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Cornea & External Disease

Unraveling the Link Between Obesity and Keratoconus Risk Based on Genetic Evidence

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Purpose: Keratoconus (KCN) is a progressive corneal disorder leading to vision impairment. While genetic and environmental factors contribute to its development, the role of obesity in KCN risk remains unclear. This study aimed to estimate the causal effect between obesity, measured by body mass index (BMI) and waist-to-hip ratio (WHR), and the risk of KCN.

Methods: This two-sample Mendelian randomization (MR) case-control study used genome-wide association study data from GIANT, MRC-IEU UK Biobank, and FinnGen. BMI and WHR were used to estimate general and central obesity, respectively. Data from 311 KCN cases and 209,287 controls were analyzed. Causal effect estimates of BMI, WHR, and obesity-related chronic diseases on KCN risk were calculated.

Results: Genetically predicted higher BMI was significantly associated with increased KCN risk (odds ratio [OR] = 2.003; 95% confidence interval [CI], 1.203–3.335; $P = 0.008$), as determined using European genetic databases. Consistent results were observed with the weighted median, MR-Egger, and MR–pleiotropy residual sum and outlier methods. No significant causal effect was found between WHR and KCN risk (OR = 0.578; 95% CI, 0.196–1.705; $P = 0.321$). Sensitivity analyses showed no evidence of pleiotropy, and no significant causal effect was observed between obesity-related chronic diseases and KCN risk.

Conclusions: Using European genetic databases, general obesity was identified as a strong, independent causal effect contributor to KCN, while central obesity showed no association. These findings provide new insights into obesity's role in KCN development and may inform future preventive strategies.

Translational Relevance: This study suggests that general obesity is a causal risk factor for keratoconus, suggesting that obesity management could help prevent or mitigate KCN progression.

Introduction

Keratoconus (KCN) is a multifactorial, progressive corneal ectasia characterized by corneal thinning and cone-like steepening, leading to significant visual impairment.[1] Studies have reported that the prevalence of KCN ranges from 50 to 2300 cases per 100,000 individuals.[2,3] Although genetic factors are implicated in KCN, with several risk genes identified, early diagnosis and treatment remain challenging due to an incomplete understanding of its mechanisms.[4] In addition, factors such as oxidative stress and abnormal iron deposition have been linked to KCN but are not fully elucidated.[5,6] Substantial efforts are still needed to explore the mechanisms and treatment modalities of KCN.

Obesity is a global health concern associated with a variety of chronic conditions, including type 2 diabetes, cardiovascular disease, and cancer.[7,8] Previous research has explored the relationship between obesity and keratoconus; however, notable discrepancies persist within the literature. Some studies have reported no correlation between body mass index (BMI), the most widely utilized metric for assessing obesity, and KCN.[9,10] Conversely, Pihlblad and Schaefer[11] indicated a higher rate of obesity in American patients with KCN, and a population-based cross-sectional study among half a million adolescents provided evidence regarding the correlation between BMI and KCN.[12] Given that these studies are constrained by potential biases and confounding factors inherent in observational research methodologies, further research is required to establish causal relationships.[13]

Mendelian randomization (MR) has emerged as a powerful tool for evaluating causal effects between risk factors and disease.[14] It employs single nucleotide polymorphisms (SNPs) as instrumental variables, effectively reducing biases associated with confounding variables and reverse causality typically encountered in observational studies.[15] In the context of KCN, if individuals with a genetic predisposition to higher BMI also exhibit increased susceptibility to KCN, this would further support a causal effect between obesity and keratoconus. Additionally, obesity can be categorized into general obesity, assessed by BMI, and central obesity, evaluated by waist-to-hip ratio (WHR). The relationship between these different types of obesity and KCN remains largely unexplored. Therefore, further investigation is warranted to elucidate these associations.

In this study, we employed a two-sample MR approach to investigate the potential causal effect between obesity and KCN (Fig. 1). To determine whether general obesity and central obesity contribute to KCN, we screened BMI-associated SNPs and WHR-associated SNPs in European genetic databases as instrumental factors. Moreover, we analyzed in depth to explore whether the obesity-mediated causal effect could be attributed to classic obesity-related chronic diseases. Our findings provide novel insights into the role of obesity in the pathogenesis of KCN and suggest promising directions for future research.

