ISSN: 2572-5971

Research Article

Advances in Nutrition & Food Science

Genetic Causal Association Between Type 2 Diabetes, Body Mass Index, Smoking Initiation And Myopia: A Mendelian Randomization Study

Chu Zhang[1*], Hui Wang[3], Xiang-Lei Chen[1] and Shu-Qin Li[2]

[1]*Chizhou Aier Ophthalmology Hospital,Chizhou,247100,China.*

[2]*Hefei Aier Ophthalmology Hospital of Anhui Medical University, Hefei,230031,China.*

[3]*Nanling County Hospital of Traditional Chinese Medicine,Wuhu,242400,China.*

[*]Corresponding Author
Chu Zhang, Chizhou Aier Ophthalmology Hospital,Chizhou,247100,China.

Submitted: 2024, Feb 09 **Accepted**: 2024, Mar 04 **Published**: 2024, Mar 14

Citation: Zhang, C., Wang, H., Chen, X. L., Li, S. Q. (2024). Genetic Causal Association Between Type 2 Diabetes, Body Mass Index, Smoking Initiation And Myopia: A Mendelian Randomization Study. *Adv Nutr Food Sci, 9*(2), 01-07.

Abstract

The purpose of this investigation was to explore the causal relationships between type 2 diabetes, body mass index(BMI), smoking initiation, and myopia. We utilized summary statistics from independent genome-wide association studies to examine the causal linkages among these factors. Our main analytical technique was the inverse-variance-weighted (IVW) method, along with weighted median and mr-egger as supplements. Univariable and multivariable mendelian randomization(MR) analyses were conducted, and reverse MR was performed to assess reverse causation. The results showed that there were associations between myopia and smoking initiation (odds ratio (OR) 0.984, 95% confidence interval (CI) 0.977-0.992, $p=6.35\times10^{-5}$), body mass index (OR 0.989, 95% CI 0.984-0.993, $p=3.84\times10^{-6}$), and type 2 diabetes (OR 1.004, 95% CI 1.002-1.006, $p=4.15\times10^{-4}$). These associations remained strong even after mutual adjustment. We observed no pleiotropy in these exposures, and no associations were found in reverse MR.In conclusion, this study is the first to use univariable and multivariate mendelian randomization to confirm a causal relationship between type 2 diabetes, smoking initiation, BMI and myopia.

1. Intraduction

Myopia has emergent as a serious global public health issue owing to its exponential escalation in prevalence over recent decades. It is estimated that by the year 2050, nearly half of the Earth's populace will suffer from this ocular disorder [1]. Consequently, it is imperative to fashion proficient measures to mitigate the onset and advancement of myopia while alleviating the strain on healthcare systems. The East Asia locality is the most afflicted, where more than 90% of Chinese teenagers and 96.5% of 19-year-old males from Seoul, South Korea are affected [2]. High myopia presents consequential dangers to the development of the fundus, such as macular degeneration, choroidal neovascularization, retinal detachment, and open-angle glaucoma [3-6]. Hence, it is quint essential to identify the risk factors correlated with myopia's development and establish innovative therapeutic management approaches to forestall or delay its progression.

Myopia is a disease that is associated with both genetic and environmental factors. Despite extensive research over the past few decades, the mechanisms underlying myopia development and its related factors are still not fully understood.Previous observational studies have identified type 2 diabetes, secondhand smoke exposure, and BMI as factors related to myopia.Those results may be biased by potential residual confounding.There is currently no research to substantiate the causal relationship between smoking initiation and myopia.Furthermore,previous studies do not establish a clear causal relationship between type 2 diabetes,BMI and myopia [7-9].

Currently, a well-established close relationship exists between BMI and type 2 diabetes, and smoking is significantly linked to an elevated risk of developing type 2 diabetes [10,11]. Additionally, there may potentially exist a correlation between smoking and obesity, although certain studies have found no connection between the two[12,13]. These findings indicate the imperative to investigate whether these factors individually possess an independent causal relationship with myopia[14].

MR is an epidemiological technique that utilizes genetic variants as IVs to strengthen causal inference. It estimates the causal contribution of reported genetic variants of exposure to disease outcomes of interest. This approach has two main benefits.

