International Journal of Women's Health

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Impact of Milk Consumption and Dietary Patterns on Pelvic Organ Prolapse: A Mendelian Randomization Study

Xinglu Xia[1], Yiqin Hu[1], Jingui Xu[1], Suhong Fan[1], Yunfeng Zhang[2]

[1]Department of Gynaecology, The Quzhou Affiliated Hospital of Wenzhou Medical University, Quzhou People's Hospital, Quzhou, 324000, People's Republic of China; [2]Department of Anaesthesiology, The Quzhou Affiliated Hospital of Wenzhou Medical University, Quzhou People's Hospital, Quzhou, 324000, People's Republic of China

Correspondence: Yunfeng Zhang, Department of Anaesthesiolog, The Quzhou Affiliated Hospital of Wenzhou Medical University, Quzhou People's Hospital, No. 100, Minjiang Avenue, Kecheng District, Quzhou, Zhejiang, 324000, People's Republic of China, Tel +86-13157001161, Email yfz1161@163.com

Background: Pelvic organ prolapse (POP) severely impacts women's quality of life and disrupts their daily routines. This study uses two-sample Mendelian randomization (MR) to explore the causal link between dietary habits and POP, providing useful insights for its treatment.

Materials and Methods: We used genome-wide association (GWAS) data from Europeans for our study. Two-sample MR analysis was utilized to explore the potential causal relationship between dietary habits and the risk of POP. Five distinct MR methods were applied, with the primary results derived from the inverse variance weighted (IVW) method. Additional sensitivity analyses were performed to assess potential horizontal pleiotropy and heterogeneity in the findings. Moreover, a two-step MR design was used to examine possible mediating factors within dietary habits.

Results: Seventeen dietary habits were identified as having a significant causal relationship with the risk of POP ($p < 0.05$). Notably, consumption of processed meat and dairy intake, including both whole and skim milk, were found to be associated with an increased risk of POP. Two-step MR analysis indicated that high-density lipoprotein cholesterol (HDL-C) may play a crucial role as a mediating factor between regular milk consumption and POP, contributing to 7.5% of the effect of whole milk consumption and 4.1% of the effect of skim milk consumption. Importantly, sensitivity analyses further validated the robustness of our findings.

Conclusion: Our findings offer compelling evidence of the causal relationship between dietary habits (especially dairy and processed meats) and the risk of POP, providing valuable recommendations for POP patients in making informed dietary decisions.

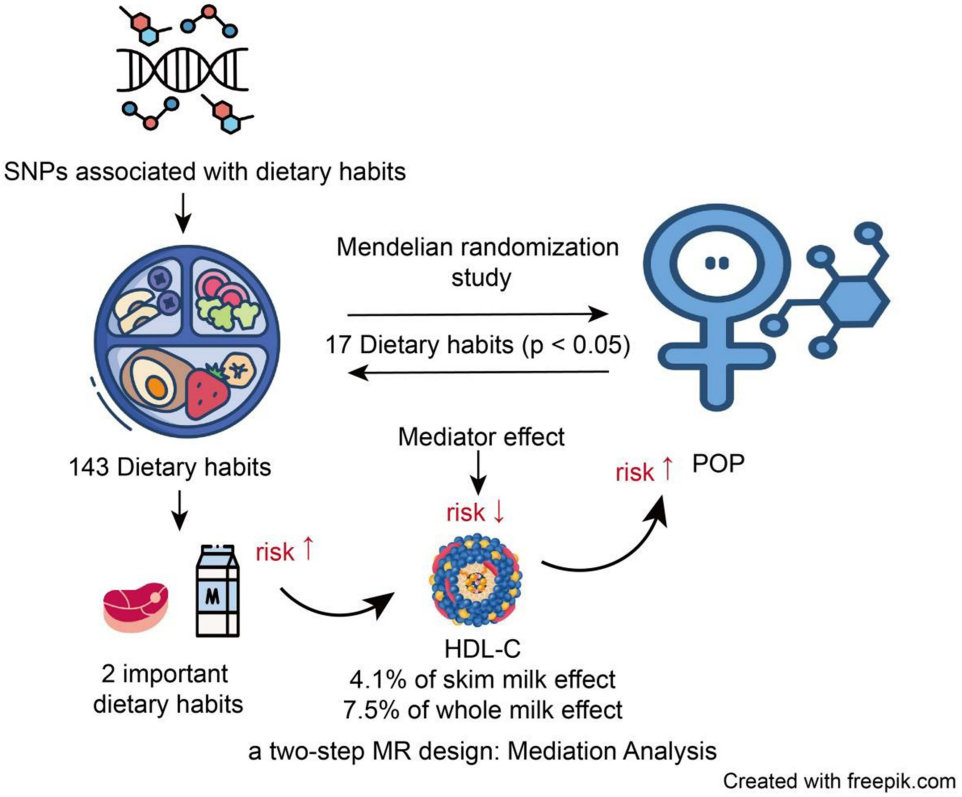
Keywords: pelvic organ prolapse, Mendelian randomization, dietary habits

Introduction

Pelvic organ prolapse (POP) is a prevalent female pelvic floor disorder characterized by symptoms such as pelvic or vaginal bulging, discomfort, urinary and bowel difficulties, and sexual dysfunction, all of which significantly impact a woman's quality of life.[1] The prevalence of POP in the general population ranges from 3% to 6%, while among individuals with mild symptoms, the rate can rise to 50%, making POP an increasingly pressing societal concern.[1,2] The primary cause of POP is dysfunction of the pelvic floor connective tissue, with reduced levels of collagen (COL) that help maintain the structural integrity of this tissue, thereby increasing the likelihood of developing POP.[3] Several observational studies have indicated that socio-economic status, educational background, and lifestyle factors may be linked to an increased risk of POP.[4–6] However, these associations may be influenced by confounding variables or other biases and are not always reflective of causal relationships predicted by genetic factors.[7] POP is likely the result of a combination of genetic and environmental factors, therefore, identifying the underlying causal elements is crucial for preventing disease progression and developing effective treatment strategies.