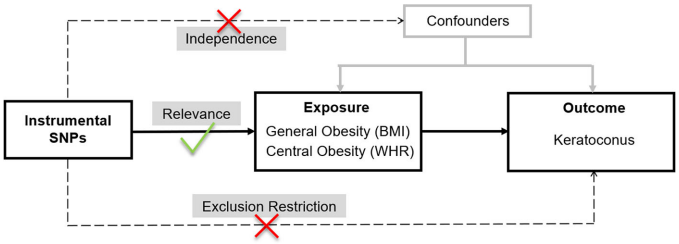

Figure 1. Overview of the present study design. The association between exposure (body mass index and waist-to-hip ratio) and the outcome (keratoconus) is analyzed adhering to the fundamental assumptions of MR analysis. These include that the selected genetic variants are directly associated with the exposure but not influenced by confounding variables, and that these variants impact the outcome exclusively through the exposure, without involving alternate pathways or phenotypes.

Materials and Methods

Genetic Instruments

The selection of BMI-associated SNPs for genetic instruments was based on previous genome-wide association studies (GWAS) summary data from the MRC-IEU UK Biobank (GWAS ID: ukb-b-19953), involving participants of European ancestry (n = 461,460). The WHR data were taken from GRANT (Genetic Investigation of Anthropometric Traits, GWAS ID: ieu-a-78), which included 210,082 European individuals. The trait "keratoconus" in the FINNGEN (GWAS ID: finn-b-H7_CORNEALDEFORM) was determined by KCN among 209,598 European individuals (311 cases, 209,287 controls) (Table 1). The KCN cases were defined by H18.6 in the International Classification of Diseases, Tenth Revision (ICD-10); 3716 in the International Classification of Diseases, Ninth Revision (ICD-9); and 37,103 in the International Classification of Diseases, Eighth Revision (ICD-8) in FinnGen. We used linkage disequilibrium clumping ($r^2 \leq 5 \times 10^{-4}$ within windows 10 MB for variants in the same locus)

Table 1. Summary of Genome-Wide Association Studies That Relate to Exposures and Outcomes

Variants	ID	Samples (*N*)	SNPs (*N*)	Population	Sex	Consortium
BMI	ukb-b-19953	461,460	9,851,867	European	Males and females	MRC-IEU UK Biobank
WHR	ieu-a-78	210,082	2,542,432	European	Males and females	GIANT
KCN	finn-b-H7 _CORNEALDEFORM	311 cases, 209, 287 controls	16,380,407	European	Males and females	FINNGEN

to obtain independent SNPs linked with the exposure, and the SNPs with genome-wide significance ($P < 5 \times 10^{-8}$) were retained. Instrument strength for each candidate SNP in MR was estimated using the *F*-statistic.[16] Notably, SNPs with an *F*-statistic greater than 10 were regarded as robust instruments. The same screening criteria outlined above were applied for choosing chronic diseases and related trait-associated SNPs.

Mendelian Randomization Analyses

The TwoSampleMR (https://mrcieu.github.io/TwoSampleMR/) and MR-PRESSO R packages (https://github.com/rondolab/MR-PRESSO) were used to conduct all MR analyses in R (version 4.1.0). Standard errors were calculated using the Delta method. Next, the multiplicative random-effect inverse-variance-weighted (IVW) method was used as the primary method to estimate the causal effect of general obesity (BMI) or central obesity (WHR) on KCN. $P < 0.05$ was considered statistically significant. The MR Steiger directionality test was performed to validate the correct direction of association between exposures and KCN.[17]

