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Causal associations between HbA1c and multiple diseases unveiled through a Mendelian randomization phenome-wide association study in East Asian populations

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Abstract

Most analyses of hemoglobin A1c (HbA1c) and multiple common diseases have focused on European populations, thus there is a need for Mendelian randomization phenome-wide association study (MR-PheWAS) in East Asian populations. We used MR-PheWAS to investigate the potential causal associations between HbA1c and 159 types of diseases in the Biobank Japan dataset, employing the inverse variance weighted as the primary statistical approach, supplemented by MR-Egger and weighted median analyses. Additionally, multiple sensitivity analyses were conducted to assess heterogeneity and pleiotropy. High HbA1c levels are associated with an increased risk of type 1 diabetes (odds ratio [OR] = 4.07; 95% confidence interval [CI]: 2.34~7.07), type 2 diabetes (OR = 4.76; 95% CI: 3.01~7.55), cataract (OR = 1.33; 95% CI: 1.18~1.51), diabetic nephropathy (OR = 5.70; 95% CI: 2.24~14.46), and peripheral arterial disease (OR = 1.62; 95% CI: 1.29~2.04). Conversely, elevated HbA1c levels are associated with a reduced risk of asthma (OR = 0.76; 95% CI: 0.67~0.86), breast cancer (OR = 0.75; 95% CI: 0.65~0.87), and cerebral aneurysm (OR = 0.71; 95% CI: 0.57~0.88). The results of the causal association between HbA1c and numerous diseases in East Asian populations provides insights for the region's specialized glycemic control and disease prevention programs, as well as new preventive and treatment options.

Abbreviations: AGEs = advanced glycation end products, ARC = age-related cataracts, CIs = confidence intervals, DN = diabetic nephropathy, EAF = effect allele frequency, GWAS = genome-wide association study, HbA1c = hemoglobin A1c, ICD = International Classification of Diseases, IGF-1 = insulin-like growth factor 1, IVs = instrumental variables, IVW = inverse variance weighted, MR = Mendelian randomization, MR-PheWAS = Mendelian randomization phenome-wide association study, ORs = odds ratios, PAD = peripheral arterial disease, PheWAS = phenome-wide association study, SNPs = single nucleotide polymorphisms, T1D = type 1 diabetes, T2D = type 2 diabetes.

Keywords: causal association, common diseases, hemoglobin A1c, Mendelian randomization, phenome-wide association study

1. Introduction

The development of hemoglobin A1c (HbA1c) happens through a non-enzymatic interaction between glucose and hemoglobin, offering insight into the average blood sugar levels maintained over the preceding 2 to 3 months.[1–3] HbA1c is widely measured in clinical studies[4–6] and serves as a key biomarker for diagnosing diabetes and monitoring patient progress, a condition linked to a range of complications.[7–14] Furthermore, extensive studies in European populations have unveiled possible relationships

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The datasets generated during and/or analyzed during the current study are publicly available.

The GWASs included in this work were approved by their relevant review board, and informed consent were given by all participants.

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between HbA1c and diabetes-related genetic variants and various conditions like cardiovascular and cerebrovascular diseases,[15,16] cancers,[17,18] bone diseases,[19–21] gastrointestinal diseases,[22,23] eye diseases,[24,25] and others. Single nucleotide polymorphisms (SNPs) that affect HbA1c in Europeans have similar correlations in Asian populations.[26,27] However, the degree of association between allele frequencies and SNPs linked to HbA1c may be impacted by variations in genetic makeup across different racial and ethnic groups.[28] Meanwhile, some hereditary kinds of anemia are more common in Asian people, indicating a higher sensitivity to HbA1c.[29] Given the different reactions of populations to genetic alterations in HbA1c, additional data is needed to better understand its genetic effects on various illnesses in East Asian cultures.

Mendelian randomization (MR) establishes causation and overcomes analytical problems in typical observational research by using genetic variation.[30–32] This method permits precise estimation of the causal effects of specific exposures on the risk of disease. Integrating MR methods with hypothesis-free phenome-wide association study (PheWAS) procedures allow for the identification of relationships between exposures and various disease outcomes or features.[33–35] Thus, we investigate the potential association between HbA1c and multiple clinical outcomes using Mendelian randomization phenome-wide association study (MR-PheWAS) techniques in persons of East Asian heritage.

2. Materials and methods

2.1. Study design

Using MR-PheWAS, we examined the potential relationships between genetic variations related to HbA1c and different disease traits in an East Asian population. The effectiveness of MR analysis depends on 3 essential assumptions: the genetic variants selected as instrumental variables (IVs) must be strongly associated with the exposure. They should remain independent of any confounders, and their influence on the outcomes should occur only through the exposure.[36–38]

2.2. Data sources

We conducted a 2-sample MR analysis using summary-level data from the Taiwan Biobank for exposure and the BioBank Japan for outcomes, ensuring independent, non-overlapping populations for exposure and outcome. The HbA1c data were obtained from 92,615 participants in Taiwan Biobank,[39] with a mean (SD) HbA1c level of 5.764% (0.743). Outcome data, covering 159 International Classification of Diseases (ICD)-coded disease phenotypes, were sourced from BioBank Japan (https://pheweb.jp/downloads).[40] Only summary-level data were used, with no access to individual-level information. We selected genetic instruments based on genome-wide significant SNPs ($P < 5 \times 10^{-8}$) associated with HbA1c. In total, 39 SNPs were identified as IVs, mapped to 31 genes. On average, each disease phenotype included around 13 million SNPs. For further details, refer to Table S1, Supplemental Digital Content, http://links.lww.com/MD/O529.

2.3. Selection of instrumental variables

In MR studies, SNPs serve as IVs to examine causal relationships. Each SNP strictly follows inclusion criteria, with a significance threshold set at a P value less than 5×10^{-8} to ensure a significant association between the IV and the exposure. Additionally, to avoid ambiguity, we excluded palindromic SNPs with intermediate allele frequencies using the default parameters of the TwoSampleMR package in R. To mitigate concerns about linkage disequilibrium, we set an r^2 threshold of 0.001 and a separation distance of 10,000 kb, as described previously.[41–44]

To quantify the strength of the IVs, we calculated the F statistic for each SNP using the formula[45]:

$$F = \frac{R^2\,(\mathrm{n} - 1 - k)}{(1 - R^2)\;k}$$

where R^2 is the proportion of variance explained. k is the number of SNP, and n is the sample size. An F statistic >10 indicates a low risk of weak instrument bias.[46]

2.4. MR-PheWAS analysis

In contrast to being confined to a single trait, MR-PheWAS enables the concurrent investigation of the relationship between a single exposure and multiple phenotypic outcomes. MR-PheWAS was employed to unveil potential correlations between HbA1c and a range of East Asian phenotypes. To reduce the probability of type I errors, we employed the false discovery rate method with a 5% threshold for multiple comparison correction.