Received: 24 February 2025
Accepted: 13 June 2025
Published: 19 June 2025

Graphical Abstract



Diet is a fundamental factor for human survival, serving as the primary source of nutrients and the energy required to sustain life.[8] A well-balanced dietary regimen can help mitigate pelvic floor dysfunction.[9] For instance, consuming fiber-rich foods such as vegetables, fruits, and whole grains can prevent constipation and reduce the pressure on the pelvic floor during bowel movements.[10] Additionally, ensuring adequate intake of vitamins (such as vitamins C and D) and minerals can aid in tissue repair, which contributes to maintaining pelvic health.[11–13] Experts have emphasized the importance of dietary interventions for individuals at risk of POP, aiming to address deficiencies of vital substances in the body.[9,14] However, the effects of different dietary patterns on health can vary. For instance, overeating, smoking, and alcohol consumption are recognized as significant risk factors for diseases such as dementia and cancer.[15–17] In contrast, adherence to Mediterranean dietary patterns has been shown to provide nutrients that facilitate beneficial interactions between the gut microbiota and the immune system, promoting overall health.[18] Currently, although some evidence suggests that diet influences pelvic health, the causal relationship between specific dietary components and POP remains unclear. For instance, high-fiber diets are believed to reduce the risk of constipation, thereby decreasing pelvic floor pressure, but the specific effects of different fiber types (soluble vs insoluble) on pelvic health require further investigation.[19,20] Additionally, dairy consumption may have a potential association with the occurrence of POP, but its role in preventing or treating pelvic organ prolapse is not yet fully elucidated.[21] This study aims to systematically explore the causal relationships between specific dietary components and pelvic health, filling the gaps in current knowledge and providing more targeted nutritional intervention strategies for clinical practice. Therefore, a comprehensive understanding of the relationship between dietary habits and POP risk is essential for developing effective preventive strategies.

Mendelian randomization (MR) analysis is a novel approach for evaluating genetic effects, wherein genetic factors serve as instrumental variables (IVs) to investigate the causal relationship between exposures and diseases.[22,23] MR helps

minimize the effects of confounding variables and reverse causality, thereby enabling more precise identification of potential causal factors.[23] Notably, mediating factors play a critical role in this context. Targeting these specific mediators could potentially intervene in and reduce the impact of exposure on disease progression.[24] In this study, we applied a two-sample MR approach to thoroughly evaluate the causal relationship between dietary habits and the risk of POP, while accounting for the potential influence of reverse causality. Notably, we leveraged recent advanced genome-wide association studies (GWAS) data to perform mediation analysis, investigating the potential role of cholesterol as a mediator in the pathway linking dietary habits to POP disease.

Materials and Methods

Study Design

This study employed two-sample MR to estimate the causal relationship between key dietary habits and POP. In this two-sample MR analysis, dietary habits were treated as the exposure, while POP was considered the outcome variable. A two-step MR design was implemented for conventional mediation analysis to investigate whether cholesterol mediates the causal relationship from dietary habits to POP.[25–27] All MR analyses were conducted under three primary assumptions: (1) instrumental variables (IVs) must be strongly associated with the exposure. (2) IVs should not be correlated with confounding factors. (3) IVs can only influence the outcome through their effect on the exposure. To minimize bias arising from population heterogeneity, the genome-wide association studies (GWAS) data used in this study were selected from populations of European ancestry, ensuring a largely independent sample. The overall MR design of this study is shown in Figure 1.

Dietary Habits Data

The GWAS summary data on dietary habits comprises 455,146 participants of European ancestry, based on the most recent large-scale dietary habits GWAS data.[28] Briefly, phenotypic derivation and genome-wide association analyses were performed on these 455,146 European-ancestry participants. A total of 143 genetically significant dietary habits were identified, encompassing both individual food intake (FI) and multivariable dietary patterns (DP).[28,29]

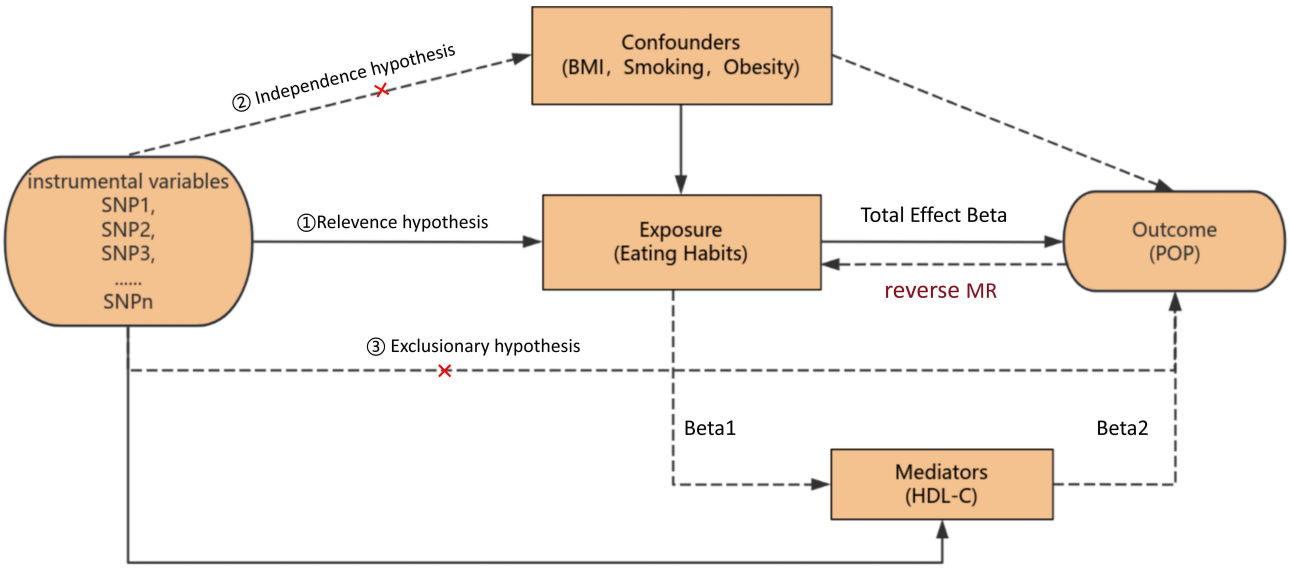


Figure 1 Flow chart of the Mendelian randomization study design. Single nucleotide polymorphisms (SNPs) were utilized as IVs to account for and mitigate the influence of confounding factors, thereby investigating the causal relationship between dietary habits and POP. Subsequently, mediation analysis was applied to explore the mediating role of cholesterol in the significant genetic predictive causal effect on POP. HDL-C: high-density lipoprotein cholesterol. Beta1 denotes the causal influence of the exposure factor on the mediator. Beta2 indicates the causal effect of the mediator on the outcome. In MR analyses, where IVs are required to satisfy three major assumptions (correlation, Independence, and exclusivity), the red "X" is used to mark null pathways, ie, pathways that negate the effect of the IV on the outcome through confounders or where the genetic variant does not act directly on the outcome through exposure.