Given that the validity of the MR approach relies on the crucial assumption of no pleiotropy, we explored the effects of potential pleiotropy on the causal estimates using a series of MR analytical approaches. Cochran's *Q* test was used to determine the heterogeneity between the causal estimates of different genetic variants, which can identify the presence of pleiotropy.[18] The weighted median is robust to invalid instruments and can offer reliable estimation even when up to 50% of the weight comes from invalid SNPs.[19] The slope of the MR-Egger regression provides robust MR estimates, and the intercept term of the MR-Egger regression that differs from zero ($P < 0.05$) indicates overall directional pleiotropy.[20] Additionally, the robustness of the causal effect between obesity and KCN incidence was further evaluated using the MR–pleiotropy residual sum and outlier (MR-PRESSO) test, and the MR-PRESSO global test was then used to identify the potential horizontal pleiotropic effects of the SNPs.[21]

Results

MR Analysis Revealed a Causal Effect of General Obesity Rather Than Central Obesity on KCN

The SNPs used as proxies for genetically predicted BMI and their relationships with the risk of KCN are shown in Supplementary Table S1. As shown in Table 2, we found that genetically predicted higher BMI was significantly associated with a higher risk of KCN based on the IVW method (odds ratio [OR] = 2.003; 95% confidence interval [CI], 1.203–3.335; $P = 0.008$). The correct causal direction was confirmed using the Steiger directionality test (P for Steiger test = 1.647×10^{-95}). Considering that MR studies are vulnerable to pleiotropic effects (effects of the SNPs on the outcomes other than via the exposures), sensitivity analyses were conducted to identify pleiotropy. As presented in Figure 2 and Table 2, the weighted median, MR-Egger, and MR-PRESSO provided consistent associations. Moreover, the intercept from the MR-Egger regression analysis, the global test from the MR-PRESSO, and heterogeneity from Cochran's *Q* test did not reach statistical significance (all $P > 0.05$, Table 2). Therefore, there is no apparent evidence of overall directional pleiotropy, and the estimate of the causal effect between obesity and KCN is robust.

Table 2. Mendelian Randomization Estimates for Associations Between Obesity and KCN

Methods	SNPs	OR	95% CI	*P*	*P*-Het	*P*-Intercept	*P*-Global
BMI							
IVW	376	2.003	1.203–3.335	0.008	0.934		
Weighted median	376	2.743	1.121–6.711	0.028			
MR-Egger	376	3.947	1.024–15.208	0.047		0.288	
MR-PRESSO	376	1.824	1.169–2.846	0.008			0.918
WHR							
IVW	36	0.578	0.196–1.705	0.321	0.367		
Weighted median	36	0.766	0.162–3.627	0.736			
MR-Egger	36	0.286	0.002–39.638	0.622		0.776	
MR-PRESSO	36	0.558	0.193–1.616	0.289			0.330

P-het = *P* value for heterogeneity using Cochran's *Q* test; *P*-intercept = *P* value for MR-Egger intercept; *P*-global = *P* value for MR-PRESSO global test.

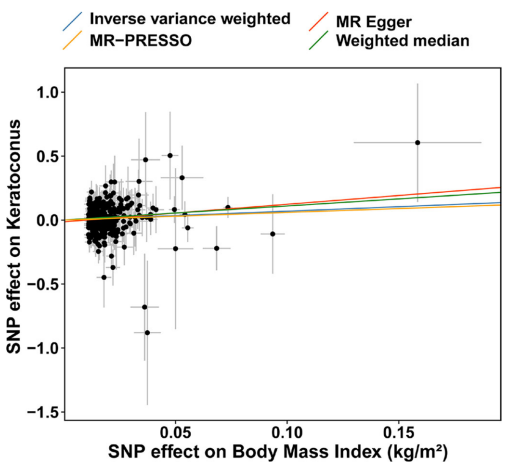

Figure 2. Mendelian randomization scatterplots for the associations between body mass index against the risk of keratoconus. MR, mendelian randomization; SNP, single nucleotide polymorphism; PRESSO, Pleiotropy RESidual Sum and Outlier.