The primary step in our analysis was the harmonization of HbA1c data with clinical outcomes. We employed the inverse variance weighted (IVW) method for MR estimation, supported by the weighted median and MR-Egger methods to improve the reliability and precision.[30] Specifically, the IVW method was conducted using a multiplicative random effects model. For sensitivity analyses, we used: MR-Egger intercept to assess horizontal pleiotropy; Cochran's Q statistic to evaluate heterogeneity among SNPs; funnel plots to visually assess potential directional pleiotropy; leave-one-out analysis to determine the influence of individual SNPs on causal estimates; MR-PRESSO to detect and correct for outliers.

MR analyses were conducted using the TwoSampleMR package in R. The primary outputs included odds ratios (ORs) with 95% confidence intervals (CIs), along with heterogeneity statistics and pleiotropy assessments. The input data comprised genome-wide association studies (GWAS) summary statistics, including effect sizes (β), standard error, P values, and effect allele frequencies (EAF), ensuring a robust analytical framework.

3. Results

3.1. Results of the MR-PheWAS analysis

We utilized 39 SNPs as IVs for HbA1c. All of the IVs exhibited an F statistic exceeding 10 (Table S2, Supplemental Digital Content, http://links.lww.com/MD/O530). After applying a 5% false discovery rate correction, 8 outcomes remained viable (Fig. 1). According to the IVW method, a significant positive association was observed between HbA1c and the following conditions: "type 1 diabetes (T1D)" (OR = 4.07; 95% confidence interval [CI]: 2.34~7.07), "type 2 diabetes (T2D)" (OR = 4.76; 95% CI: 3.01~7.55), "cataract" (OR = 1.33; 95% CI: 1.18~1.51), "diabetic nephropathy (DN)" (OR = 5.70; 95% CI: 2.24~14.46), and "peripheral arterial disease (PAD)" (OR = 1.62; 95% CI: 1.29~2.04). Moreover, an elevation in HbA1c levels was concurrently linked with decreased risks of asthma (OR = 0.76; 95% CI: 0.67~0.86), breast cancer (OR = 0.75; 95% CI: 0.65~0.87), and cerebral aneurysm (OR = 0.71; 95% CI: 0.57~0.88). Other than the opposite direction of beta for cerebral aneurysms observed in MR-Egger compared to IVW, the beta directions for the remaining 7 diseases were consistent across all 3 statistical methods (see Figs. 2 and 3 and Table S3, Supplemental Digital Content, http://links.lww.com/MD/O531).

3.2. Results of the sensitivity analysis

Table S4, Supplemental Digital Content, http://links.lww.com/MD/O532 and Figure 4 depict the results of Cochran's

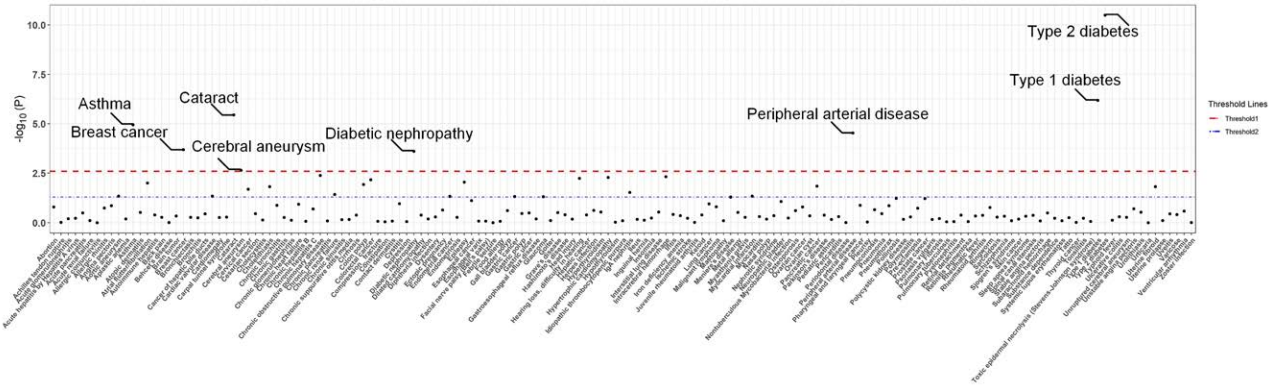

Figure 1. The distribution of *P* values for the associations between HbA1c and 159 phenotypes in the MR analysis. Line 1 indicates the significance threshold adjusted for the false discovery rate, while line 2 represents the significance threshold set at $P = .05$. HbA1c = hemoglobin A1c, MR = Mendelian randomization.