https://doi.org/10.2147/IJWH.S519596

Table 1 Detailed Information of the GWAS in Our Analysis

Exposure/Outcome	Year	ID	Population	Sample Size	Control	Case
Dietary habit	2020	/	European	455,146	/	/
POP	2021	finn-b-N14_FEMGENPROL	European	78,061	68,969	9,092
Cholesterol	2013	ebi-a-GCST002221	European	94,595	/	/
HDL-C	2013	ebi-a-GCST002223	European	94,595	/	/
LDL-C	2013	ebi-a-GCST002222	European	94,595	/	/

Data Related to POP

The GWAS data for POP comprises 78,061 individuals of European ancestry, including 9,092 cases and 68,969 controls. The corresponding GWAS catalog ID is finn-b-N14_FEMGENPROL (https://gwas.mrcieu.ac.uk/).

Data Related to Mediation

GWAS data for potential mediators were included to investigate the intermediate factors involved in the pathogenic pathway of POP. The potential mediators considered are total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). The GWAS data for total cholesterol comprises 94,595 individuals of European ancestry, with the corresponding GWAS catalog ID ebi-a-GCST002221 (https://gwas.mrcieu.ac.uk/). Similarly, the GWAS data for HDL-C and LDL-C are also based on 94,595 individuals of European ancestry, with catalog IDs ebi-a-GCST002223 (https://gwas.mrcieu.ac.uk/) and ebi-a-GCST002222 (https://gwas.mrcieu.ac.uk/), respectively.[30] Table 1 presents the GWAS information for the data used in this study.

Selection of Instrumental Variables

The criteria for selecting IVs are as follows: (1) SNPs were used as instrumental variables, with a genome-wide significance threshold of $p < 5e\text{-}08$. For exposures with few or no loci, a more relaxed significance threshold $p < 5e\text{-}06$ was applied. (2) SNPs were clumped to exclude the effects of linkage disequilibrium ($r^2 = 0.001$, allele distance = 10,000 kb). (3) The *F-statistic* was used to test for weak instrumental variables. A larger *F-statistic* indicates stronger instrument strength. Weak instruments were excluded by calculating the *F-statistic*, ensuring that the *F-statistic* for included SNPs was greater than 10.[31] (4) SNPs for exposure and outcome were harmonized, with allele orientation aligned. SNPs for which the directionality could not be determined or were incompatible were excluded. (5) Outlier SNPs identified by MR-PRESSO were removed. SNPs closely associated with confounding factors (body mass index (BMI), smoking, and obesity) were also excluded. These common confounders acted as common influencers of dietary habits and POP, and SNPs associated with them were excluded from this study. For other potential residual confounders, sensitivity analyses were used to assess model robustness in order to minimize this effect.

Analysis of MR

Five regression models were employed for the two-sample MR analysis: MR-Egger regression, random effects inverse variance weighted (IVW), weighted median estimator, weighted mode, and simple mode, with IVW as the primary analysis method.[32] SNPs were used as instrumental variables. Initially, a two-sample MR analysis was conducted to investigate the causal relationship between the exposure (dietary habits) and the outcome (POP). Following this, reverse MR analysis was performed on the positive results to assess whether POP, as an exposure factor, could causally influence dietary habits, using the same workflow for the two-sample MR analysis.

Additionally, a two-step MR design was applied for mediation analysis to explore whether cholesterol mediates the causal pathway from dietary habits to POP. The overall effect was decomposed into direct effects (without the mediator) and indirect effects (via the mediator). The total effect of dietary habits on POP was separated into (1) the direct effect of dietary habits on POP and (2) the indirect effect mediated by cholesterol. The percentage of mediation was calculated by dividing the indirect effect by the total effect, and 95% confidence intervals were derived using the delta method.

MR Sensitivity Assessments

To assess the robustness of the associations, three approaches were applied: heterogeneity testing, pleiotropy testing, and leave-one-out analysis. Cochran's *Q* test was used to check for heterogeneity among SNPs. If heterogeneity was observed ($p < 0.05$), a random-effects IVW model was applied, otherwise, a fixed-effects model was used. MR-Egger regression and MR-PRESSO evaluated the directional pleiotropy of the instrumental variables. A significant MR-Egger intercept ($p < 0.05$) indicated horizontal pleiotropy. MR-PRESSO also helped identify outlier SNPs, and a global test was used to confirm pleiotropy.[33] Lastly, a leave-one-out sensitivity analysis was performed to assess the impact of individual SNPs on the causal relationship.[34]

Statistical Analyses

MR analyses were performed using R software (version 4.3.1) and the R packages Two Sample MR (version 0.6.8) and MR-PRESSO (version 1.0). We primarily used the IVW analysis to determine the causal relationship between exposure and outcome. When the number of SNPs was 1, the Wald ratio method was employed to assess causality.[35] Additionally, MR-Egger regression, Weighted median, Weighted mode, and Simple mode were utilized as supplementary analysis methods. A p-value below 0.05 was used to identify a significant causal relationship between the exposure and the outcome.

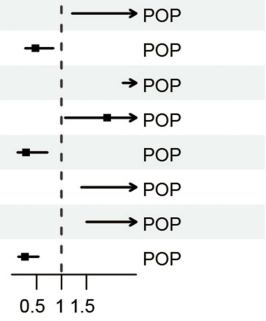
Results

The Effect of Causal Relationship Between Dietary Habits and POP

We selected SNPs strongly associated with 143 dietary habits through conditional screening, and then applied MR-PRESSO to exclude outliers, using the remaining SNPs as IVs. Subsequent MR analysis was conducted to investigate the potential causal relationship between dietary habits and POP. The MR analysis primarily relied on the IVW method. The