Firstly, genetic variants are randomly allocated at conception, which minimizes confounding and eliminates the effects of self-adopted and environmental factors. Secondly, genetic variants cannot be modified by disease development, thus diminishing reverse causation [15].Consequently, MR has been likened to a randomized trial by genotype.In this study, we employed MR to investigate the causal relationship between exposures and disease outcomes by utilizing genetic variants as tools.

2. Methods

2.1 Data Source

GWAS summary statistics were obtained from the IEU Open GWAS project website(https://gwas.mrcieu.ac.uk/).These three traits from different GWASs, serve as exposure factors in this study, including body mass index (dataset ieu-b-40; n = 681,275),smoking initiation (ieu-b-4877; n = 607,291),type 2 diabetes(ebi-a-GCST006867; n=655,665).The myopia GWAS summary statistics were obtained from the open GWAS with ID "ukb-b-6353" included 460,536 Europeans, with 37,362 cases and 423,174 controls. All participants were of European descent, thus avoiding ancestry-specific heterogeneity that could bias causal estimates. Please note that data in this study was not collected from any specific countries, and the GWAS data used were at the summary-level only. Further details of the GWAS can be found in Table 1. Our visit to the website was on June 6, 2023.

Phenotype	Consortm	First author	Participants included in analysis	Year	Note
Myopia	MRC-IEU	Ben Elsworth	460,536European-descent individuals	2018	https://gwas.mrcieu.ac.uk/datasets/ukb-b-6353/
BMI	GIANT	Yengo, L	681,275European-descent individuals	2018	https://gwas.mrcieu.ac.uk/datasets/ieu-b-40/
Smoking initiation	GSCAN	Liu M	607,291European-descent individuals	2019	https://gwas.mrcieu.ac.uk/datasets/ieu-b-4877/
Type 2 diabetes	NA	Xue A	655,666European-descent individuals	2018	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST006867/

Table 1: Description of GWAS summary statistics for myopia,BMI,smoking initiation and type 2 diabetes.*BMI* body mass index.

2.2 Study Design

Preliminarily, body mass index, smoking initiation, type 2 diabetes were treated as exposures, and myopia was the outcome. A reverse MR was performed as well, where myopia was the exposure and body mass index, smoking initiation and type 2 diabetes were the outcomes, hoping to clarify reverse causation. A brief demonstration of the study design can be found in Figure 1.

The MR design relies on three assumptions (Fig. 1).First, the genetic instruments must be robustly associated with the alleged biomarker of interest. Second, the genetic instruments must be associated with the outcome only via the exposure and not via a different biological pathway independent of the exposure. Third, the genetic instruments must not be associated with any confounders of the exposure– outcome relationship.

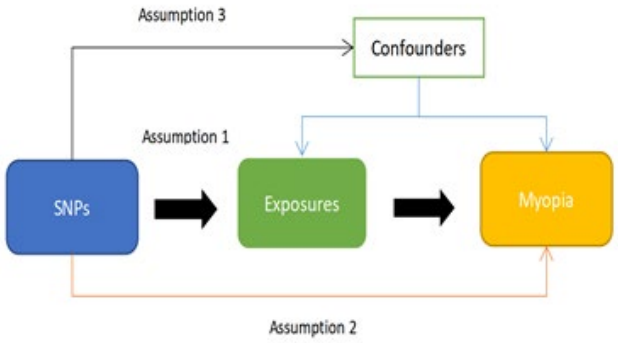

Figure 1: Diagram of MR analyses process and major assumptions.

2.3 MR Analysis and Sensitivity Analysis

MR analysis between the exposures and myopia was performed using the TwoSampleMR (version 0.5.6) package (R Foundation for Statistical Computing, Vienna, Austria)in R Software 4.2.3.This package makes causal inference about an exposure on an outcome using GWAS summary statistics, generates linkage disequilibrium pruning of exposure SNVs and harmonizes exposure and outcome datasets [16]. Data visualization was performed using the R package “forestplot”.The R package “MRPRESSO” was used to carry out The MR-PRESSO analysis.