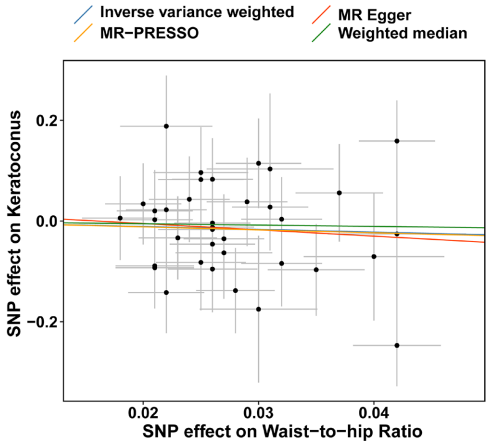

Figure 3. Mendelian randomization scatterplots for the associations between waist-to-hip ratio against the risk of keratoconus.

However, genetically determined WHR was not causally associated with the risk of KCN (OR = 0.578; 95% CI, 0.196–1.705; $P = 0.321$) based on the IVW analysis. Three additional MR methods yielded consistent results; that is, there was no significantly lower or upper risk of KCN with an increased level of WHR (Fig. 3). MR-Egger regression suggested no evidence of horizontal pleiotropy ($P = 0.776$), and there seemed no substantial heterogeneity ($P = 0.367$) among individual SNPs.

The Causal Impact of General Obesity on KCN Is Independent of Multiple Obesity-Related Chronic Diseases

There is a broad consensus that obesity is a health-threatening factor that exacerbates chronic diseases like hypertension,[22] dyslipidemia,[23] and diabetes.[24] To further determine whether the contribution of obesity to the risk of KCN is associated with classic obesity-related chronic diseases, we conducted multiple MR analyses to explore the causal effect between chronic diseases and KCN. Three diseases (hypertension, dyslipidemia, and diabetes) and associated traits (hypertension: systolic and diastolic blood pressure; dyslipidemia: high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides; diabetes: fasting blood glucose) were analyzed separately as exposures. Overall, we found that none of the obesity-related chronic diseases and associated traits had any significant causal effects on KCN (Table 3), indicating that the causal effect of obesity on KCN is unrelated to the risk of hypertension, dyslipidemia, and diabetes.

Discussion

In this MR study, we showed that genetically predicted higher BMI, rather than WHR, contributed to the increased risk of KCN, using the large-scale

Table 3. Mendelian Randomization Estimates for Associations Between Multiple Exposures and KCN

Exposure	Outcome	Exposure ID	Number of SNPs	Effect [95% CI]	*P*
Hypertension	KCN	ukb-b-14057	193	0.543 (−1.089 to 2.175)	0.515
SBP		ieu-b-38	65	0.040 (−0.024 to 0.104)	0.226
DBP		ieu-b-39	390	−0.008 (−0.061 to 0.045)	0.766
Dyslipidemia	KCN	ukb-b-12651	16	5.054 (−6.401 to 16.509)	0.387
HDL		ieu-b-109	307	−0.211 (−0.584 to 0.162)	0.267
LDL		ieu-b-110	156	0.010 (0.162 to 0.433)	0.962
TG		ieu-b-111	261	0.113 (−0.286 to 0.511)	0.579
Diabetes	KCN	ukb-b-12948	60	4.766 (−1.481 to 11.013)	0.135
Fasting glucose		ieu-b-113	19	−0.024 (−1.795 to 1.747)	0.979

DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TG, triglycerides.

GWAS data sets in the European populations. Our study offers several methodological strengths. On the one hand, leveraging big data analytics in genomics allows for efficient and resource-saving analyses. On the other hand, the MR design mitigates confounding, reverse causation, and measurement error by using genetic variations (SNPs) as proxies for exposures, strengthening causal inference. By selecting robust SNPs ($P < 5 \times 10^{-8}$, $F > 10$) from extensive GWAS studies on BMI ($n = 461{,}460$) and WHR ($n = 210{,}082$), we minimized the likelihood of weak instrument bias, increasing the reliability of our findings. Importantly, as SNPs remain stable throughout an individual's life, our results reflect a lifetime risk of KCN related to elevated BMI.