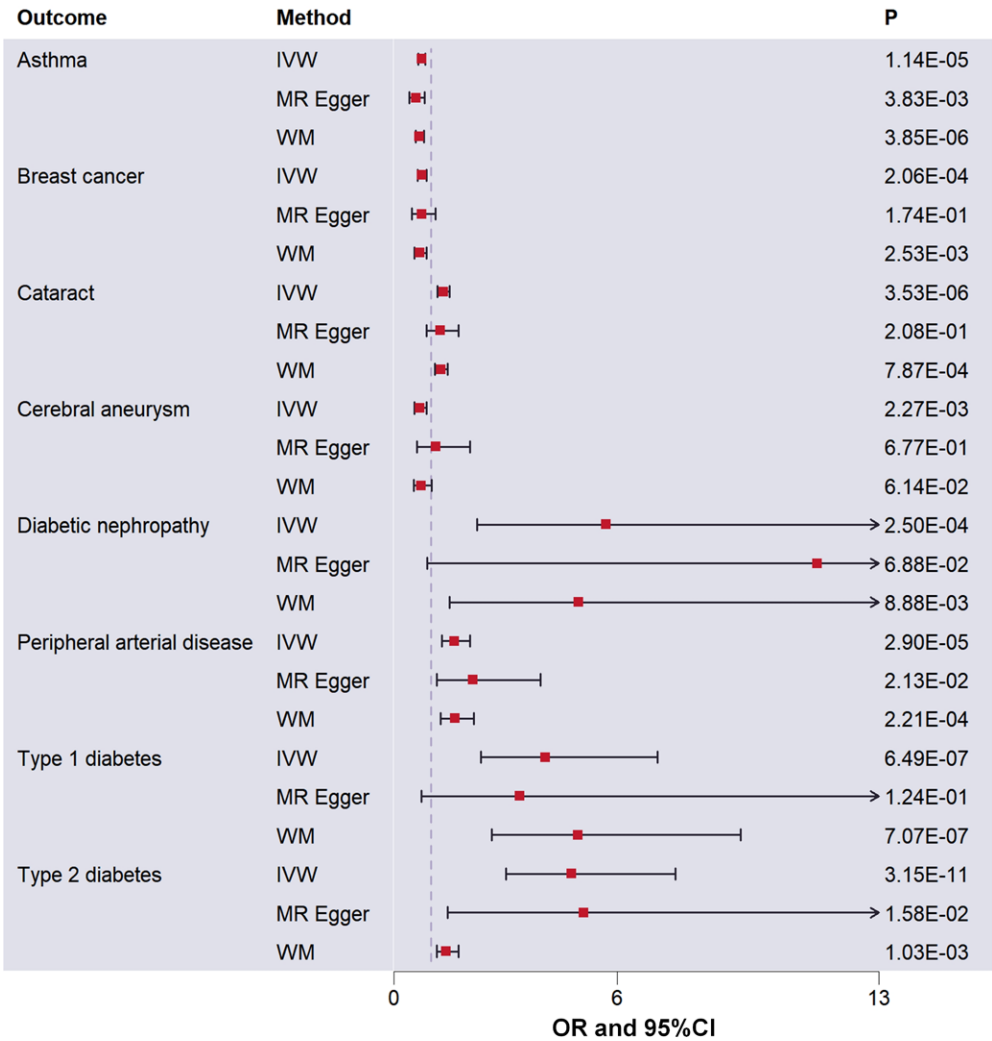

Figure 2. Causal effects of HbA1c on 8 diseases in the MR analysis, showing ORs and corresponding 95% CIs. CIs = confidence intervals, HbA1c = hemoglobin A1c, IVW = inverse-variance weighted, MR = Mendelian randomization, ORs = odds ratios, WM = weighted median.

Q statistic and funnel plots, revealing heterogeneity ($P < .05$) in several analyses. Table S5, Supplemental Digital Content, http://links.lww.com/MD/O533 and Figure 3 present the results of the MR-Egger test, which did not detect the presence of horizontal pleiotropy. Outliers were detected ($P_{\text{Global Test}} < .05$) within the MR-PRESSO analysis (refer to Table S6, Supplemental Digital Content, http://links.lww.com/MD/O534). Nevertheless, these outliers did not significantly influence the final outcomes. Moreover, as depicted in Figure 5, the outcome remained unaffected when SNPs were eliminated one by one in the leave-one-out analysis.

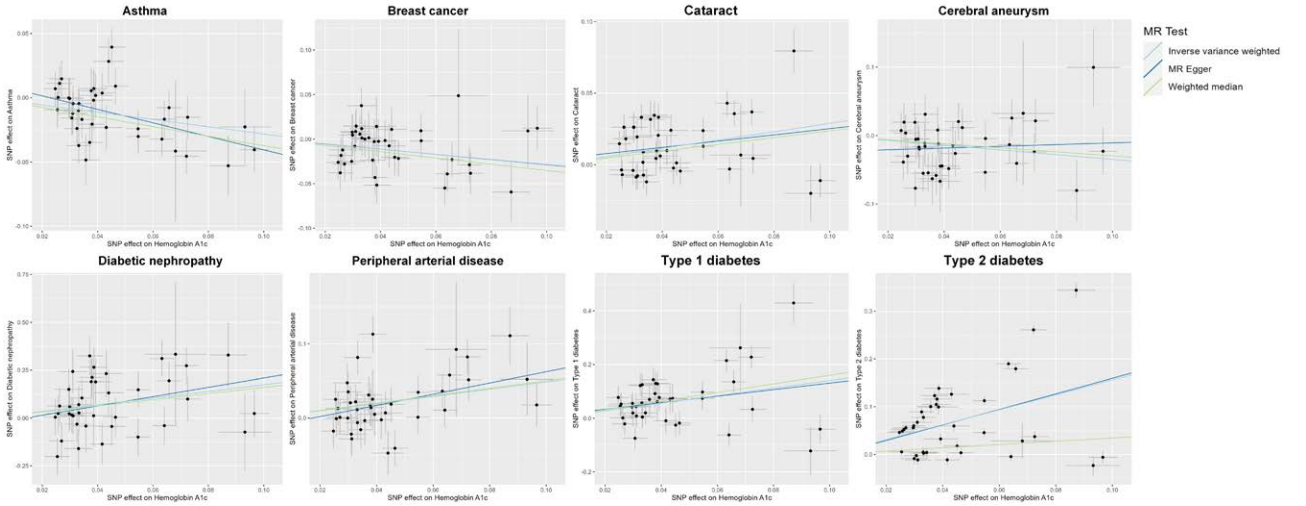

Figure 3. Scatter plots indicating the causal associations between HbA1c and 8 diseases. HbA1c = hemoglobin A1c, MR = Mendelian randomization, SNP = single nucleotide polymorphism.

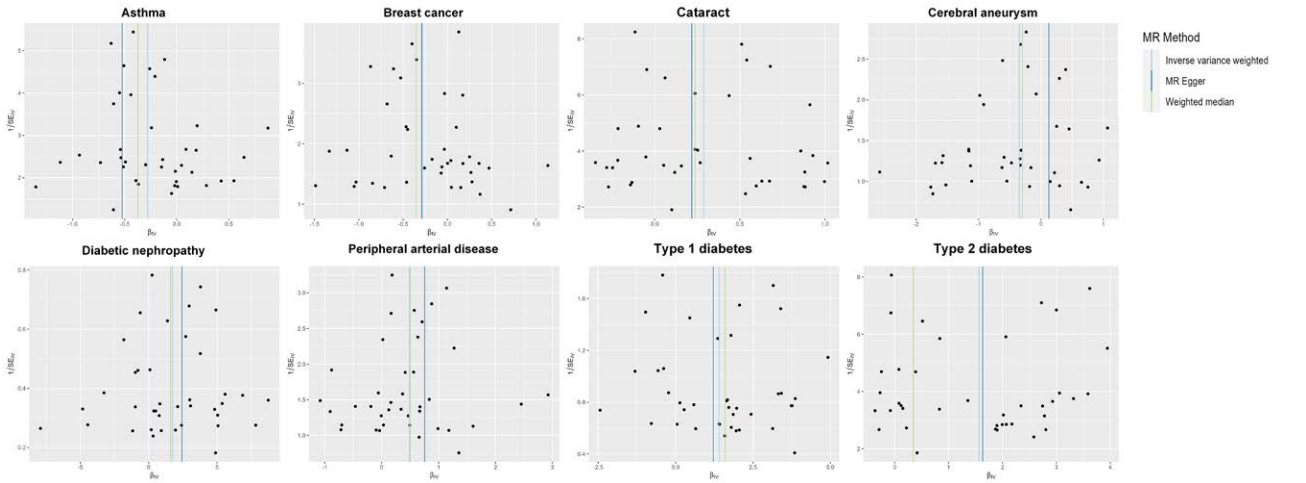

Figure 4. Funnel plots of the analyses. MR = Mendelian randomization, SE = standard error.