A

Exposure	Method	nSNP	Pval	OR(95%CI)	Outcome
PC14(cups of tea per day)	IVW	9	0.0158	2.7711(1.2113−6.3396)	POP
PC19(slices of bread per week)	IVW	25	0.0100	0.4776(0.2721−0.8382)	POP
PC29(overall cheese intake)	IVW	6	0.0021	9.1072(2.2283−37.2226)	POP
PC43(cups of coffee per day)	IVW	17	0.0285	1.9165(1.0706−3.4306)	POP
PC9(sugar)	IVW	12	0.0077	0.2896(0.1164−0.7203)	POP
milk type: any milk vs. never	IVW	3	0.0293	27.6338(1.3976−546.3744)	POP
milk type: skimmed vs. never	Wald ratio	1	0.0078	4.6757(1.5002−14.5726)	POP
overall processed meat intake	IVW	16	0.0002	0.2673(0.1321−0.5408)	POP



B

Exposure	Method	nSNP	Pval	OR(95%CI)	Outcome
POP	IVW	7	0.0236	1.0120(1.0016−1.0225)	PC34(low fat spread)
POP	IVW	7	0.0349	1.0078(1.0006−1.0151)	PC47(milk)
POP	IVW	7	0.0377	1.0087(1.0005−1.0170)	spread type: tub margarine vs. any other
POP	IVW	7	0.0458	0.9677(0.9369−0.9994)	spread type: flora + benecol vs. never
POP	IVW	7	0.0092	0.9880(0.9791−0.9970)	spread type: flora + benecol vs. any other

Figure 2 The causal relationship between dietary habits and the risk of POP. (**A**) MR analysis with dietary habits as the exposure factor and POP as the outcome factor. (**B**) Reverse MR analysis with dietary habits as the outcome factor and POP as the exposure factor. The IVW results were used as the primary reference, with $p < 0.05$ indicating a statistically significant causal relationship.

Abbreviations: POP, pelvic organ prolapse; OR, Odds Ratio; CI, Confidence Interval; OR > 1, risk factor; OR < 1, protective factor.

https://doi.org/10.2147/IJWH.S519596

results from additional analytical methods are provided in Supplementary Tables S1 and S2. As illustrated in Figure 2A, the results showed that 8 of the 143 dietary habits had a significant causal association with POP ($p < 0.05$). Specifically, these included: PC14 (cups of tea per day) (Odds Ratio (OR): 2.7711, 95% Confidence Interval (CI): 1.2113–6.3396, p = 0.0158), PC19 (slices of bread per week) (OR: 0.4778, 95% CI: 0.2721–0.8382, p = 0.01), PC29 (overall cheese intake) (OR: 9.1072, 95% CI: 2.2283–37.2226, p = 0.0021), PC43 (cups of coffee per day) (OR: 1.9165, 95% CI: 1.0706–3.4306, p = 0.0285), PC9 (sugar) (OR: 0.2896, 95% CI: 0.1164–0.7203, p = 0.0077), milk type: any milk vs never (OR: 27.6338, 95% CI: 1.3976–546.3744, p = 0.0293), milk type: skimmed vs never (OR: 4.6757, 95% CI: 1.5002–14.5726, p = 0.0078), overall processed meat intake (OR: 0.2673, 95% CI: 0.1321–0.5408, p = 0.0002). These findings provide further insights into the causal relationships between dietary components and POP compared to previous observational studies. For example, observational studies typically emphasize the importance of high-fiber diets and Mediterranean dietary patterns in reducing pelvic floor pressure.[10,36] However, our MR analysis identified causal effects of specific dietary components, such as dairy products (milk and cheese) and processed meats, which may have been underestimated or undetected in observational studies. Furthermore, reverse MR analysis identified causal relationships between POP and 5 dietary habits ($p < 0.05$, Figure 2B). Specifically, the genetic susceptibility to POP was positively associated with PC34 (low fat spread) (OR: 1.0120, 95% CI: 1.0016–1.0225, p = 0.0236), and with PC47 (milk) (OR: 1.0078, 95% CI: 1.0006–1.0151, p = 0.0349). Additionally, there was a positive association with the spread type: tub margarine vs any other (OR: 1.0087, 95% CI: 1.0005–1.0170, p = 0.0377). Conversely, negative associations were observed with the spread type: flora + benecol vs never (OR: 0.9677, 95% CI: 0.9369–0.9994, p = 0.0458), and with flora + benecol vs any other (OR: 0.9880, 95% CI: 0.9791–0.9970, p = 0.0092). A number of previous reviews have summarised the role of diet in pelvic support disorder.[9] These findings for better management of patients with POP help to focus on the changing dietary preferences of patients with POP over time and highlight noteworthy aspects of these patients' diets.

An Inverse Causal Relationship Between High Cholesterol and POP

To explore potential factors in dietary habits that may influence the development of POP, we incorporated cholesterol as a mediator. SNPs strongly associated with total cholesterol, LDL-C, and HDL-C were selected, and after controlling for confounders and eliminating outliers, these SNPs were utilized as IVs in a two-step MR analysis. The MR results were primarily derived from the IVW method, additional results are presented in Supplementary Table S3. Our findings revealed a significant causal relationship between HDL-C and POP, suggesting that HDL-C may serve as a protective factor against POP (OR: 0.8968, 95% CI: 0.8077–0.9957, p = 0.0414, Figure 3). This is consistent with previous finding.[37]

Investigation of the Association Between Dietary Habits and HDL-C

Based on the aforementioned study, we identified a significant causal association between HDL-C and POP ($p < 0.05$). Following the fundamental principles of two-step MR, HDL-C was selected as a representative cholesterol factor for subsequent mediation analysis. We used dietary habits as the exposure factor and HDL-C as the outcome for the analysis. The results of the IVW method indicated that three dietary habits were significantly causally associated with HDL-C ($p < 0.05$). Specifically, these included: milk type: any milk vs never (OR: 0.1049, 95% CI: [0.0301–0.3658], p = 0.0004),

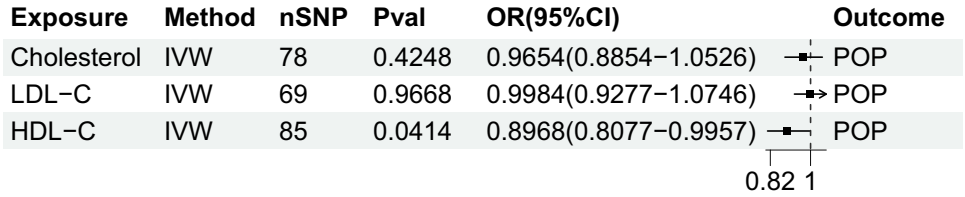


Figure 3 Types of cholesterol and POP of MR results. Incorporating cholesterol as a mediator. MR analysis with cholesterol as the exposure factor and POP as the outcome factor. $p < 0.05$ indicating a statistically significant causal relationship.