The following standards were applied in the selection of genetic

instruments for each trait: (1) $P < 5 \times 10^{-8}$ for each trait; (2) linkage disequilibrium r2 < 0.001; and (3) linkage disequilibrium distance > 10,000 kb. In this study, IVW method was the main method used to estimate associations between exposures and outcome[17]. For sensitivity analysis, two additional approaches based on the TwoSampleMR R package were used, including MR-Egger regression, weighted median method [18,19].The IVW method can give the most accurate estimate if all instruments were valid. This method combines the Wald ratio causal estimates obtained from each of the SNPs and yields a pooled causal effect of the exposure on the outcome using a meta-analysis approach [20]. The MR-Egger method can still provide unbiased estimators even if pleiotropy exists for all selected instrumental variables [21]. The weighted median model has the ability to identify true causality if up to 50% of IVs are invalid, by measuring the weighted medium value of the IV ratios [22]. The MR-PRESSO analysis can detect outliers and generate estimates after outliers removing [23].

To assess whether genetic liability to type 2 diabetes is associated with myopia risk independently of BMI and smoking initiation, we performed the multivariable MR analysis with adjustment for genetically predicted BMI and smoking initiation. The same approach was then used to assess whether genetic susceptibility to BMI and smoking initiation was associated with myopia risk.

The Bonferroni method was utilized to correct for multiple comparisons, and the p-value was <0.017 (0.05 was divided by 3).Associations with p value < 0.017 (0.05/3 exposures) were deemed signifcant associations, and associations with a p value ≥ 0.017 and < 0.05 were regarded as suggestive associations. To further assess the robustness of these identified associations, the impact was assessed for potential horizontal pleiotropy. If heterogeneity was present, the multiplicative random-effects IVW model was used and provided valid estimates under the assumption of balanced pleiotropy.Two methods were utilized to judge horizontal pleiotropy, including the MR-Egger intercept and MR-PRESSO.

3. Results

3.1 Univariable Mendelian Randomization Analyses

The main results indicated that genetically elevated body mass index was found to be significantly and inversely associated with the risk of myopia.(IVW OR = 0.989; 95% CI0.984-0.993, p= 3.84×10^{-6}). The consistent direction of body mass index suggests that it has a protective role against myopia. (Table 2,Figur2)
In addition, casual associations were observed between the type 2 diabetes and myopia. The multiplicative random-effects IVW approach showed that higher HbA1c levels were strongly associated with an increased risk of myopia (OR = 1.004; 95% CI, 1.002-1.006; P = 4.15×10-4). Consistent MR analysis results were found using the other two MR methods, including MR Egger (OR = 1.006; 95% CI, 1.002-1.011; 1.03×10-2), weighted median (OR = 1.006; 95% CI, 1.003-1.008; P =2.11×10-5).(Table 2,Figure 2)

The risk of myopia is inversely associated with smoking initiation. The multiplicative random-effects IVW approach was utilized due to the presence of heterogeneities (P□0.05), revealing that early smoking initiation is strongly linked to an decreased risk of myopia (OR = 0.984; 95% CI, 0.980-0.997; P = 0.006). The result is consistent with MR Egger (OR = 0.998; 95% CI, 0.960-1.038; P =0.907) and weighted median (OR = 0.993; 95% CI, 0.984-1.002; P =0.121).(Table 2,Figure 2)

No heterogeneity or horizontal pleiotropy was detected (IVW Q p-value >0.05 and MR-Egger intercept p-value >0.05),which indicate the robustness of the causal association.MR-PRESSO detected outliers,we manually removed this outlier and the causality remained.In the reverse model, no significant association was observed (Supplementary Table S1).

Exposures	SNPs	Weighted median			MR-Egger			pleiotropy	heterogenrity
		OR	95% CI	*P*	OR	95% CI	P	*P*	*P*
BMI	492	0.990	0.984-0.997	5.44×10^{-3}	0.995	0.982-1.007	0.400	0.333	6.690×10^{-31}
Smoking initiation	85	0.993	0.984-1.002	0.121	0.998	0.960-1.038	0.907	0.499	3.739×10^{-9}
Type 2 diabetes	115	1.006	1.003-1.008	2.106×10^{-5}	1.006	1.002-1.011	0.010	0.242	3.039×10^{-5}

Table 2: Associations of genetically predicted risk factors with myopia in univariable mendelian randomization sensitivity analyses.*BMI* body mass index; *CI* Confdence interval;*OR* Odds ratio; SNPs Single-nucleotide polymorphisms.

