四川大学学报（医学版） 2024，55（2）：490－500
J Sichuan Univ（Med Sci） doi: 10.12182/20240360508

在线全文

基于纵向研究的胆囊结石发病风险因素研究新进展*

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【摘要】 胆囊结石是常见的消化系统疾病。已有多篇文献对胆囊结石发病风险因素进行了报道和归纳，但是其纳入的研究主要为横断面设计，因其研究设计的固有缺陷，研究结果有待更多纵向研究进行验证。而且近年来多项研究陆续发现了多个新的胆囊结石风险因素，如减肥手术、乙肝病毒感染、丙肝病毒感染、肾结石、结肠切除术、骨质疏松等因素，但未被纳入既往综述研究中。本研究对基于纵向研究（队列、随机对照试验和巢式病例对照）发现的101个胆囊结石发病相关风险因素进行综述，将胆囊结石发病相关风险因素归纳为不可调控因素和可调控因素。其中不可调控因素包括年龄、性别、种族和家族史4个因素，而可调控因素包括37个生物环境因素、25个社会环境因素和35个理化环境因素。本研究可为胆囊结石的发病机制研究提供全面和综合的线索，为胆囊结石发病高危人群识别和预防策略的制定提供基础。

【关键词】 胆囊结石 纵向研究 风险因素 综述

New Progress in Longitudinal Research on the Risk Factors for Cholelithiasis *WANG Xin*[1], *BAI Ye*[2], *YU Wenqian*[1], *XIE Linjun*[1], *LI Shiyi*[1], *JIANG Guoheng*[1], *LI Hongyu*[1], *ZHANG Ben*[1△]. 1. *West China School of Public Health and West China Fourth Hospital, Sichuan University*, Chengdu 610041, China; 2. *Gene Diagnosis Center, Bethune First Hospital, Jilin University*, Changchun 130021, China

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【**Abstract**】 Cholelithiasis is a common disease of the digestive system. The risk factors for cholelithiasis have been reported and summarized many times in the published literature, which primarily focused on cross-sectional studies. Due to the inherent limitations of the study design, the reported findings still need to be validated in additional longitudinal studies. Moreover, a number of new risk factors for cholelithiasis have been identified in recent years, such as bariatric surgery, hepatitis B virus infection, hepatitis C virus infection, kidney stones, colectomy, osteoporosis, etc. These new findings have not yet been included in published reviews. Herein, we reviewed the 101 cholelithiasis-associated risk factors identified through research based on longitudinal investigations, including cohort studies, randomized controlled trials, and nested case control studies. The risk factors associated with the pathogenesis of cholelithiasis were categorized as unmodifiable and modifiable factors. The unmodifiable factors consist of age, sex, race, and family history, while the modifiable factors include 37 biological environmental factors, 25 socioenvironmental factors, and 35 physiochemical environmental factors. This study provides thorough and comprehensive ideas for research concerning the pathogenesis of cholelithiasis, supplying the basis for identifying high-risk groups and formulating relevant prevention strategies.

【**Key words**】 Cholelithiasis Longitudinal study Risk factor Review

1 胆囊结石流行病学研究现状

胆囊结石是一种常见的消化系统疾病。欧洲成年人胆囊结石患病率约10%～20%，亚洲人患病率约为5%～8%[1]。大多数胆囊结石患者无明显症状，仅约20%的患者会出现腹痛等症状或发生急性胆囊炎、胆管炎等并发症，需要进行临床治疗[2]。胆囊切除术是胆囊结石治疗的标准手段，美国每年手术量超过80万次，直接经济花费高达60亿美元[3]。研究显示约98%的胆道系统疾病的发病与胆囊结石有关。此外，胆囊结石也是结直肠癌和心血管疾病发病的重要风险因素，且会显著增加全因死亡风险，给患者带来严重的经济和疾病负担[4]。因此，全面识别胆囊结石发病的风险因素对于胆囊结石的发病机制探讨以及人群疾病预防和风险分层管理具有重要意义。