Abbreviations: POP, pelvic organ prolapse; LDL-C, Low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol; OR, Odds Ratio; CI, Confidence Interval; OR > 1, risk factor; OR < 1, protective factor.

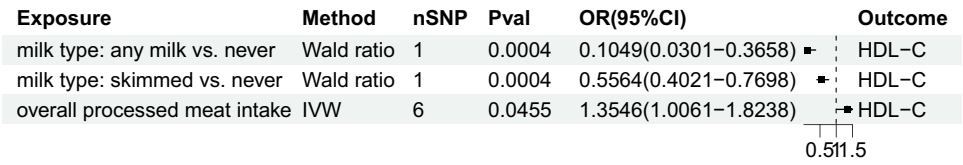


Figure 4 Investigation of the causal relationship between dietary habits and HDL-C. MR analysis with dietary habits as the exposure factor and HDL-C as the outcome factor. A p-value of < 0.05 indicates a statistically significant causal relationship.
Abbreviations: POP, pelvic organ prolapse; HDL-C, High-density lipoprotein cholesterol; OR, Odds Ratio; CI, Confidence Interval; OR > 1, risk factor; OR < 1, protective factor.

milk type: skimmed vs never (OR: 0.5564, 95% CI: [0.4021–0.7698], p = 0.0004), and overall processed meat intake (OR: 1.3546, 95% CI: [1.0061–1.8238], p = 0.0455) (Figure 4). The supplementary results can be found in Supplementary Table S4. This was consistent with a previous MR study in which high milk intake was associated with lower HDL-C levels.[38] In addition, a cohort study showed that dietary habits with high consumption of processed meat were often associated with overweight, and elevated HDL-C levels were observed in the overweight group.[39]

Causal Relationship Between Dietary Habits and HDL-C Mediated POP

To further evaluate the proportion of the mediating effect of HDL-C in the causal relationship between dietary habits and POP, we calculated the mediation effect proportions. As shown in Table 2, this study found that HDL-C primarily mediated the causal associations between two dietary patterns, milk type: any milk vs never and milk type: skimmed vs never, on POP risk. The proportion of the mediating effect of HDL-C was 7.5% for milk type: any milk vs never and 4.1% for milk type: skimmed vs never. Supplementary Table S5 presents additional data regarding the absence of positive results. Our results reported a mediating role of HDL-C between dairy consumption and POP risk, a mechanism that had not been reported in previous studies.

Sensitivity Evaluation of Heterogeneity and Pleiotropy

This study emphasizes the use of various sensitivity analyses to enhance the reliability of our findings. We observed that for most exposure variables, the p-values from Cochran's *Q* test for heterogeneity exceeded 0.05, suggesting that the data were homogeneous. Furthermore, the global test from MR-PRESSO yielded p-values greater than 0.05, indicating no significant horizontal pleiotropy bias in the analysis. Detailed results are provided in the Tables 3 and 4. Sensitive analysis of the

Table 2 Mediating Role of HDL-C in the Causal Relationship Between Dietary Habits and POP

Exposure	Mediation	Outcome	Mediated Effect	Mediated Proportion	Direct Effect	Total Effect	Beta1	Beta2
Milk type: any milk vs never	HDL-C	POP	−0.25(−0.564, −0.0079)	7.5% (0.23%, 16.9%)	3.069	3.3190	−2.2547	−0.1089
Milk type: skimmed vs never	HDL-C	POP	−0.064(−0.147, −0.0021)	4.1% (0.14%, 9.5%)	1.4783	1.54237	−0.5864	−0.1089

Notes: The total effect represents the causal effect of the exposure on the outcome. Beta1 represents the causal effect of the exposure on the mediator. Beta2 reflects the causal effect of the mediator on the outcome. Mediated effect=Beta1*Beta2, Mediated proportion=Mediated effect/Total effect, Direct effect=Total effect-Beta1*Beta2.

Table 3 Sensitivity Analysis of Causal Relationship Between Exposure (Dietary Habits) and Outcome (POP)

Outcome	Exposure	Method	Cochran's Q	Egger-Intercept	Standard Error	p. Value	MR-PRESSO
POP							
	PC14 (cups of tea per day)	MR Egger	0.1055	−0.0164	0.0546	0.7717	0.408
	PC14 (cups of tea per day)	IVW	0.1509				
	PC19 (slices of bread per week)	MR Egger	0.0388	−0.0163	0.0152	0.2958	0.892
	PC19 (slices of bread per week)	IVW	0.0342				
	PC29 (overall cheese intake)	MR Egger	0.8631	0.0281	0.0396	0.5176	0.146
	PC29 (overall cheese intake)	IVW	0.8771				
	PC43 (cups of coffee per day)	MR Egger	0.4108	0.0125	0.0101	0.2351	0.643

(*Continued*)

Table 3 (Continued).

Outcome	Exposure	Method	Cochran's Q	Egger-Intercept	Standard Error	p. Value	MR-PRESSO
	PC43 (cups of coffee per day)	IVW	0.3751				
	PC9 (sugar)	MR Egger	0.0042	−0.0196	0.0814	0.8143	0.075
	PC9 (sugar)	IVW	0.0070				
	Milk type: any milk vs never	MR Egger	0.0898	0.0483	0.0988	0.7102	0.493
	Milk type: any milk vs never	IVW	0.1680				
	Overall processed meat intake	MR Egger	0.7242	0.0320	0.0293	0.2938	0.087
	Overall processed meat intake	IVW	0.7018				

Table 4 Sensitivity Analysis of Causal Relationship Between Exposure (POP) and Outcome (Dietary Habits)

Outcome	Exposure	Method	Cochran's Q	Egger_Intercept	Standard Error	p. Value	MR-PRESSO
PC34 (low fat spread)	POP	MR Egger	0.0664	0.00159	0.0046	0.7443	0.156
PC34 (low fat spread)		IVW	0.1024				
PC47 (milk)		MR Egger	0.5086	0.0012	0.0022	0.6048	0.658
PC47 (milk)		IVW	0.5969				
Spread type: tub margarine vs any other		MR Egger	0.1190	−0.0036	0.0033	0.3303	0.823
Spread type: tub margarine vs any other		IVW	0.0949				
Spread type: flora + benecol vs never		MR Egger	0.6838	−0.0033	0.0101	0.7517	0.438
Spread type: flora + benecol vs never		IVW	0.7812				
Spread type: flora + benecol vs any other		MR Egger	0.2794	−0.0001	0.0032	0.9833	0.722
Spread type: flora + benecol vs any other		IVW	0.3920				

mediation analysis is shown in Supplementary Table S6. Additionally, leave-one-out analysis confirmed that the results were not driven by any single SNP. Both scatter and funnel plots further validated the stability of our findings (Supplementary Figures S1–S3). In summary, our findings strongly support the presence of a significant causal relationship between the genetically predicted exposure and the outcome variables.