4. Discussion

Our MR-PheWAS analysis focused on the East Asian population to elucidate the causal relationships between HbA1c and various diseases. The findings indicate that elevated HbA1c levels were associated with an increased risk of diabetes, PAD, DN, and cataracts. Notably, genetically higher HbA1c levels were found to be negatively associated with the risk of asthma, breast cancer, and cerebral aneurysms.

4.1. HbA1c and diabetes and associated complications

This study found that elevated HbA1c levels were significantly associated with an increased risk of diabetes and its complications in the East Asian population. HbA1c is a well-established diagnostic marker for diabetes and a predictor of diabetes-related complications,[47–49] with similar clinical applications reported in both Western and Eastern populations.[50–54] However, its accuracy as a diagnostic tool for T2D varies across ethnic groups. A large multiethnic GWAS identified 42 novel and 18 previously known genetic variants associated with HbA1c, explaining 4% to 14% of trait variation. Notably, the genetic contributions to HbA1c levels differed significantly across populations, with particularly pronounced variations in African American individuals, which substantially affected the accuracy of HbA1c as a diagnostic marker for T2D.[55]

The association of HbA1c and DN is supported by previous studies, including multiple European studies that have demonstrated a significant correlation between HbA1c levels and DN risk.[56–58] For instance, a Swedish cohort study involving 10,398 children and adults found no statistically significant difference in the risk of retinopathy or nephropathy between individuals with an average HbA1c level of <6.5% (<48 mmol/mol) and those with HbA1c levels of 6.5% to 6.9% (48–52 mmol/mol) after 8 to 20 years of follow-up following a diagnosis of T1D. However, when the average HbA1c level exceeded 7.0% (≥53 mmol/mol), the prevalence of any retinopathy (defined as simplex or more severe forms) and microalbuminuria became slightly more common.[56] Additionally, a Cox regression analysis of 3220 Chinese patients with T2D aged ≥ 30 years without DN found that annual fluctuations in HbA1c were predictive of DN risk in patients aged 30 to 89 years. Compared with an HbA1c coefficient of variation ≤ 6.68%, an HbA1c–coefficient of variation > 13.44% was associated with a 1.58-fold increased risk of DN.[59] The potential mechanisms underlying this association may involve HbA1c-induced oxidative stress. Elevated HbA1c levels stimulate the polyol pathway, promote the formation of advanced glycation end products (AGEs), and

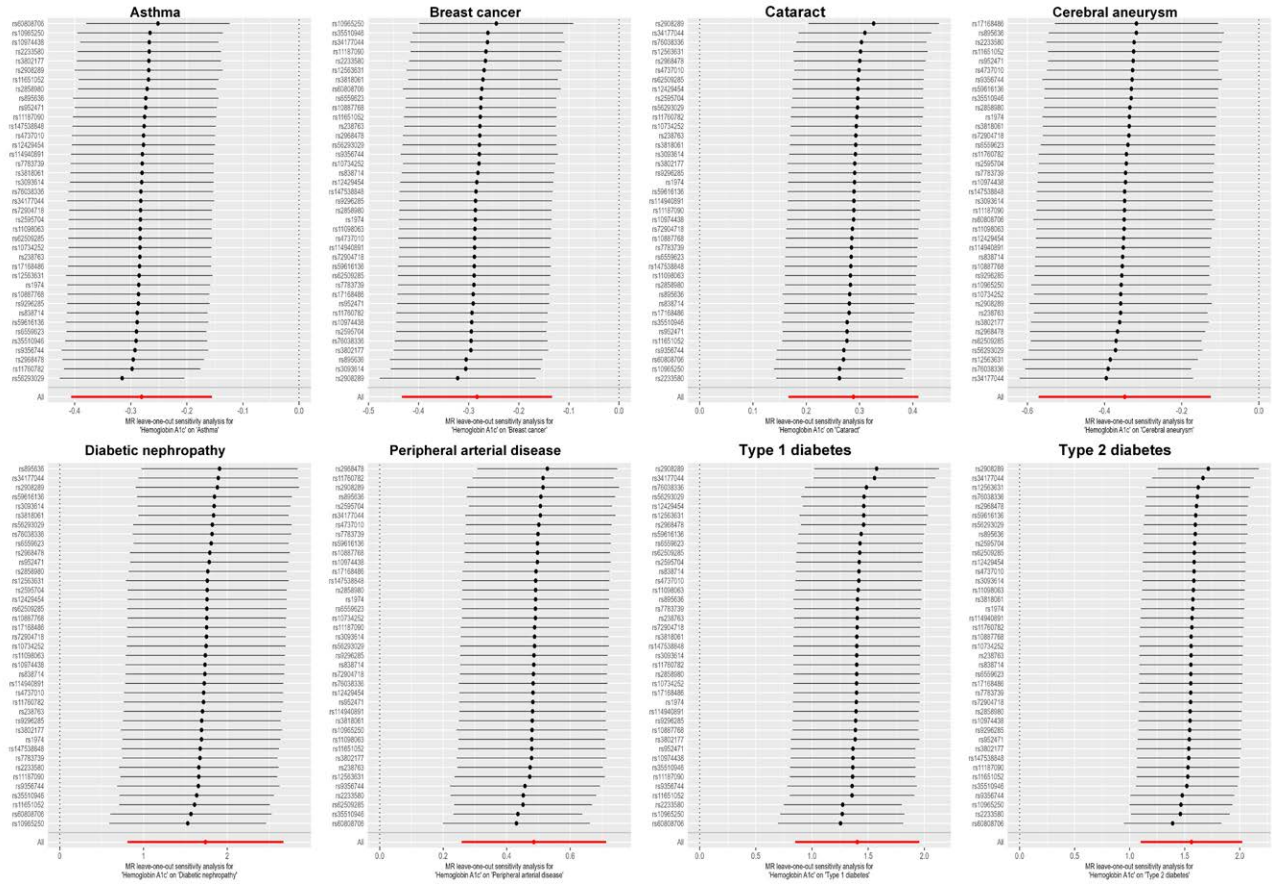

Figure 5. Leave-one-out sensitivity analyses using the IVW method to investigate the causal estimates of HbA1c on 8 diseases after excluding a particular SNP from the analysis. HbA1c = hemoglobin A1c, IVW = inverse-variance weighted, SNP = single nucleotide polymorphism.

activate protein kinase, all of which contribute to increased reactive oxygen species levels and oxidative stress.[60–63] Elevated renal reactive oxygen species levels can result in damage to crucial cellular components and DNA, along with endothelial impairments,[64,65] a characteristic of T2D and diabetic kidney disease.[66–68]