胆囊结石是一种遗传因素和环境因素共同作用的复杂疾病。研究显示胆囊结石发病存在明显的家族聚集性和种族差异性，遗传因素可解释约25%的人群变异[5-6]。此外，多项全基因组关联研究也先后发现*HNF4A*、*FUT2*、*SERPINA1*、*JMJD1C*、*AC074212.3*、*SLC10A2*、*ABCG5/G8*、*SULT2A1*、*CYP7A1*、*TM4SF4*、*ABCB4*、*TTC39B*、*UGT1A1*、*GCKR*和*CYP8B1*等基因与胆囊结石

* 国家自然科学基金（No. 81673255、No. 81874283、No. 81903398），中央高校基本科研基金（No.YJ2021112），中国青年专业人员招聘计划，四川省科学技术厅杰出青年科学基金（No. 2023NSFSC1927），四川省科技厅2023年中央引导地方项目（No. 2023ZYD0097），四川省医学会医学科研青年创新课题（No. Q21016），四川天府峨眉计划青年人才项目（川峨眉第1841号），四川大学基础医学推广计划和尖端学科发展计划和四川大学“从0到1”创新项目（No. 2023SCUH0026），四川大学2024年度“国家级大学生创新创业训练计划”项目（C2024130124）资助

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出版日期：2024-03-20

的患病风险显著相关, 为胆囊结石的发病风险评估提供了基础[7-9]。在胆囊结石环境风险因素研究方面, 报道显示胆囊结石具有“5F特征”, 即白色人种(fair)、肥胖(fat)、40岁(forty)、多产(fertile)和女性(female)[10]。随后的研究也发现高脂饮食、吸烟、酗酒和缺乏运动等饮食生活习惯, 肥胖、糖尿病和非酒精性脂肪肝等疾病以及避孕药和胃切除术等药物和治疗手段亦会增加胆囊结石的发病风险[11-12]。但既往多项关于胆囊结石发病的风险因素的综述, 其纳入的研究多来自现况调查或病例对照设计, 研究结果可能会受到回忆偏倚和时序倒置的影响, 因此其因果关联性尚需要队列研究等纵向研究的进一步验证; 并且随着研究的进展, 越来越多新的胆囊结石发病风险因素如肾结石和骨质疏松等陆续被发现, 但这些因素未被纳入既往综述中[13]。

本研究基于胆囊结石发病相关的纵向研究(队列研究、随机对照试验和巢式病例对照研究), 参照病因轮状模型(图1)对胆囊结石发病相关的风险因素进行全面综述, 为胆囊结石发病高危人群的识别和人群预防策略的制定提供基础。本文将胆囊结石发病的环境因素分为不可调控风险因素和可调控风险因素, 其中不可调控因素包括年龄、性别、种族和家族史等, 而可调控因素包括社会环境因素、生物环境因素和理化环境因素等(表1)。

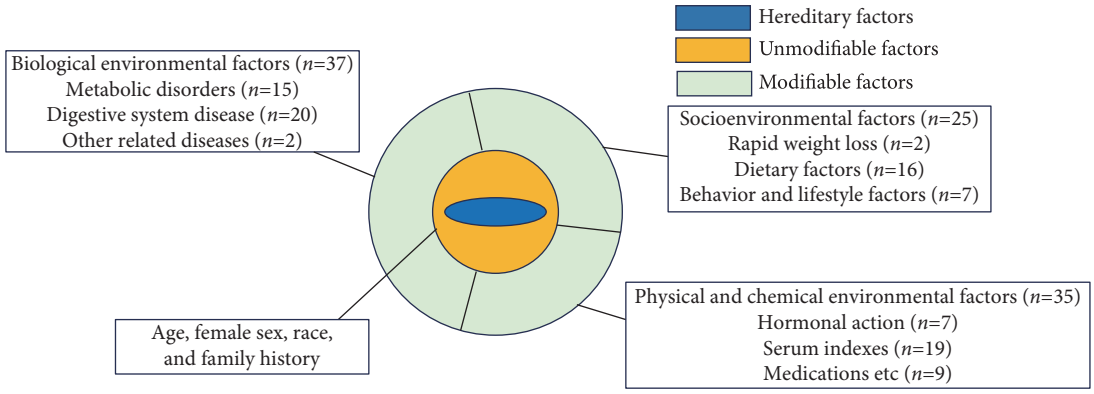

图 1 胆囊结石危险因素模型图

Fig 1 Wheel model of risk factors for cholelithiasis

n indicates the number of influencing factors.