3.2 Multivariable Mendelian Randomization Analyses

After adjusting for type 2 diabetes and smoking initiation, the association between genetically predicted body mass index and myopia attenuated slightly (OR = 0.991; 95% CI, 0.985-0.997; P = 0.003). Similarly, after adjusting for BMI and smoking initiation, the association between genetically predicted type 2 diabetes and myopia also showed a slight attenuation (OR = 1.003; 95% CI, 1.001-1.006; P = 0.006). Additionally, after adjusting for BMI and type 2 diabetes, the association between smoking initiation and myopia was slightly attenuated (OR = 0.986; 95% CI 0.977-0.994; P = 0.001).(Figure 3)

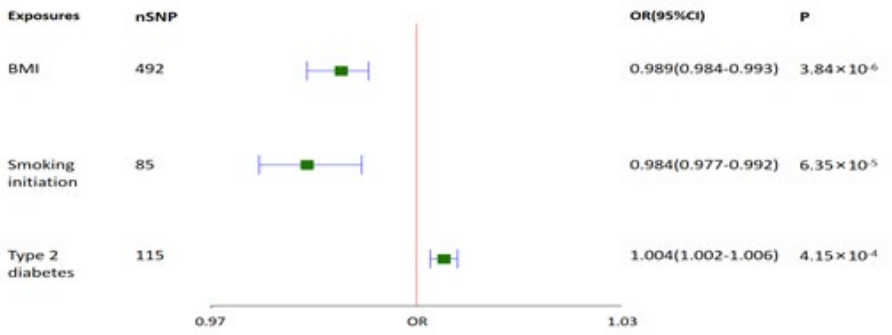

Figure 2: Causal association between type 2 diabetes, body mass index, smoking Initiation and myopia. Estimates were derived from univariable Mendelian randomization analyses using the multiplicative random-effects inverse-variance weighted method.BMI, body mass index; CI, confdence interval; OR, odds ratio.

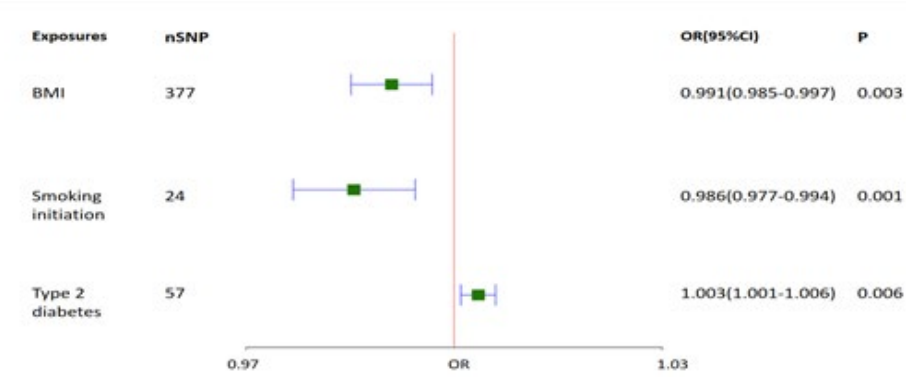

Figure 3: Causal association between type 2 diabetes, body mass index, smoking Initiation and myopia. Estimates were derived from the multivariable inverse-variance weighted model with multiplicative random effects.BMI, body mass index; CI, confdence interval; OR, odds ratio.

4. Discussion

In our study, we provided evidence for a causally independent relationship between type 2 diabetes, BMI, smoking initiation and myopia.