Discussion

POP significantly impairs women's quality of life, leading to a dramatic decline in daily functioning.[40] This study employed a two-sample MR approach to systematically evaluate the causal relationship between dietary habits and the risk of POP, with the aim of providing theoretical support for mitigating the pathological symptoms of POP through dietary improvements. Our findings revealed a significant causal relationship between 17 dietary habits and POP, with the majority of these habits acting as protective factors, while 9 were identified as risk factors for the condition. These discoveries offer critical references for developing targeted nutritional intervention strategies and underscore the necessity of validating these associations in more diverse populations. Additionally, mediation analysis suggested that HDL-C may serve as an important mediator in the relationship between dietary habits and POP risk. This mechanism has not been reported by previous studies. This mediating effect was particularly evident in the pathways involving regular milk consumption and skim milk consumption, where HDL-C played a significant intermediary role in modulating POP risk.

HDL-C is a heterogeneous molecule primarily involved in the reverse cholesterol transport mechanism, which helps clear excess cholesterol and produces beneficial effects on the body.[41] Additionally, HDL-C exhibits vascular endothelial protective and antioxidant properties. By reducing reactive oxygen species (ROS) levels, HDL-C may alleviate oxidative stress-induced collagen metabolic imbalances in pelvic tissues, thereby contributing to the structural integrity of pelvic floor tissues, a critical aspect of normal physiological function.[42] Moreover, HDL-C may influence the degradation and remodeling processes of pelvic connective tissues by regulating the balance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs).[43,44] Previous studies have demonstrated that excessive MMPs activity is closely associated with pelvic floor tissue fragility in patients with POP. HDL-C, through its anti-inflammatory properties, could inhibit the aberrant activation of MMPs, thereby mitigating the degradation of pelvic

floor tissues.[45,46] These findings suggest that HDL-C may play a positive role in preventing the progression of POP, aligning with the point presented in our study.

Meat, particularly certain animal-based foods rich in vitamin D, serves as a significant dietary source of this essential nutrient. As a fat-soluble vitamin, vitamin D not only plays a critical role in calcium and phosphorus metabolism but also contributes to muscle function and tissue health, which are of particular importance in the prevention of POP.[47,48] Notably, a randomized trial revealed that vitamin D deficiency is more prevalent in POP patients.[49] Vitamin D insufficiency is closely associated with reduced muscle strength. Adequate vitamin D intake may enhance pelvic floor stability by promoting muscle fiber contractility and endurance.[47] Additionally, the anti-inflammatory and anti-oxidant properties of vitamin D can alleviate inflammation-driven collagen metabolic imbalances, potentially mitigating connective tissue degradation associated with POP.[50,51] In conclusion, the intake of vitamin D-rich meat products may have a protective effect, potentially reducing the risk of POP.

In conclusion, our study highlights the mediating role of HDL-C in the pathway through which milk consumption influences the risk of POP. However, there are several limitations to this research. First, the GWAS data utilized in this research were exclusively derived from European populations, introducing potential ancestry bias that may limit the generalizability of our findings. Future studies should validate these results in larger and more diverse cohorts. Secondly, the dietary GWAS data relied on self-reported information, which may introduce misclassification bias. Notably, the lack of quantitative measurements of dietary intake limited our ability to provide precise dietary recommendations. To address this, future studies could employ meta-analyses (meta-GWAS) or stratified analyses to enhance the precision and reliability of estimates. These methods can help reduce potential biases and provide more robust results. Thirdly, longitudinal studies are crucial for confirming the observed associations. Through longitudinal designs, we can better capture the temporal relationship between dietary habits and the risk of POP, and assess the long-term effects of dietary interventions on POP. Fourthly, residual confounding remains a concern. Even with the use of MR analysis and the exclusion of common confounders, unconsidered confounders may still affect the interpretation of results. Future studies should consider using more advanced methods, such as instrumental variable analysis, to further control for residual confounding. Moreover, mediation analysis also has limitations. Although we explored the role of high-density lipoprotein cholesterol (HDL-C) as a mediator, future studies can incorporate additional mediators, such as inflammatory markers (eg, IL-6 and TNF-α) or gut microbiota composition, to further elucidate the causal pathways between diet and POP. Finally, although we have conducted the first systematic analysis of the causal relationship between different dietary habits and POP risk, the molecular mechanisms underlying these associations remain poorly understood and merit further exploration. Nevertheless, our findings offer new perspectives and valuable insights into dietary considerations for POP patients and potential strategies for mitigating pathological symptoms.

Conclusion

In summary, this study provides a comprehensive evaluation of the causal relationship between dietary habits and the risk of POP, identifying 17 dietary habits that are significantly associated with an increased risk of POP. Furthermore, we explored the mediating role of HDL-C in the relationship between regular milk consumption and POP. To enhance the robustness of our conclusions, we plan to further assess the strength of the instrumental variables and utilize more advanced methods to detect horizontal pleiotropy. Future studies should validate these findings in diverse populations and confirm the observed associations using longitudinal designs. Additionally, further mechanistic studies will help elucidate the biological pathways underlying the dietary influences on POP, providing more targeted nutritional intervention strategies for clinical practice. Our findings offer valuable insights into nutritional management of POP, and we will continue to conduct in-depth research to further advance this field and validate these discoveries in independent cohorts.

Data Sharing Statement

The data and materials in the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Medical Ethics Review Committee of Quzhou People's Hospital.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors declare that they have no potential conflicts of interest in this work.