2 胆囊结石发病不可调控环境风险因素

目前的一些研究表明, 发生胆囊结石的不可调控环境风险因素主要为高龄、女性、种族、家族史。基于日本静冈县队列60余万人群的一项队列研究显示, 随着年龄增加胆囊结石发病风险显著增加, 与40岁以下人群相比, 80岁以上人群胆囊结石发病风险增加3.44倍[14]。这可能是由于高龄人群胆囊功能性减退导致胆汁酸合成减少和胆固醇分解下降, 进而导致胆固醇过饱和形成结石[15]。同时, 该研究还显示, 女性人群胆囊结石发病风险是男性人群的1.21倍[14], 其原因可能是女性内源性雌激素可参与肝脏胆固醇的合成代谢和促进结晶成核的过程, 导致胆固醇水平过高, 进而形成结石[13]。

虽然目前尚无对种族和家族史与胆囊结石发病风险的关联性进行报道的纵向研究, 但是大量横断面研究显示不同国家地区之间胆囊结石患病率存在差异, 美洲土著居民较高(>20%)[16], 其次分别是欧洲(约10%)[17]、亚洲(约5%)[18]和非洲(<5%)[19]。此外, 多项病例对照研究结果提示家族史也可能是胆囊结石发病的重要风险因素[20-21]。一项基于上海人群的研究显示, 有胆囊结石家族史人群的胆囊结石患病风险是无家族史人群的2.8倍[21]; 而且胆囊结石人群一级亲属患有胆囊结石的家族史比例显著高于非胆囊结石人群[20]。未来需要开展纵向研究进一步验证种族和家族史与胆囊结石发病风险之间的关联性。

3 胆囊结石发病可调控环境风险因素

目前认为影响胆囊结石发病的可调控环境风险因素主要分为社会环境因素、生物环境因素和理化环境因素三方面。

3.1 社会环境因素

3.1.1 体质量迅速降低

研究显示减肥术或胃部切除术导致的体质量短时间内持续降低与胆囊结石的发病显著相关[22]。2019年我国一项基于台湾国民健康保险研究资料库4 197名肥胖人群随访10年的队列研究发现, 与未行减肥手术的人群相比, 行减肥术人群的胆囊结石发病风险显著增高[22]。另一项