Over the years, researchers have been investigating the relationship between type 2 diabetes and myopia. Type 2 diabetes patients experience relative insulin deficiency in their bodies, and some of them even have higher insulin levels than normal people. Initially, it was discovered during internal experiments that insulin may promote eye growth [24]. This finding has raised concerns about the potential role of insulin in axial growth in the eyes and its possible connection to myopia.In 2002, Cordain et al. found that chronic hyperinsulinemia may play a key role in the pathogenesis of adolescent myopia because of its interaction with hormone regulation of vitreous cavity growth [25]. This suggests that type 2 diabetes may cause myopia. Subsequently, more studies have confirmed this point. Tarczy-Hornoch et al found that the presence of diabetes is an independent risk factor for myopia, and the incidence rate of type 2 diabetes in women is significantly higher than that in non-diabetic women (20.60% vs. 16.26%)[26]. However, the Blue Mountains Eye Study found no association between them [27]. The Beaver Dam Eye Study found that DM2 patients had changes in farsightedness rather than myopia [28]. These studies may be affected by confounding factors such as education level and outdoor exposure. A previous Mendelian randomization study found a causal relationship between adiponectin, HbA1c and myopia, where low adiponectin levels and high HbA1c can increase the risk of myopia [29]. However, the study did not adjust for confounding factors such as BMI using multivariate Mendelian randomization, so its results require further validation. This study is the first to use multivariate Mendelian randomization to confirm a causal relationship between type 2 diabetes and myopia. The mechanism by which type 2 diabetes causes myopia has yet to be elucidated, but some possible mechanisms that have been explored include the fact that some type 2 diabetes patients have insulin resistance, which may be involved in the progression of myopia [25]. Secondly, it has been observed that some individuals with type 2 diabetes possess higher levels of insulin in their bodies. This increase in insulin can stimulate the secretion of insulin-like growth factor-1 (IGF-1), which is known to play a role in eye growth. IGF-1 may contribute to the elongation of the eyes and ultimately lead to myopia in these patients [30].This finding suggests that preventing the occurrence of type 2 diabetes is also

an important measure for controlling myopia.

BMI, representing overall obesity, has been associated with myopia in observational studies. Tu Y et al. found that BMI was an important influencing factor for myopia and that the prevalence of myopia was significantly higher in obese students than in overweight students and other groups [31]. A nationwide study in Israel involving 1.3 million adolescents found a J-shaped association between BMI and myopia [32]. In contrast, some studies have found that young adult men with low BMI have a higher risk of myopia, while others believe that there is no relationship between BMI and myopia [33-35].The reason for these discrepancies in research may be that some studies did not include factors such as screen time exposure, outdoor time, dietary habits, and physical activity habits, and different studies may also be influenced by race and regional factors. The mechanism by which BMI influences myopia is still unclear. Gunes et al. reported that retrobulbar fat is significantly constrained by the orbital space [36].Due to limited orbital space, the eyes of obese individuals may not develop as well as those of lean individuals. Therefore, obese individuals may exhibit more farsightedness and a shorter vitreous chambers[33]. The mendelian randomization study by Li et al. did not find a causal relationship between BMI and myopia [29]. This is inconsistent with our current research result that BMI is an important protective factor for myopia. Taking into account the fact that our study employed a substantial sample size of GWAS summary datasets on BMI and utilized the multivariate Mendelian randomization method to adjust for type 2 diabetes, a confounding factor, it can be asserted that the findings of our study are of higher validity.

Previously, there was no research exploring the relationship between smoking initiation and myopia. Some studies have confirmed the association between passive smoking in children and myopia. Chua SY et al. found that exposure to passive smoking in Asian children from birth to 6 months of age slightly increases the risk of early-onset myopia [37]. Another study in Hong Kong indicated that exposure to secondhand smoke was associated with higher myopic refraction, longer axial length, a greater probability of developing moderate and high myopia, and earlier onset of myopia [38]. In some cross-sectional studies, contradictory results have been identified. A study analyzing data from the National Health and Nutrition Examination Survey (NHANES) in the United States found a reduced odds of myopia among 12-19 year-old adolescents with smokers in the household (OR = 0.79, 95% CI: 0.66-0.97) [39]. In a sample of 323 patients from a U.S. ophthalmology clinic, the prevalence of myopia was lower among patients with at least one smoking parent (12.4% vs. 25.4%, p-value = 0.004) [40]. However, S-M Saw's study did not observe a correlation between parental smoking and childhood refractive errors [41]. The mechanism through which smoking influences myopia remains unclear, but recent research suggests that nicotinic acetylcholine receptors may play a crucial role in eye development. Animal experiments have demonstrated that antagonists of nicotinic acetylcholine receptors can inhibit myopia [42]. Due to the complex pharmacological properties of nicotinic acetylcholine receptors, nicotine can induce a variety of intricate and sometimes conflicting biological effects [43]. This MR study supports for the first time a causal association between smoking initiation and myopia after adjusting for type 2 diabetes and BMI. This finding suggests that in addition to focusing on children's passive smoking, the initiation of children's smoking also deserves our attention in the field of myopia development.It is worth noting that considering smoking's potential detrimental effects on the physical development of adolescents, we do not advocate smoking as a means of managing myopia.