Our study suggests a causal effect between elevated BMI and an increased risk of KCN, whereas no such association was found with WHR (Table 2). This finding addresses the longstanding controversy regarding the relationship between obesity and KCN. Previous studies have reported no association between obesity and KCN in Middle Eastern populations.[10,11] Conversely, other research has identified a correlation between obesity and KCN among American populations,[11] which aligns with our findings. We propose that the shared genetic background between American and European populations may explain these observed similarities. Therefore, we suggest that general obesity is associated with an increased risk of KCN, particularly within populations with this hereditary profile. Moreover, our results indicated that WHR does not play an etiological role in KCN (Table 2). Many previous studies have elucidated that WHR and BMI are both independently associated with several diseases, including type 2 diabetes, coronary artery disease, and mortality,[25] and WHR is more strongly associated with risk than BMI, even in some diseases like stroke.[26] Our findings proposed that KCN is not correlated with body fat distribution.

Further MR analyses revealed no significant associations between KCN and obesity-related chronic diseases such as type 2 diabetes, coronary artery disease, or stroke (Table 3), suggesting that obesity's effect on KCN is independent of these conditions. Previously published reports supported our findings.[27,28] For example, Akowuah et al.[27] noted no significant association between diabetes and KCN based on systematic reviews and meta-analyses. According to a population-based study, the levels of blood lipids and blood pressure were not significantly associated with the prevalence of KCN.[28] It is unclear exactly how obesity contributes to KCN. A possible explanation is that obesity reduces the amount of elastin in the tarsal plate, which results in weak eyelid skin and subsequently suppresses the function of the eyelids in protecting the cornea.[12] Another possible mechanism involves the levels of various hormones in the body. As several studies have pointed out, increased weight is a critical reason for the disorders of thyroid hormones and sex hormones.[29] Interestingly, hormonal imbalances have been linked to KCN both clinically and experimentally.[30] Therefore, it can be speculated that the contribution of obesity to KCN risk might be attributed to the disorders in hormone levels. It is necessary to thoroughly investigate the causal relationships between obesity and KCN.

Of note is that Wang et al.[31] recently published a two-sample MR study, confirming a causal effect between BMI and KC risk. However, our studies differ in depth and scope. Our study provides essential complementary insights by refining obesity subtypes. Specifically, we suggest that BMI-related KC risk is more closely associated with general overweight rather than abnormal fat distribution linked to metabolic syndrome (Table 2). Moreover, we used multiple MR analyses and ruled out the confounding effects of hypertension, diabetes, and dyslipidemia (Table 3). Furthermore, we proposed that hormonal influences or mechanical eyelid friction may contribute to KC development. These findings offer a clearer direction for future mechanistic studies.

Lastly, although this MR-designed investigation has several strengths to complement traditional epidemiological studies, there were some limitations. First, MR reflects an average lifetime risk,[32] and thus it cannot answer whether being overweight or obese during a certain period has any impact on the risk of KCN—a disease that typically has an onset during puberty and may progress throughout life. Moreover, due to the inherent nature of MR analysis, it estimates causal effects using genetic proxies but does not establish direct causality. Furthermore, our study was limited to individuals of European ancestry, so the findings may not be generalizable to other populations. Although we did not detect evidence of pleiotropy, the possibility remains that some SNPs may influence KCN through pleiotropic pathways. Future research is warranted to further explore these mechanisms and extend our findings to broader populations.

In conclusion, our results from European genetic databases provide further insight into the epidemiology of KCN.[33] We found that the prevalence of KCN has been increasing in the past decade, possibly because of increased obesity. This study provides evidence for a strong, independent, and causal effect between BMI and KCN. These results strongly support the hypothesis that obesity plays a role in the onset and progression of KCN. Ultimately, this research inspires a multidis-

ciplinary approach, integrating insights from genetics, ophthalmology, and nutrition, to forge comprehensive strategies for KCN management.

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Ethics Approval: All publicly available deidentified summary data used in this study have ethical permissions from their respective institutional review boards. No additional ethical approval was required for this study.

Availability of Data and Materials: The data sets supporting the conclusions of this article are included within the article and its additional file.

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