In Taiwan, a case-control study demonstrated an association between high-risk PAD and significant variability in HbA1c readings.[69] Similarly, in Koreans diagnosed with T2D, HbA1c was significantly correlated with PAD.[70] However, the UK Prospective Diabetes Study found that improving HbA1c management did not reduce the incidence of severe vascular disorders, such as PAD.[71] This observation is complex, as HbA1c only reflects average blood glucose over the previous 8 to 12 weeks, without accounting for glucose fluctuations,[3,72] suggesting that blood glucose fluctuations beyond HbA1c levels may also contribute to vascular complications.[73–76]

A study based on the Korean KoGES cohort (≥50 years old; 1972 age-related cataracts [ARC] cases and 38,290 healthy controls) investigated the association between metabolic syndrome and its components with ARC. The results showed that elevated HbA1c levels were significantly associated with an increased risk of ARC (OR = 1.92),[77] consistent with the findings of the present study. The potential mechanism may involve the accumulation of AGEs, which increase with rising HbA1c levels and accumulate in the lens, leading to structural and functional abnormalities.[78–81] AGEs may also induce oxidative stress, further damaging lens proteins and accelerating cataract development.[82–85] However, a community-based cross-sectional study in Saudi Arabia (334 patients with T2D) found no association between HbA1c and cataracts.[86] Similarly, Esteves et al[87] in Brazil reported comparable findings, attributing the discrepancy to study design or good metabolic control in their sample.

4.2. HbA1c and asthma, cerebral aneurysm, breast cancer

This study found a negative association between HbA1c levels and the risk of asthma and cerebral aneurysms, which is not entirely consistent with previous studies. For instance, a prior cross-sectional study of 47,606 UK adults with asthma found a significant positive correlation between HbA1c levels, prediabetes or diabetes (defined by elevated HbA1c), and increased asthma-related hospitalization rates.[88] Additionally, a retrospective cohort study of 5722 US adults aged 18 to 64 with obesity and asthma also reported that higher HbA1c levels were associated with an increased frequency of asthma attacks.[89] These discrepancies may be explained by factors such as inadequate treatment of individuals with HbA1c levels in the diabetic range, potentially exacerbating asthma due to other chronic disease factors. Moreover, the lack of data on potential confounding or modifying factors, such as asthma medications and dyslipidemia treatment, may contribute to these differences. A cross-sectional study conducted in China involving 223 patients with a single ruptured intracranial aneurysm and diabetes found a nonlinear relationship between HbA1c levels and aneurysm rupture, with inflection points at 5.5 and 8.9.[90] A retrospective study in the United States, analyzing medical records of 4701 patients with 6411 intracranial aneurysms from 2 hospitals, examined the relationship between aneurysmal subarachnoid hemorrhage and HbA1c levels using logistic regression and propensity score weighting, and found no significant correlation between HbA1c levels and aneurysmal subarachnoid hemorrhage.[91] These

differences may also be attributed to the observational nature of the studies, which cannot fully exclude the influence of confounding factors.

Breast cancer primarily affects women and is a leading cause of death globally, with a significant proportion of fatalities occurring in developing countries.[92–95] The relationship between HbA1c levels and breast cancer risk has been supported by previous studies. A prospective research found an inverse relationship between HbA1c levels and estrogen receptor-negative breast tumor risk in postmenopausal women.[96] Concomitantly, HbA1c is significantly inversely related to stage I breast tumor risk but might increase the risk for stage II–IV tumors.[97] A possible underlying mechanism may involve insulin-like growth factor 1 (IGF-1), which has been implicated in cancer development.[98] Higher IGF-1 levels have been positively correlated with HbA1c,[99,100] and IGF-1 gene polymorphisms have been associated with breast cancer risk, with potential variations based on menopausal status or tumor subtype.[101] Moreover, the role of insulin in breast cancer progression may be attenuated in individuals with low or absent estrogen levels,[96] suggesting that estrogen modulates IGF-1 function in breast cancer. The complex interplay between female hormones and HbA1c levels contributes to the heterogeneity of breast cancer subtypes, warranting further investigation.

While previous studies have examined the association between HbA1c and diabetes-related diseases, our study systematically applies an MR-PheWAS approach in an East Asian population. Unlike traditional observational studies, MR analysis mitigates confounding and reverse causality, providing stronger evidence for causal relationships. By leveraging public GWAS data, our study efficiently explores the causal effects of genetically predicted HbA1c on a broad spectrum of diseases, uncovering both established and potentially novel associations. This approach not only enhances the reliability of our findings but also offers a cost-effective and scalable framework for future research.

Nonetheless, studies limited to East Asian populations may fail to generalize persuasively to other ethnic groups. Furthermore, MR studies' linear causation assumption may oversimplify the complex link between HbA1c and illness. Finally, because of the sample size limits inherent in GWAS datasets, there is still a danger of selection bias, since they may not completely reflect the larger population.

5. Conclusion

The MR-PheWAS analysis generally revealed a significant positive causal association between HbA1c and T2D, T1D, cataract, PAD, and DN, while a negative correlation was observed between HbA1c and asthma, breast cancer, and cerebral aneurysms. These findings highlight the complex role of HbA1c in various diseases in East Asian populations, offering potential guidance for tailored medical interventions and disease prevention strategies aimed at improving public health outcomes.

Author contributions

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Writing – review & editing: Sen Li, Binsheng He, Meihua Bao.

References

[1] Hanas R, John G; International HBA1c Consensus Committee. 2010 consensus statement on the worldwide standardization of the hemoglobin A1C measurement. Diabetes Care. 2010;33:1903–4.

[2] Consensus Committee. Consensus statement on the worldwide standardization of the hemoglobin A1C measurement: the American Diabetes Association, European Association for the Study of Diabetes, International Federation of Clinical Chemistry and Laboratory Medicine, and the International Diabetes Federation. Diabetes Care. 2007;30:2399–400.

[3] Chehregosha H, Khamseh ME, Malek M, Hosseinpanah F, Ismail-Beigi F. A view beyond HbA1c: role of continuous glucose monitoring. Diabetes Ther. 2019;10:853–63.

[4] Zhou Y, Chai X, Yang G, Sun X, Xing Z. Changes in body mass index and waist circumference and heart failure in type 2 diabetes mellitus. Front Endocrinol (Lausanne). 2023;14:1305839.

[5] Xiao D, Guo Y, Li X, et al. The impacts of SLC22A1 rs594709 and SLC47A1 rs2289669 polymorphisms on metformin therapeutic efficacy in Chinese type 2 diabetes patients. Int J Endocrinol. 2016;2016:4350712.

[6] Little RR, Rohlfing C, Sacks DB. The national glycohemoglobin standardization program: over 20 years of improving hemoglobin A(1c) measurement. Clin Chem. 2019;65:839–48.