References

1. Raju R, Linder BJ. Evaluation and Management of Pelvic Organ Prolapse. *Mayo Clin Proc*. 2021;96(12):3122–3129. doi:10.1016/j.mayocp.2021.09.005
2. Collins S, Lewicky-Gaupp C. Pelvic Organ Prolapse. *Gastroenterol Clin North Am*. 2022;51(1):177–193. doi:10.1016/j.gtc.2021.10.011
3. Pizzoferrato AC, Thuillier C, Vénara A, et al. Management of female pelvic organ prolapse-Summary of the 2021 hAS guidelines. *J Gynecol Obst Human Reproduct*. 2023;52(3):102535. doi:10.1016/j.jogoh.2023.102535
4. Schulten SFM, Claas-Quax MJ, Weemhoff M, et al. Risk factors for primary pelvic organ prolapse and prolapse recurrence: an updated systematic review and meta-analysis. *Am J Clin Exp Obstet Gynecol*. 2022;227(2):192–208. doi:10.1016/j.ajog.2022.04.046
5. Fitz FF, Bortolini MAT, Pereira GMV, Salerno GRF, Castro RA. PEOPLE: lifestyle and comorbidities as risk factors for pelvic organ prolapse-a systematic review and meta-analysis PEOPLE: pElvic Organ Prolapse Lifestyle comorbiditiEs. *Intl Urogynecol J*. 2023;34(9):2007–2032. doi:10.1007/s00192-023-05569-3
6. Devkota HR, Sijali TR, Harris C, Ghimire DJ, Prata N, Bates MN. Bio-mechanical risk factors for uterine prolapse among women living in the hills of west Nepal: a case-control study. *Women Health*. 2020;16:1745506519895175. doi:10.1177/1745506519895175
7. Meuli L, Dick F. Understanding Confounding in Observational Studies. *Eur J Vasc Endovasc Surg*. 2018;55(5):737. doi:10.1016/j.ejvs.2018.02.028
8. Loughman A, Staudacher HM, Rocks T, et al. Diet and Mental Health. *Modern Trends Psychiatry*. 2021;32:100–112.
9. Wojcik M, Jarzabek-Bielecka G, Merks P, et al. The role of visceral therapy, Kegel's muscle, core stability and diet in pelvic support disorders and urinary incontinence - including sexological aspects and the role of physiotherapy and osteopathy. *Ginekologia polska*. 2022;93(12):1018–1027. doi:10.5603/GP.a2022.0136
10. Shariati A, Maceda JS, Hale DS. High-fiber diet for treatment of constipation in women with pelvic floor disorders. *Obstet Gynecol*. 2008;111(4):908–913. doi:10.1097/01.AOG.0000308660.48204.7f
11. Pecorella G, Sparic R, Morciano A, Babovic I, Panese G, Tinelli A. Fortifying the foundation: assessing the role of uterine ligament integrity in uterine prolapse and beyond. *Arch Gynecol Obstet*. 2024;310(5):2333–2343. doi:10.1007/s00404-024-07732-7
12. Badalian SS, Rosenbaum PF. Vitamin D and pelvic floor disorders in women: results from the National Health and Nutrition Examination Survey. *Obstet Gynecol*. 2010;115(4):795–803. doi:10.1097/AOG.0b013e3181d34806
13. Sesti F, Capozzolo T, Pietropolli A, Collalti M, Bollea MR, Piccione E. Dietary therapy: a new strategy for management of chronic pelvic pain. *Nutr Res Rev*. 2011;24(1):31–38. doi:10.1017/S0954422410000272
14. Walton LM, Raigangar V, Abraham MS, et al. Effects of an 8-week pelvic core stability and nutrition community programme on maternal health outcomes. *Physiother Res Iint*. 2019;24(4):e1780. doi:10.1002/pri.1780
15. JD Steinmetz, KM Seeher, N Schiess, et al. Global, regional, and national burden of disorders affecting the nervous system, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Neurol*. 2024;23(4):344–381. doi:10.1016/S1474-4422(24)00038-3
16. Béland M, Lavoie KL, Briand S, White UJ, Gemme C, Bacon SL. Aerobic exercise alleviates depressive symptoms in patients with a major non-communicable chronic disease: a systematic review and meta-analysis. *Br J Sports Med*. 2020;54(5):272–278. doi:10.1136/bjsports-2018-099360
17. Janssen F, Trias-Llimós S, Kunst AE. The combined impact of smoking, obesity and alcohol on life-expectancy trends in Europe. *Int J Epidemiol*. 2021;50(3):931–941. doi:10.1093/ije/dyaa273
18. García-Montero C, Fraile-Martínez O, Gómez-Lahoz AM, et al. Nutritional Components in Western Diet Versus Mediterranean Diet at the Gut Microbiota-Immune System Interplay. *Implications Health Dis Nutr*. 2021;13(2):1.
19. Allenby TH, Crenshaw ML, Mathis K, et al. A systematic review of home-based dietary interventions during radiation therapy for cancer. *Tech Innov Patient Supp Radiat Oncol*. 2020;16:10–16. doi:10.1016/j.tipsro.2020.08.001
20. Wedlake L, Shaw C, McNair H, et al. Randomized controlled trial of dietary fiber for the prevention of radiation-induced gastrointestinal toxicity during pelvic radiotherapy. *Am J Clin Nutr*. 2017;106(3):849–857. doi:10.3945/ajcn.116.150565
21. Torres-Gonzalez M, Rice Bradley BH. Whole-Milk Dairy Foods: biological Mechanisms Underlying Beneficial Effects on Risk Markers for Cardiometabolic Health. *Adv Nutr*. 2023;14(6):1523–1537. doi:10.1016/j.advnut.2023.09.001
22. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ*. 2018;362:k601. doi:10.1136/bmj.k601
23. Birney E. Mendelian Randomization. *Cold Spring Harbor Perspect Med*. 2022;12(4):41302.
24. Sanderson E. Multivariable Mendelian Randomization and Mediation. *Cold Spring Harbor Perspect Med*. 2021;11(2):a038984. doi:10.1101/cshperspect.a038984
25. Sologuren-García G, Linares CL, Flores JR, Escobar-Bermejo G, Sotelo-Gonzales S, Fagerstrom CK. Epidemiology of Pelvic Floor Dysfunction in the Tacna Region of Peru, 2023. *Intl Urogynecol J*. 2024;35(6):1211–1218. doi:10.1007/s00192-024-05792-6