One of the principal strengths of this study lies in the implementation of MR methodology to scrutinize vast datasets. This approach is less susceptible to confounding factors or biases stemming from reverse causation,compared to conventional studies.Nevertheless,several limitations must be acknowledged herein. Firstly, given that this study was confined to participants of European ancestry, further study is warranted to determine the extent to which our findings can be extrapolated to other ethnic groups. Secondly, protracted follow-up investigations are needed to fully apprehend the impact of type 2 diabetes and BMI on myopia progression over time. Thirdly, the effects of smoking initiation on the risk of myopia have yet to be experimentally investigated, requiring additional laboratory investigations.

Our study reveals that type 2 diabetes, body mass index, and smoking initiation have genetically predetermined causal relationship with myopia. This study paves the way for novel insights on preventing nearsightedness.

Data Availability

Publicly available datasets were analyzed in this study.Data from UK Biobank are available at https://www.ebi.ac.uk/gwas/.Further inquiries can be directed to the corresponding authors.

Acknowledgments

We would like to thank all participants and investigators of the FinnGen study and UK Biobank.

Author Contributions

Z.C. and L.S.Q. mainly designed and performed analysis, and wrote the manuscript;Z.C. and L.S.Q. contributed equally to this paper.W.H. supervised the entire project. L.Y. and L.Q. revised the manuscript and advised on statistical methods. C.X.L. was responsible for the accuracy and integrity of this study. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by Aier Eye Hospital Group Free Exploration Program (AF2208D04) ,Anhui Medical University Youth Science Foundation (2022XKJ136)