[7] He K, Chen R, Xu S, et al. Environmental endocrine disruptor-induced mitochondrial dysfunction: a potential mechanism underlying diabetes and its complications. Front Endocrinol (Lausanne). 2024;15:1422752.

[8] Su M, Hu R, Tang T, Tang W, Huang C. Review of the correlation between Chinese medicine and intestinal microbiota on the efficacy of diabetes mellitus. Front Endocrinol (Lausanne). 2022;13:1085092.

[9] Xu Z, Zhang P, Chen Y, Jiang J, Zhou Z, Zhu H. Comparing SARC-CalF with SARC-F for screening sarcopenia in adults with type 2 diabetes mellitus. Front Nutr. 2022;9:803924.

[10] Chen J, Li X, Liu H, et al. Bone marrow stromal cell-derived exosomal circular RNA improves diabetic foot ulcer wound healing by activating the nuclear factor erythroid 2-related factor 2 pathway and inhibiting ferroptosis. Diabet Med. 2023;40:e15031.

[11] Luo M, Cao Q, Wang D, et al. The impact of diabetes on postoperative outcomes following spine surgery: a meta-analysis of 40 cohort studies with 2.9 million participants. Int J Surg. 2022;104:106789.

[12] Yu T, Xu B, Bao M, et al. Identification of potential biomarkers and pathways associated with carotid atherosclerotic plaques in type 2 diabetes mellitus: a transcriptomics study. Front Endocrinol (Lausanne). 2022;13:981100.

[13] Yang YY, Shi L-X, Li J-H, Yao L-Y, Xiang D-X. Piperazine ferulate ameliorates the development of diabetic nephropathy by regulating endothelial nitric oxide synthase. Mol Med Rep. 2019;19:2245–53.

[14] Mi W, Xia Y, Bian Y. Meta-analysis of the association between aldose reductase gene (CA)n microsatellite variants and risk of diabetic retinopathy. Exp Ther Med. 2019;18:4499–509.

[15] Georgakis MK, Harshfield EL, Malik R, et al. Diabetes mellitus, glycemic traits, and cerebrovascular disease. Neurology. 2021;96:e1732–42.

[16] Au Yeung SL, Luo S, Schooling CM. The impact of glycated hemoglobin (HbA1c) on cardiovascular disease risk: a Mendelian randomization study using UK Biobank. Diabetes Care. 2018;41:1991–7.

[17] Yuan S, Kar S, Carter P, et al. Is type 2 diabetes causally associated with cancer risk? Evidence from a two-sample Mendelian randomization study. Diabetes. 2020;69:1588–96.

[18] Murphy N, Song M, Papadimitriou N, et al. Associations between glycemic traits and colorectal cancer: a Mendelian randomization analysis. J Natl Cancer Inst. 2022;114:740–52.

[19] Ji X, Hong J, Qu Z, et al. HemoglobinA1c is a risk factor for changes of bone mineral density: a Mendelian randomization study. Front Endocrinol (Lausanne). 2022;13:942878.

[20] Tang Y, Zhang L, Ye D, Zhao A, Liu Y, Zhang M. Causal relationship between type 1 diabetes and osteoporosis and fracture occurrence: a two-sample Mendelian randomization analysis. Osteoporos Int. 2023;34:1111–7.

[21] Zhao P, Sheng Z, Xu L, et al. Deciphering the complex relationship between type 2 diabetes and fracture risk with both genetic and observational evidence. eLife. 2024;12:RP89281.

[22] Chen J, Yuan S, Fu T, et al. Gastrointestinal consequences of type 2 diabetes mellitus and impaired glycemic homeostasis: a Mendelian randomization study. Diabetes Care. 2023;46:828–35.

[23] Qing X, Wang L, Fang S, et al. Association of antidiabetic drug target genes with inflammatory bowel disease: a Mendelian randomization study. J Inflamm Res. 2024;17:1389–96.

[24] Chen R, Xu S, Ding Y, et al. Dissecting causal associations of type 2 diabetes with 111 types of ocular conditions: a Mendelian randomization study. Front Endocrinol. 2023;14:1307468.

[25] Hu Z, Zhou F, Kaminga AC, Xu H. Type 2 diabetes, fasting glucose, hemoglobin A1c levels and risk of primary open-angle glaucoma: a Mendelian randomization study. Invest Ophthalmol Vis Sci. 2022;63:37–37.

