52.7.1695
32. Kim RJ, Wilson CG, Wabitsch M, et al. HIV protease inhibitor-specific alterations in human adipocyte differentiation and metabolism. *Obesity*. 2006;14(6):994–1002. doi:10.1038/oby.2006.114
33. Bastard JP, Caron M, Vidal H, et al. Association between altered expression of adipogenic factor SREBP1 in lipoatrophic adipose tissue from HIV-1–infected patients and abnormal adipocyte differentiation and insulin resistance. *Lancet*. 2002;359(9311):1026–1031. doi:10.1016/S0140-6736(02)08094-7
34. Caron M, Auclair M, Vigouroux C, et al. The HIV protease inhibitor indinavir impairs sterol regulatory element binding protein 1 intranuclear localization, inhibits preadipocyte differentiation, and induces insulin resistance. *Diabetes*. 2001;50(6):1378–1388. doi:10.2337/diabetes.50.6.1378
35. Samuel VT, Petersen KF, Shulman GI. Lipid-induced insulin resistance: unravelling the mechanism. *Lancet*. 2010;375(9733):2267–2277. doi:10.1016/S0140-6736(10)60408-4
36. Parker RA, Flint OP, Mulvey R, et al. Endoplasmic reticulum stress links dyslipidemia to inhibition of proteasome activity and glucose transport by HIV protease inhibitors. *Mol Pharmacol*. 2005;67(6):1909–1919. doi:10.1124/mol.104.010165
37. Hotamisligil GS. Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. *Cell*. 2010;140(6):900–917. doi:10.1016/j.cell.2010.02.034
38. Barile M, Valenti D, Hobbs GA, et al. Mechanisms of toxicity of 3′-azido-3′-deoxythymidine: its interaction with adenylate kinase. *Biochem Pharmacol*. 1994;48(7):1405–1412. doi:10.1016/0006-2952(94)90564-9
39. Barile M, Valenti D, Passarella S, Quagliariello E. 3′-Azido-3′-deoxythymidine uptake into isolated rat liver mitochondria and impairment of ADP/ATP translocator. *Biochem Pharmacol*. 1997;53(7):913–920. doi:10.1016/S0006-2952(96)00831-3
40. Cao K, Lv W, Wang X, et al. Hypermethylation of hepatic mitochondrial ND6 provokes systemic insulin resistance. *Adv Sci*. 2021;8(11):2004507. doi:10.1002/advs.202004507
41. Vos AG, Chersich MF, Klipstein-Grobusch K, et al. Lipid levels, insulin resistance and cardiovascular risk over 96 weeks of antiretroviral therapy: a randomized controlled trial comparing low-dose stavudine and tenofovir. *Retrovirology*. 2018;15(1):77. doi:10.1186/s12977-018-0460-z
42. Honnapurmath VK, Patil VW. Antiretroviral therapy-induced insulin resistance and oxidative deoxynucleic acid damage in human immunodeficiency virus-1 patients. *Indian J Endocrinol Metab*. 2017;21(2):316–321. doi:10.4103/2230-8210.202029
43. Dirajlal Fargo S, Shan L, Sattar A, et al. Insulin resistance and intestinal integrity in children with and without HIV infection in Uganda. *HIV Med*. 2020;21(2):119–127. doi:10.1111/hiv.12808
44. Dirajlal Fargo S, Strah M, Ailstock K, et al. Factors associated with insulin resistance in a longitudinal study of Ugandan youth with and without HIV. *AIDS*. 2024;38(2):177–184. doi:10.1097/QAD.0000000000003741
45. Brown TT, Cole SR, Li X, et al. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the Multicenter AIDS Cohort Study. *Arch Intern Med*. 2005;165(10):1179–1184. doi:10.1001/archinte.165.10.1179
46. Tien PC, Schneider MF, Cox C, et al. Association of HIV infection with incident diabetes mellitus: impact of using hemoglobin A1C as a criterion for diabetes. *J Acquir Immune Defic Syndr*. 2012;61(3):334–340. doi:10.1097/QAI.0b013e31826bfc32
47. Galli L, Salpietro S, Pellicciotta G, et al. Risk of type 2 diabetes among HIV-infected and healthy subjects in Italy. *Eur J Epidemiol*. 2012;27 (8):657–665. doi:10.1007/s10654-012-9707-5
48. Petoumenos K, Huang R, Hoy J, et al. Prevalence of self-reported comorbidities in HIV-positive and HIV-negative men who have sex with men over 55 years—the Australian Positive & Peers Longevity Evaluation Study (APPLES). *PLoS One*. 2017;12(9):e0184583. doi:10.1371/journal.pone.0184583
49. Butt AA, McGinnis K, Rodriguez-Barradas MC, et al. HIV infection and the risk of diabetes mellitus. *AIDS*. 2009;23(10):1227–1234. doi:10.1097/QAD.0b013e32832bd7af
50. Bratt G, Brännström J, Missalidis C, Nyström T. Development of type 2 diabetes and insulin resistance in people with HIV infection: prevalence, incidence and associated factors. *PLoS One*. 2021;16(6):e0254079. doi:10.1371/journal.pone.0254079
51. Sarkar S, Brown TT. Diabetes in people living with HIV. In: Feingold KR, Ahmed SF, Anawalt B, et al, editors. *Endotext*. South Dartmouth, MA: MDText.com, Inc.; 2000.