26. Kato J, Nagata C, Miwa K, Ito N, Morishige KI. Pelvic organ prolapse and Japanese lifestyle: prevalence and risk factors in Japan. *Intl Urogynecol J*. 2022;33(1):47–51. doi:10.1007/s00192-021-04672-7
27. Kopčeková J, Holovičová M, Gažarová M, et al. Association between Selected Dietary Habits and Lipid Profiles of Patients with Cardiovascular Disease. *Int J Environ Res Public Health*. 2020;17(20):7605. doi:10.3390/ijerph17207605
28. Cole JB, Florez JC, Hirschhorn JN. Comprehensive genomic analysis of dietary habits in UK Biobank identifies hundreds of genetic associations. *Nat Commun*. 2020;11(1):1467. doi:10.1038/s41467-020-15193-0
29. Xu J, Li S, Wu Y, et al. Assessing the Association between Important Dietary Habits and Osteoporosis: a Genetic Correlation and Two-Sample Mendelian Randomization Study. *Nutrients*. 2022;14(13):3683. doi:10.3390/nu14183683
30. Willer CJ, Schmidt EM, Sengupta S, et al. Discovery and refinement of loci associated with lipid levels. *Nature Genet*. 2013;45(11):1274–1283.
31. Ji D, Chen WZ, Zhang L, Zhang ZH, Chen LJ. Gut microbiota, circulating cytokines and dementia: a Mendelian randomization study. *J Neuroinflammation*. 2024;21(1):2. doi:10.1186/s12974-023-02999-0
32. Zhang T, Cao Y, Zhao J, Yao J, Liu G. Assessing the causal effect of genetically predicted metabolites and metabolic pathways on stroke. *J Transl Med*. 2023;21(1):822. doi:10.1186/s12967-023-04677-4
33. Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. *Eur J Epidemiol*. 2017;32(5):377–389. doi:10.1007/s10654-017-0255-x
34. Zhong Y, Wang F, Meng X, Zhou L. The associations between gut microbiota and inflammatory skin diseases: a bi-directional two-sample Mendelian randomization study. *Front Immunol*. 2024;15:1297240. doi:10.3389/fimmu.2024.1297240
35. Lin Y, Wang G, Li Y, et al. Circulating Inflammatory Cytokines and Female Reproductive Diseases: a Mendelian Randomization Analysis. *J Clin Endocrinol Metab*. 2023;108(12):3154–3164. doi:10.1210/clinem/dgad376
36. Daykan Y, Ovadia M, Dokic D, et al. Correlation between Mediterranean diet, bowel function, and isolated posterior vaginal defect: a cross-sectional study. *Int J Gynaecol Obstet*. 2023;161(3):847–853. doi:10.1002/ijgo.14685
37. Liu H, Wu W, Xiang W, Yuan J. Lifestyle factors, metabolic factors and socioeconomic status for pelvic organ prolapse: a Mendelian randomization study. *Eur J Med Res*. 2023;28(1):183. doi:10.1186/s40001-023-01148-w
38. Vimaleswaran KS, Zhou A, Cavadino A, Hyppönen E. Evidence for a causal association between milk intake and cardiometabolic disease outcomes using a two-sample Mendelian Randomization analysis in up to 1,904,220 individuals. *Int J Obes Lond*. 2021;45(8):1751–1762. doi:10.1038/s41366-021-00841-2
39. Somnuk S, Komindr S, Monkhai S, Poolsawat T, Nakphaichit M, Wanikorn B. Metabolic and inflammatory profiles, gut microbiota and lifestyle factors in overweight and normal weight young Thai adults. *PLoS One*. 2023;18(7):e0288286. doi:10.1371/journal.pone.0288286
40. Fatton B, de Tayrac R, Letouzey V, Huberlant S. Pelvic organ prolapse and sexual function. *Nat Rev Urol*. 2020;17(7):373–390. doi:10.1038/s41585-020-0334-8
41. Pedrini S, Chatterjee P, Hone E, Martins RN. High-density lipoprotein-related cholesterol metabolism in Alzheimer's disease. *J Neurochem*. 2021;159(2):343–377. doi:10.1111/jnc.15170
42. Ossoli A, Wolska A, Remaley AT, Gomaraschi M. High-density lipoproteins: a promising tool against cancer. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2022;1867(1):159068. doi:10.1016/j.bbalip.2021.159068
43. Salminen A, Åström P, Metso J, et al. Matrix metalloproteinase 8 degrades apolipoprotein A-I and reduces its cholesterol efflux capacity. *FASEB J*. 2015;29(4):1435–1445. doi:10.1096/fj.14-262956
44. Liu P, Wang Y, Tian K, Bai X, Wang Y, Wang Y. Artesunate inhibits macrophage-like phenotype switching of vascular smooth muscle cells and attenuates vascular inflammatory injury in atherosclerosis via NLRP3. *Biomed Pharm*. 2024;172:116255. doi:10.1016/j.biopha.2024.116255
45. Li L, Ma Y, Yang H, Sun Z, Chen J, Zhu L. The polymorphisms of extracellular matrix-remodeling genes are associated with pelvic organ prolapse. *Intl Urogynecol J*. 2022;33(2):267–274. doi:10.1007/s00192-021-04917-5
46. Wu H, Yang L, Yuan J, et al. Potential therapeutic targets for pelvic organ prolapse: insights from key genes related to blood vessel development. *Front Med*. 2024;11:1435135. doi:10.3389/fmed.2024.1435135
47. Legan M, Barbič M, Osredkar J, Blaganje M. Association of vitamin D deficiency and pelvic organ prolapse in postmenopausal women: a cross-sectional study. *Women's Midlife Health*. 2022;8(1):9. doi:10.1186/s40695-022-00078-7
48. Paul ZR, Khanam NN, Barai SC, et al. Association of Low Vitamin D Level with Pelvic Organ Prolapse in Post Menopausal Women: a Case Control Study. *MMJ*. 2023;32(4):1109–1117.
49. Kurniawati EM, Rahmawati NA, Widyasari A. Differences Between 25-hydroxyvitamin D Levels in Patients with Pelvic Organ Prolapse and Non-Pelvic Organ Prolapse: a Systematic Review. *JOGC*. 2023;45(12):102198. doi:10.1016/j.jogc.2023.102198
50. Chen J, Tang Z, Slominski AT, et al. Vitamin D and its analogs as anticancer and anti-inflammatory agents. *Eur J Med Chem*. 2020;207:112738. doi:10.1016/j.ejmech.2020.112738
51. Tarantino D, Mottola R, Sirico F, et al. Exploring the impact of vitamin D on tendon health: a comprehensive review. *J Basic Clin Physiol Pharmacol*. 2024;35(3):143–152. doi:10.1515/jbcpp-2024-0061