[26] Chen P, Ong RT, Tay W-T, et al. A study assessing the association of glycated hemoglobin A1C (HbA1C) associated variants with HbA1C, chronic kidney disease and diabetic retinopathy in populations of Asian ancestry. PLoS One. 2013;8:e79767.
[27] Tan JT, Ng DPK, Nurbaya S, et al. Polymorphisms identified through genome-wide association studies and their associations with type 2 diabetes in Chinese, Malays, and Asian-Indians in Singapore. J Clin Endocrinol Metab 2010;95:390–7.
[28] Grimsby JL, Porneala BC, Vassy JL, et al.; MAGIC Investigators. Race-ethnic differences in the association of genetic loci with HbA1c levels and mortality in U.S. adults: the third National Health and Nutrition Examination Survey (NHANES III). BMC Med Genet. 2012;13:30.
[29] Fucharoen S, Winichagoon P. Haemoglobinopathies in southeast Asia. Indian J Med Res. 2011;134:498–506.
[30] Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. Hum Mol Genet. 2014;23:R89–98.
[31] Bochud M, Rousson V. Usefulness of Mendelian randomization in observational epidemiology. Int J Environ Res Public Health. 2010;7:711–28.
[32] Sekula P, Del Greco M F, Pattaro C, Köttgen A. Mendelian randomization as an approach to assess causality using observational data. J Am Soc Nephrol. 2016;27:3253–65.
[33] Bowden J. Realising the full potential of MR-PHeWAS in cancer. Br J Cancer. 2021;124:529–30.
[34] Millard LAC, Davies NM, Timpson NJ, Tilling K, Flach PA, Davey Smith G. MR-PheWAS: hypothesis prioritization among potential causal effects of body mass index on many outcomes, using Mendelian randomization. Sci Rep. 2015;5:16645.
[35] Denny JC, Bastarache L, Roden DM. Phenome-wide association studies as a tool to advance precision medicine. Annu Rev Genomics Hum Genet. 2016;17:353–73.
[36] Fu Q, Chen R, Xu S, et al. Assessment of potential risk factors associated with gestational diabetes mellitus: evidence from a Mendelian randomization study. Front Endocrinol (Lausanne). 2023;14:1276836.
[37] Huang C, Xu S, Chen R, et al. Assessing causal associations of bile acids with obesity indicators: a Mendelian randomization study. Medicine (Baltimore). 2024;103:e38610.
[38] Fu Q, Chen R, Ding Y, et al. Sodium intake and the risk of various types of cardiovascular diseases: a Mendelian randomization study. Front Nutr. 2023;10:1250509.
[39] Chen CY, Chen T-T, Feng YA, et al. Analysis across Taiwan Biobank, Biobank Japan, and UK Biobank identifies hundreds of novel loci for 36 quantitative traits. Cell Genom. 2023;3:100436.
[40] Sakaue S, Kanai M, Tanigawa Y, et al.; FinnGen. A cross-population atlas of genetic associations for 220 human phenotypes. Nat Genet. 2021;53:1415–24.
[41] Han L, Xu S, Zhou D, et al. Unveiling the causal link between metabolic factors and ovarian cancer risk using Mendelian randomization analysis. Front Endocrinol (Lausanne). 2024;15:1401648.
[42] Jiang Y, Chen R, Xu S, et al. Endocrine and metabolic factors and the risk of idiopathic pulmonary fibrosis: a Mendelian randomization study. Front Endocrinol (Lausanne). 2023;14:1321576.
[43] Wang L, Xu S, Chen R, et al. Exploring the causal association between epigenetic clocks and menopause age: insights from a bidirectional Mendelian randomization study. Front Endocrinol (Lausanne). 2024;15:1429514.
[44] Jiang Y, Chen R, Xu S, et al. Assessing causal associations of hyperparathyroidism with blood counts and biochemical indicators: a Mendelian randomization study. Front Endocrinol (Lausanne). 2023;14:1295040.
[45] Pierce BL, Burgess S. Efficient design for Mendelian randomization studies: subsample and 2-sample instrumental variable estimators. Am J Epidemiol. 2013;178:1177–84.
[46] Pierce BL, Ahsan H, Vanderweele TJ. Power and instrument strength requirements for Mendelian randomization studies using multiple genetic variants. Int J Epidemiol. 2011;40:740–52.
[47] The International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care. 2009;32:1327–34.
[48] Lee S, Liu T, Zhou J, Zhang Q, Wong WT, Tse G. Predictions of diabetes complications and mortality using hba1c variability: a 10-year observational cohort study. Acta Diabetol. 2021;58:171–80.
[49] Sherwani SI, Khan HA, Ekhzaimy A, Masood A, Sakharkar MK. Significance of HbA1c test in diagnosis and prognosis of diabetic patients. Biomark Insights. 2016;11:95–104.
[50] Yan S, Liu S, Zhao Y, et al. Diagnostic accuracy of HbA1c in diabetes between Eastern and Western. Eur J Clin Invest. 2013;43:716–26.
[51] Hajat C, Harrison O, Al Siksek Z. Diagnostic testing for diabetes using HbA1c in the Abu Dhabi population: Weqaya: the Abu Dhabi cardiovascular screening program. Diabetes Care. 2011;34:2400–2.
[52] Herath HMM, Weerarathna TP, Dahanayake MU, Weerasinghe NP. Use of HbA1c to diagnose type 2 diabetes mellitus among high risk Sri Lankan adults. Diabetes Metab Syndr. 2017;11:251–5.
[53] Umayahara Y, Fujita Y, Watanabe H, et al. Association of glycated albumin to HbA1c ratio with diabetic retinopathy but not diabetic nephropathy in patients with type 2 diabetes. Clin Biochem. 2017;50:270–3.
[54] Luo M, Lim WY, Tan CS, et al. Longitudinal trends in HbA1c and associations with comorbidity and all-cause mortality in Asian patients with type 2 diabetes: a cohort study. Diabetes Res Clin Pract. 2017;133:69–77.
[55] Wheeler E, Leong A, Liu C-T, et al.; EPIC-CVD Consortium. Impact of common genetic determinants of hemoglobin A1c on type 2 diabetes risk and diagnosis in ancestrally diverse populations: a transethnic genome-wide meta-analysis. PLoS Med. 2017;14:e1002383.
[56] Lind M, Pivodic A, Svensson A-M, Ólafsdóttir AF, Wedel H, Ludvigsson J. HbA(1c) level as a risk factor for retinopathy and nephropathy in children and adults with type 1 diabetes: Swedish population based cohort study. BMJ. 2019;366:l4894.
[57] Fares JE, Kanaan M, Chaaya M, Azar ST. Fluctuations in glycosylated hemoglobin (HbA1C) as a predictor for the development of diabetic nephropathy in type 1 diabetic patients. Int J Diabetes Mellit. 2010;2:10–4.
[58] Yun KJ, Kim HJ, Kim MK, et al. Risk factors for the development and progression of diabetic kidney disease in patients with type 2 diabetes mellitus and advanced diabetic retinopathy. Diabetes Metab J. 2016;40:473–81.
[59] Lin CC, Chen C-C, Chen F-N, et al. Risks of diabetic nephropathy with variation in hemoglobin A1c and fasting plasma glucose. Am J Med. 2013;126:1017.e1–10.
[60] Sharma D, Bhattacharya P, Kalia K, Tiwari V. Diabetic nephropathy: new insights into established therapeutic paradigms and novel molecular targets. Diabetes Res Clin Pract. 2017;128:91–108.
[61] Lin YC, Chang Y-H, Yang S-Y, Wu K-D, Chu T-S. Update of pathophysiology and management of diabetic kidney disease. J Formos Med Assoc. 2018;117:662–75.
[62] Warren AM, Knudsen ST, Cooper ME. Diabetic nephropathy: an insight into molecular mechanisms and emerging therapies. Expert Opin Ther Targets. 2019;23:579–91.
[63] Cepas V, Collino M, Mayo JC, Sainz RM. Redox signaling and advanced glycation endproducts (AGEs) in diet-related diseases. Antioxidants (Basel). 2020;9:142.
[64] Honda T, Hirakawa Y, Nangaku M. The role of oxidative stress and hypoxia in renal disease. Kidney Res Clin Pract. 2019;38:414–26.
[65] Verma S, Singh P, Khurana S, et al. Implications of oxidative stress in chronic kidney disease: a review on current concepts and therapies. Kidney Res Clin Pract. 2021;40:183–93.
[66] Yang DR, Wang M-Y, Zhang C-L, Wang Y. Endothelial dysfunction in vascular complications of diabetes: a comprehensive review of mechanisms and implications. Front Endocrinol (Lausanne). 2024;15:1359255.
[67] Gil CL, Hooker E, Larrivée B. Diabetic kidney disease, endothelial damage, and podocyte-endothelial crosstalk. Kidney Med. 2021;3:105–15.
[68] Cheng H, Harris RC. Renal endothelial dysfunction in diabetic nephropathy. Cardiovasc Hematol Disord Drug Targets. 2014;14:22–33.
[69] Lee I-T. Mean and variability of annual haemoglobin A1c are associated with high-risk peripheral artery disease. Diab Vasc Dis Res. 2020;17:1479164120909030.
[70] Choi SW, Shin M-H, Yun W-J, et al. Association between hemoglobin A1c, carotid atherosclerosis, arterial stiffness, and peripheral arterial disease in Korean type 2 diabetic patients. J Diabetes Complications. 2011;25:7–13.
[71] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352:837–53.
[72] Gomez-Peralta F, Choudhary P, Cosson E, Irace C, Rami-Merhar B, Seibold A. Understanding the clinical implications of differences between glucose management indicator and glycated haemoglobin. Diabetes Obes Metab. 2022;24:599–608.
[73] Smith-Palmer J, Brändle M, Trevisan R, Orsini Federici M, Liabat S, Valentine W. Assessment of the association between glycemic variability and diabetes-related complications in type 1 and type 2 diabetes. Diabetes Res Clin Pract. 2014;105:273–84.