表 1 与胆结石发病相关的环境风险因素

Table 1 Environmental risk factors associated with the onset of cholelithiasis

Environmental risk factor			Risk factor	Protective factor	Underlying factor
Unmodifiable factors			Advanced age, female sex, race, and family history	/	/
Modifiable factors	Socioenvironmental factors	Rapid weight loss	Bariatric surgery and gastrectomy	/	/
		Dietary factors	High energy intake (high cholesterol and high carbohydrate), ultra-low calorie diet (dieting), high saturated fatty acids, trans fatty acids, long-term overnight fasting, intake of red meat, low calcium, and excess heme iron	High unsaturated fatty acids, intake of fruits, vegetables, nuts, vegetable oils, fish (white meat), dietary fiber, and moderate magnesium (supplements)	/
		Behavior and lifestyle	Smoking, alcohol consumption, sedentariness, and physical inactivity	Moderate drinking, exercise, and coffee and tea consumption	/
	Biological environmental factors	Metabolic disorders	Obesity, high waist circumference, high waist-to-hip ratio, type 2 diabetes mellitus, insulin resistance, dyslipidemia, nonalcoholic fatty liver disease, gallstones, and Hashimoto's thyroiditis	Type 1 diabetes mellitus	Hemolytic disease and cystic fibrosis
		Digestive system disease	Liver cirrhosis, hepatitis C virus (HCV), gallbladder polyps, gallbladder infections and inflammation, gallbladder dysfunction, inflammatory bowel disease (Crohn's disease and ulcerative colitis), ileum and colon resection, appendectomy, prolonged hospital stay, postoperative parenteral hypertrophic therapy, peptic ulcer, gastroesophageal reflux, dyspepsia, acute enteritis, duodenal diverticulum, and other gastrointestinal disorders	/	Hepatitis B virus (HBV), *Helicobacter pylori*, and gastrointestinal microecological imbalance
		Other related diseases	Spinal cord injury, osteoporosis, coronary heart disease, myocardial infarction, and stroke	/	/
	Physical and chemical environmental factors	Hormonal action	Estrogen, hormone replacement therapy, elevated testosterone, multiple births (multiple pregnancies), high thyroid hormone, and high parathyroid hormone	/	Contraceptive medication
		Serum indexes	Abnormal lipid levels (high TC, high TG, high LDL-C, and low HDL-C), apolipoprotein A/B/E, high leptin, high insulin, high uric acid and high lipids, elevated fasting blood glucose, high bilirubin levels, and abnormal liver function	High HDL-C, low LDL-C, low TC, and low TG	High serum C-reactive protein, adiponectin, low vitamin D, low vitamin C, and high cystein C
		Drug effect	Thiazide diuretics, non-steroidal anti-inflammatory drugs, aspirin, octreotide (somatostatin analogue), and ceftriaxone sodium	Statins and ursodeoxycholic acid	Antolamine and cyclosporine

/: No information was found in the published literature. TC: total cholesterol; TG: triglyceride; LDL-C: low density lipoprotein cholesterin; HDL-C: high density lipoprotein cholesterin.

基于韩国国民健康保险服务队列人群中1 998名经历胃切除术的患者和1∶4匹配的近8 000名对照人群随访11年的队列研究也发现，胃部切除术患者胆囊结石发病率显著高于非胃部切除人群(3.5% vs. 2.0%)[23]。这可能是由于减肥术或胃部切除术后患者的胃部结构发生非生理性重建，导致胆汁胆固醇过饱和以及促成核因子的释放等，从而导致胆固醇型结石的形成，同时术后继发的胆囊体积增大或胆道感染等也是造成胆囊结石的原因之一[23]。此外，研究显示胃部切除术可能切断迷走神经肝支导致胃排空变慢，继发胃食管反流等也可能是导致胆囊结石发病的重要原因[24]。

3.1.2 膳食因素

饮食习惯与胆囊结石发病风险的关联性一直备受关注[25]。一项基于美国88 837名护士人群的队列研究显示，高能量饮食(> 8 200 J/d)的中年女性与低能量饮食(< 4 730 J/d)女性相比，胆囊结石发病风险上升1.1倍[26]。但是另一项基于瑞典28个中心进行健康节食减肥的队列研究显示，超低热量饮食人群(< 500 kcal/d)胆囊结石的发病风险是低热量饮食(1 200 ~ 1 500 kcal/d)人群的2.5倍[27]。因此，膳食热量与胆囊结石发病风险可能呈现U型关联性，过高和过低能量的饮食均会增加胆囊结石的发病风险。另一项基于中年男性人群随访长达25年的队列研究显示，高糖饮食显著增加胆囊结石的发病风险，这可能是因为高糖摄入导致三酰甘油(triacylglycerol, TG)升高和高密度脂蛋白胆固醇(high density lipoprotein cholesterol, HDL-C)降低，使得胆汁酸合成减少，造成胆固醇过饱和