Ethics Statement

Ethical approval for each data set had been obtained in the original

studies.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Holden, B. A., Fricke, T. R., Wilson, D. A., Jong, M., Naidoo, K. S., Sankaridurg, P., ... & Resnikoff, S. (2016). Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology, 123*(5), 1036-1042.
2. Dolgin, E. (2015). The myopia boom. *Nature, 519*(7543), 276.
3. Saw, S. M., Gazzard, G., Shih-Yen, E. C., & Chua, W. H. (2005). Myopia and associated pathological complications. *Ophthalmic and Physiological Optics, 25*(5), 381-391.
4. Xu, L., Wang, Y., Wang, S., Wang, Y., & Jonas, J. B. (2007). High myopia and glaucoma susceptibility: the Beijing Eye Study. *Ophthalmology, 114*(2), 216-220.
5. Iwase, A., Araie, M., Tomidokoro, A., Yamamoto, T., Shimizu, H., Kitazawa, Y., & Tajimi Study Group. (2006). Prevalence and causes of low vision and blindness in a Japanese adult population: the Tajimi Study. *Ophthalmology, 113*(8), 1354-1362.
6. Hsu, W. M., Cheng, C. Y., Liu, J. H., Tsai, S. Y., & Chou, P. (2004). Prevalence and causes of visual impairment in an elderly Chinese population in Taiwan: the Shihpai Eye Study. *Ophthalmology, 111*(1), 62-69.
7. Lin, H. T., Zheng, C. M., Fang, Y. A., Liu, J. C., Wu, Y. C., Chang, Y. H., ... & Lin, Y. F. (2021). Prevalence and risk factors for myopia in Taiwanese diabetes mellitus patients.
8. Zhang, Y., Zhang, X. J., Yuan, N., Zhang, Y., Wang, Y. M., Tang, F., ... & Yam, J. C. (2023). Analysis of Secondhand Smoke Exposure and Myopia Among Children Aged 6 to 8 Years in Hong Kong. *JAMA Network Open, 6*(5), e2313006-e2313006.
9. Peled, A., Nitzan, I., Megreli, J., Derazne, E., Tzur, D., Pinhas-Hamiel, O., ... & Twig, G. (2022). Myopia and BMI: a nationwide study of 1.3 million adolescents. *Obesity, 30*(8), 1691-1698.
10. Toplak, H., Hoppichler, F., Wascher, T. C., Schindler, K., & Ludvik, B. (2016). Obesity and type 2 diabetes. *Wiener klinische Wochenschrift, 128*, 196-200.
11. Pan, A., Wang, Y., Talaei, M., Hu, F. B., & Wu, T. (2015). Relation of active, passive, and quitting smoking with incident type 2 diabetes: a systematic review and meta-analysis. *The lancet Diabetes & endocrinology, 3*(12), 958-967.
12. Fang, H., Ali, M. M., & Rizzo, J. A. (2009). Does smoking affect body weight and obesity in China?. *Economics Human Biology, 7*(3), 334-350.
13. Jong-Hyuck, K., & Wi-Young, S. (2012). Association of smoking frequency and cigarette consumption with obesity in Korean adolescents. *Bratislavske lekarske listy, 113*(10), 599-603.
14. Gasperin, L. D. O. F., Neuberger, M., Tichy, A., & Moshammer, H. (2014). Cross-sectional association between cigarette smoking and abdominal obesity among Austrian bank employees. *BMJ open, 4*(7), e004899.
15. Davies, N. M., Holmes, M. V., & Smith, G. D. (2018). Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *bmj*, 362.
16. Choquet, H.et al. Association Between Myopic Refractive Error and Primary Open-Angle Glaucoma: A 2-Sample Mendelian Randomization Study. *JAMA Ophthalmol. 140*(9):864-871(2022).
17. Burgess, S., Butterworth, A., & Thompson, S. G. (2013). Mendelian randomization analysis with multiple genetic variants using summarized data. *Genetic epidemiology, 37*(7), 658-665.
18. Bowden, J., Davey Smith, G., & Burgess, S. (2015). Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *International journal of epidemiology, 44*(2), 512-525.
19. Bowden, J., Davey Smith, G., Haycock, P. C., & Burgess, S. (2016). Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genetic epidemiology, 40*(4), 304-314.
20. Cai, J., Wei, Z., Chen, M., He, L., Wang, H., Li, M., & Peng, Y. (2022). Socioeconomic status, individual behaviors and risk for mental disorders: A Mendelian randomization study. *European Psychiatry, 65*(1), e28.
21. Yuan, R., Liu, K., Cai, Y., He, F., Xiao, X., & Zou, J. (2022). Body shape and risk of glaucoma: A Mendelian randomization. *Frontiers in Medicine, 9,* 999974.
22. Chong, R. S., Li, H., Cheong, A. J., Fan, Q., Koh, V., Raghavan, L., ... & Cheng, C. Y. (2023). Mendelian Randomization Implicates Bidirectional Association between Myopia and Primary Open-Angle Glaucoma or Intraocular Pressure. *Ophthalmology, 130*(4), 394-403.
23. Verbanck, M., Chen, C. Y., Neale, B., & Do, R. (2018). Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nature genetics, 50*(5), 693-698.
24. Feldkaemper, M. P., Neacsu, I., & Schaeffel, F. (2009). Insulin acts as a powerful stimulator of axial myopia in chicks. *Investigative ophthalmology & visual science, 50*(1), 13-23.
25. Cordain, L., Eaton, S. B., Brand Miller, J., Lindeberg, S., & Jensen, C. (2002). An evolutionary analysis of the aetiology and pathogenesis of juvenile-onset myopia. *Acta Ophthalmologica Scandinavica, 80*(2), 125-135.
26. Tarczy-Hornoch, K., Ying-Lai, M., Varma, R.,& Los Angeles Latino Eye Study Group.Myopic refractive error in adult Latinos: the Los Angeles Latino Eye Study. *Invest Ophthalmol Vis Sci. 47*(5):1845-1852(2006).
27. Guzowski, M., Wang, J. J., Rochtchina, E., Rose, K. A., & Mitchell, P. (2003). Five-year refractive changes in an older population: the Blue Mountains Eye Study. *Ophthalmology, 110*(7), 1364-1370.
28. Lee, K. E., Klein, B. E., Klein, R., & Wong, T. Y. (2002). Changes in refraction over 10 years in an adult population: the Beaver Dam Eye study. *Investigative ophthalmology & visual*