[74] Gorst C, Kwok CS, Aslam S, et al. Long-term glycemic variability and risk of adverse outcomes: a systematic review and meta-analysis. Diabetes Care. 2015;38:2354–69.
[75] Belli M, Bellia A, Sergi D, Barone L, Lauro D, Barillà F. Glucose variability: a new risk factor for cardiovascular disease. Acta Diabetol. 2023;60:1291–9.
[76] Kusunoki Y, Konishi K, Tsunoda T, Koyama H. Significance of glycemic variability in diabetes mellitus. Intern Med. 2022;61:281–90.
[77] Jee D, Park S. Hyperglycemia and hypo-HDL-cholesterolemia are primary risk factors for age-related cataract, and a Korean-style balanced diet has a negative association, based on the Korean genome and epidemiology study. J Korean Med Sci. 2021;36:e155.
[78] Turk Z, Mesić R, Benko B. Comparison of advanced glycation end-products on haemoglobin (Hb-AGE) and haemoglobin A1c for the assessment of diabetic control. Clin Chim Acta. 1998;277:159–70.
[79] Prasad K. Does HbA1cc play a role in the development of cardiovascular diseases? Curr Pharm Des. 2018;24:2876–82.
[80] Kandarakis SA, Piperi C, Topouzis F, Papavassiliou AG. Emerging role of advanced glycation-end products (AGEs) in the pathobiology of eye diseases. Prog Retin Eye Res. 2014;42:85–102.
[81] Kim J, Kim OS, Kim CS, Sohn E, Jo K, Kim JS. Accumulation of arg-pyrimidine, a methylglyoxal-derived advanced glycation end product, increases apoptosis of lens epithelial cells both in vitro and in vivo. Exp Mol Med. 2012;44:167–75.
[82] Gul A, Rahman MA, Hasnain SN, Salim A, Simjee SU. Could oxidative stress associate with age products in cataractogenesis? Curr Eye Res. 2008;33:669–75.
[83] Nagaraj RH, Linetsky M, Stitt AW. The pathogenic role of Maillard reaction in the aging eye. Amino Acids. 2012;42:1205–20.
[84] Berthoud VM, Beyer EC. Oxidative stress, lens gap junctions, and cataracts. Antioxid Redox Signal. 2009;11:339–53.
[85] Indyk D, Bronowicka-Szydełko A, Gamian A, Kuzan A. Advanced glycation end products and their receptors in serum of patients with type 2 diabetes. Sci Rep. 2021;11:13264.
[86] Alabdulwahhab KM. Senile cataract in patients with diabetes with and without diabetic retinopathy: a community-based comparative study. J Epidemiol Glob Health. 2022;12:56–63.
[87] Esteves JF, Dal Pizzol MM, Sccoco CA, et al. Cataract and type 1 diabetes mellitus. Diabetes Res Clin Pract. 2008;82:324–8.
[88] Yang G, Han Y-Y, Forno E, et al. Glycated hemoglobin A(1c), lung function, and hospitalizations among adults with asthma. J Allergy Clin Immunol Pract. 2020;8:3409–15.e1.
[89] Wu TD, Brigham EP, Keet CA, Brown TT, Hansel NN, McCormack MC. Association between prediabetes/diabetes and asthma exacerbations in a claims-based obese asthma cohort. J Allergy Clin Immunol Pract. 2019;7:1868–73.e5.
[90] Su SX, Wang X-T, Li X-F, Duan C-Z, Bi Y-M, Zhang X. Nonlinear association of glycosylated hemoglobin with single intracranial aneurysm rupture in patients with diabetes mellitus: a cross-sectional study. Front Neurol. 2022;13:854008.
[91] Can A, Castro VM, Yu S, et al. Antihyperglycemic agents are inversely associated with intracranial aneurysm rupture. Stroke. 2018;49:34–9.
[92] Wilkinson L, Gathani T. Understanding breast cancer as a global health concern. Br J Radiol. 2022;95:20211033.
[93] Francies FZ, Hull R, Khanyile R, Dlamini Z. Breast cancer in low-middle income countries: abnormality in splicing and lack of targeted treatment options. Am J Cancer Res. 2020;10:1568–91.
[94] Jiang ZR, Yang L-H, Jin L-Z, et al. Identification of novel cuproptosis-related lncRNA signatures to predict the prognosis and immune microenvironment of breast cancer patients. Front Oncol. 2022;12:988680.
[95] Zhang Y, Lin L, Wu Y, Bing P, Zhou J, Yu W. Upregulation of TIMM8A is correlated with prognosis and immune regulation in BC. Front Oncol. 2022;12:922178.
[96] Lin J, Ridker PM, Rifai N, et al. A prospective study of hemoglobin A1c concentrations and risk of breast cancer in women. Cancer Res. 2006;66:2869–75.
[97] Cust AE, Stocks T, Lukanova A, et al. The influence of overweight and insulin resistance on breast cancer risk and tumour stage at diagnosis: a prospective study. Breast Cancer Res Treat. 2009;113:567–76.
[98] Brahmkhatri VP, Prasanna C, Atreya HS. Insulin-like growth factor system in cancer: novel targeted therapies. Biomed Res Int. 2015;2015:538019.
[99] He S, He Y, Jin F, Liu Y. Correlation analysis of IGF-1, ZAG, nesfatin-1, HbA1c levels, and type 2 diabetes mellitus complicated with hypothyroidism. Medicine (Baltimore). 2021;100:e25432.
[100] Liu K, Wu HY, Xu YH. Study on the relationship between the expression of IGF-1 in umbilical cord blood and abnormal glucose metabolism during pregnancy. Eur Rev Med Pharmacol Sci. 2017;21:647–51.
[101] Shi J, Aronson KJ, Grundy A, et al. Polymorphisms of insulin-like growth factor 1 pathway genes and breast cancer risk. Front Oncol. 2016;6:136.