进而增加胆囊结石的发病风险[28]。

既往多项队列对血脂和胆囊结石的发病风险进行关联研究，结果表明高水平饱和脂肪酸和反式脂肪酸的摄入显著增加胆囊结石的发病风险，而不饱和脂肪酸的摄入可能是胆囊结石发病的保护因素[29]。一项基于队列研究的系统综述和Meta分析表明，每天增加200 g的水果和蔬菜摄入量胆囊结石发病风险分别下降3%和4%[30]。这可能是由于水果和蔬菜富含膳食纤维，可降低体内总胆固醇（total cholesterol, TC）和低密度脂蛋白胆固醇（low density lipoprotein cholesterol, LDL-C）的水平，进而抑制胆固醇合成促进胆汁酸分泌，降低胆囊结石的发病风险[31]。另一项基于全国健康与营养调查人群队列中4 730名年龄在25到74岁之间女性的随访研究显示，较长的隔夜空腹时间会显著增加胆囊结石的发病风险，且两者关联性呈现显著的线性趋势，这可能是较长的空腹时间会降低胆囊的动力性，导致胆汁淤积且成分发生改变所致[32]。此外，研究还显示摄入坚果、蔬菜、橄榄油、鱼（白肉）、膳食纤维和适量镁元素（补充剂）可显著降低胆囊结石和胆囊切除术的发生风险[33]，而红肉、低钙和过量血红素铁的摄入可能是胆囊结石发病的危险因素[34]。

3.1.3　行为和生活习惯因素

基于27项队列研究的系统综述和Meta分析表明，吸烟是胆囊结石发病的风险因素，与对照组相比，吸烟人群胆囊结石发病风险上升约17%，且随每包年的吸烟量与胆囊结石发病风险呈线性上升趋势[35]。其原因可能是吸烟可导致胆汁成分合成异常，进而导致胆固醇过饱和形成结石[36]。另一项基于队列研究的系统综述和Meta分析研究显示，与低水平酒精摄入量人群相比，高水平酒精摄入人群胆囊结石发病风险显著降低，且酒精摄入量与胆囊结石发病风险降低呈现线性关联，每天增加10 g酒精消耗胆囊结石发病风险平均降低12%[37]。这可能是因为酒精成分能降低胆汁胆固醇浓度，升高HDL-C水平，促进胆汁酸合成及分泌，进而抑制胆囊结石形成[38]。然而，最新发表的基于队列研究的系统综述和Meta分析并未发现饮酒量增加与胆囊结石发病风险降低之间的线性关联性[35]。

既往研究显示饮用咖啡和茶会降低胆囊结石的发病风险。基于队列研究的系统综述和Meta分析结果显示，每天增加1杯的咖啡摄入量，胆囊结石发病风险平均降低5% [35, 39]。同时，基于队列研究结果指出饮茶与胆囊结石之间的关联性可能为非线性关联，且孟德尔随机化研究进一步也证实了饮茶与胆囊结石发病风险之间的因果关联性[35]。这种关联可能是由于咖啡和茶叶中富含的咖啡因能通过刺激胆囊收缩素（cholecystokinin, CCK）释放，促进胆汁分泌，抑制胆固醇结晶成核[40]。而且咖啡中富含的镁元素也一定程度上降低了胆囊结石的发病风险[41]。此外茶叶中富含的茶多酚能刺激肠道运动，促进脂肪的分解和吸收，这可能也是降低胆囊结石发病风险的机制之一[42]。但研究显示，饮用咖啡和胆囊结石发病风险的负向关联性仅在女性中得到验证[39]。另有研究指出，咖啡与女性胆囊结石的负向关联性，仅限于绝经前或使用激素替代疗法的女性，即那些女性性激素水平较高的女性，而在没有使用激素替代疗法的女性中，这种关联性与男性人群相似，这表明，观察到的咖啡摄入和胆囊切除术之间的联系取决于女性性激素的水平，但机制尚不清楚[43]。

队列研究还显示久坐和缺乏运动会显著增加胆囊结石的发病风险[44]。同时基于队列研究的系统综述和Meta分析结果也表明每周增加20代谢当量/h的运动量，胆囊结石发病风险平均下降13%，这也进一步验证运动与胆囊结石发病风险的关联性[45]。