52. Larsson A, Larsson SE. The effects of ethylene-1-hydroxy-1,1-diphosphonate on cellular transformation and organic matrix of the epiphyseal growth plate of the rat—a light microscopic and ultrastructural study. *Acta Pathol Microbiol Scand A*. 1978;86(3):211–223. doi:10.1111/j.1699-0463.1978.tb02035.x

53. Samaras K. The burden of diabetes and hyperlipidemia in treated HIV infection and approaches for cardiometabolic care. *Curr HIV/AIDS Rep*. 2012;9(3):206–217. doi:10.1007/s11904-012-0124-x
54. Woerle HJ, Mariuz PR, Meyer C, et al. Mechanisms for the deterioration in glucose tolerance associated with HIV protease inhibitor regimens. *Diabetes*. 2003;52(4):918–925. doi:10.2337/diabetes.52.4.918
55. Kalra S, Kalra B, Agrawal N, Unnikrishnan A. Understanding diabetes in patients with HIV/AIDS. *Diabetol Metab Syndr*. 2011;3(1):2. doi:10.1186/1758-5996-3-2
56. Zannou DM, Denoeud L, Lacombe K, et al. Incidence of lipodystrophy and metabolic disorders in patients starting non-nucleoside reverse transcriptase inhibitors in Benin. *Antivir Ther*. 2009;14(3):371–380. doi:10.1177/135965350901400307
57. Dirajlal Fargo S, Moser C, Brown TT, et al. Changes in insulin resistance after initiation of raltegravir or protease inhibitors with tenofovir-emtricitabine: AIDS Clinical Trials Group A5260s. *Open Forum Infect Dis*. 2016;3(3):ofw174. doi:10.1093/ofid/ofw174
58. Bengtson AM, Madlala H, Matjila MJ, et al. Associations of HIV and antiretroviral therapy with gestational diabetes in South Africa. *AIDS*. 2023;37(13):2069–2079. doi:10.1097/QAD.0000000000003678
59. Soepnel LM, Norris SA, Schrier VJ, et al. The association between HIV, antiretroviral therapy, and gestational diabetes mellitus. *AIDS*. 2017;31(1):113–125. doi:10.1097/QAD.0000000000001277
60. Bukasa LL, Cortina-Borja M, Peters H, et al. Gestational diabetes in women living with HIV in the UK and Ireland: insights from population-based surveillance data. *J Int AIDS Soc*. 2023;26(4):e26078. doi:10.1002/jia2.26078
61. Phoswa WN. The role of HIV infection in the pathophysiology of gestational diabetes mellitus and hypertensive disorders of pregnancy. *Front Cardiovasc Med*. 2021;8:613930. doi:10.3389/fcvm.2021.613930
62. Papp E, Balogun K, Banko N, et al. Low prolactin and high 20α-hydroxysteroid dehydrogenase levels contribute to lower progesterone levels in HIV-infected pregnant women exposed to protease inhibitor–based combination antiretroviral therapy. *J Infect Dis*. 2016;213(10):1532–1540. doi:10.1093/infdis/jiw004
63. Nagy GS, Tsiodras S, Martin LD, et al. Human immunodeficiency virus type 1–related lipoatrophy and lipohypertrophy are associated with serum concentrations of leptin. *Clin Infect Dis*. 2003;36(6):795–802. doi:10.1086/367859
64. Collazos J, Mayo J, Martínez E, Ibarra S. Serum cortisol in HIV-infected patients with and without highly active antiretroviral therapy. *AIDS*. 2003;17(1):123–126. doi:10.1097/00002030-200301030-00018
65. Esemu LF, Yuosembom EK, Fang R, et al. Impact of HIV-1 infection on the IGF-1 axis and angiogenic factors in pregnant Cameroonian women receiving antiretroviral therapy. *PLoS One*. 2019;14(5):e0215825. doi:10.1371/journal.pone.0215825
66. Laron Z. Insulin-like growth factor 1 (IGF-1): a growth hormone. *Mol Pathol*. 2001;54(5):311–316. doi:10.1136/mp.54.5.311