science, 43(8), 2566-2571.
29. Li, F. F., Zhu, M. C., Shao, Y. L., Lu, F., Yi, Q. Y., & Huang, X. F. (2023). Causal Relationships Between Glycemic Traits and Myopia. *Investigative Ophthalmology & Visual Science, 64*(3), 7-7.
30. Ritchey, E. R., Zelinka, C. P., Tang, J., Liu, J., & Fischer, A. J. (2012). The combination of IGF1 and FGF2 and the induction of excessive ocular growth and extreme myopia. *Experimental eye research, 99*, 1-16.
31. Tu, Y., Hu, X., Zeng, C., Ye, M., Zhang, P., Jin, X., ... & Zhou, L. (2022). A machine-learning approach to discerning prevalence and causes of myopia among elementary students in Hubei. *International Ophthalmology, 42*(9), 2889-2902.
32. Peled, A., Nitzan, I., Megreli, J., Derazne, E., Tzur, D., Pinhas-Hamiel, O., ... & Twig, G. (2022). Myopia and BMI: a nationwide study of 1.3 million adolescents. *Obesity, 30*(8), 1691-1698.
33. Lee, D. C., Lee, S. Y., & Kim, Y. C. (2018). An epidemiological study of the risk factors associated with myopia in young adult men in Korea. *Scientific reports, 8*(1), 511.
34. Jung, S. K., Lee, J. H., Kakizaki, H.,& Jee, D.Prevalence of myopia and its association with body stature and educational level in 19-year-old male conscripts in Seoul, South Korea. *Invest Ophthalmol Vis Sci. 53*(9):5579-5583(2012).
35. Yue, Y., Liu, X., Yi, S., Liu, B., Yi, H., & Li, H. (2022). High prevalence of myopia and low hyperopia reserve in 4411 Chinese primary school students and associated risk factors. *BMC ophthalmology, 22*(1), 1-9.
36. Gunes, A., Uzun, F., Karaca, E. E., & Kalaycı, M. (2015). Evaluation of anterior segment parameters in obesity. *Korean Journal of Ophthalmology, 29*(4), 220-225.
37. Chua, S. Y. L., Ikram, M. K., Tan, C. S., Stone, R. A., Cai, S., Gluckman, P. D., ... & GUSTO Study Group. (2016). Is there a link between passive smoke exposure and early-onset myopia in preschool Asian children?. *Ophthalmic and Physiological Optics, 36*(4), 370-380.
38. Zhang, Y., Zhang, X. J., Yuan, N., Zhang, Y., Wang, Y. M., Tang, F., ... & Yam, J. C. (2023). Analysis of Secondhand Smoke Exposure and Myopia Among Children Aged 6 to 8 Years in Hong Kong. *JAMA Network Open, 6*(5), e2313006-e2313006.
39. Chiang, S. Y., Weng, T. H., Lin, C. M., & Lin, S. M. (2020). Ethnic disparity in prevalence and associated risk factors of myopia in adolescents. *Journal of the Formosan Medical Association, 119*(1), 134-143.
40. Stone, R. A., Wilson, L. B., Ying, G. S., Liu, C., Criss, J. S., Orlow, J., ... & Quinn, G. E. (2006). Associations between childhood refraction and parental smoking. *Investigative ophthalmology & visual science, 47*(10), 4277-4287.
41. Saw, S. M., Chia, K. S., Lindstrom, J. M., Tan, D. T. H., & Stone, R. A. (2004). Childhood myopia and parental smoking. *British journal of ophthalmology, 88*(7), 934-937.
42. Stone, R. A., Sugimoto, R., Gill, A. S., Liu, J., Capehart, C., & Lindstrom, J. M. (2001). Effects of nicotinic antagonists on ocular growth and experimental myopia. *Investigative ophthalmology & visual science, 42*(3), 557-565.
43. Iyer, J. V., Low, W. C., Dirani, M., & Saw, S. M. (2012). Parental smoking and childhood refractive error: the STARS study. *Eye, 26*(10), 1324-1328.