3.2　生物环境因素

3.2.1　代谢异常疾病

肥胖人群由于体内胆固醇代谢异常、胆囊体积变大且胆汁酸排空变慢等可导致胆固醇过饱和形成结石，因此肥胖可能是胆囊结石发病风险升高的因素[46]。一项基于队列研究的系统综述和Meta研究指出体重指数（body mass index, BMI）与胆囊结石发病风险呈非线性关联，在BMI< 40 kg/m^{2}范围内，随BMI增加胆囊结石发病风险呈现陡坡样上升；而在40 ~ 45 kg/m^{2}区间内，BMI与胆囊结石的发病风险呈现平台样增长[47]。孟德尔随机化研究也进一步证实BMI水平升高与胆囊结石发病风险上升的关联性可能是直接的因果关联[48]。此外，研究还显示较高的腰围（waist circumference, WC）和高腰臀比（waist-to-hip ratio, WHtR）也是胆囊结石发病的风险因素，而且两者均与胆囊结石发病风险呈现线性关联[47]。然而，在不同肥胖评价指标中，哪种指标对胆囊结石的发病风险预测更有价值存在争议[49]。有研究表明在男性人群中，联合BMI+WC可能是预测胆囊结石发病风险的有效模型，而女性人群则倾向于选择BMI+WHtR的组合[50]。

2018年，一项基于台湾7 015名1型糖尿病（type 1 diabetes mellitus, T1DM）和51 689名2型糖尿病（type 2 diabetes mellitus, T2DM）的队列研究显示，T2DM与胆囊结石发病风险呈现正向关联；但是T1DM与胆囊结石发病风险呈现负向关联，而且两者的关联性在21 ~ 40岁人群之间更为显著[51]。T2DM患者由于胰岛素代谢异常导

致CCK释放减少以及胆囊排空变慢,可能是其所致胆囊结石的机制之一[46]。而发病年龄(<40岁)和胰岛素分泌不足等作用可能是T1DM导致胆囊结石发病风险降低的主要原因[52]。2014年,基于台湾健康体检人群2 386名健康人群的队列研究显示,较高的血糖水平与胆囊结石发病风险显著相关,提示胰岛素抵抗(insulin resistance, IR)也可能与胆囊结石的发病风险显著相关,这可能是IR可参与调节胆汁合成导致胆固醇代谢异常,同时抑制胆囊发挥正常的功能所致[53]。而且,研究显示参与胰岛素代谢调控的*ABCG5/G8*基因过表达也会增加胆囊结石的发病风险,这也进一步证实IR与胆囊结石的发病相关[8]。

近年研究发现非酒精性脂肪肝(nonalcoholic fatty liver disease, NAFLD)和肾结石(kidney stone disease, KSD)是胆囊结石发病的独立危险因素[54-55]。2019年,基于韩国国民健康保险服务队列中10余万人群的研究显示,KSD是胆囊结石的发病风险因素,同时,胆囊结石也会增加KSD的发病风险,此外,2018年,一项基于韩国2万余名参加健康体检人群的队列研究显示,NAFLD与胆囊结石存在互为风险关联[55-56]。同期,基于我国1万余名参加定期健康体检人群为期6年的随访结果指出,NAFLD会显著增加胆囊结石的发病风险,但是两者的关联性仅存在于女性人群中[54]。另有研究显示桥本氏甲状腺炎患者胆囊结石发病风险显著高于正常对照组,尤其在>50岁和女性人群中这种关联性更为显著[57]。这可能与甲状腺功能减退会导致胆囊收缩性和肠道蠕动变弱,而且甲状腺激素能影响胆汁合成异常等有关[58]。此外,横向研究还提示代谢类疾病如溶血性疾病和囊性纤维化也与胆囊结石的发病风险升高相关,但是目前尚无队列研究等纵向研究的证据支持[59]。

3.2.2 消化系统疾病

基于意大利618名肝硬化患者长达8年的随访结果显示胆囊结石年发病率约为5%,显著高于一般人群(0.5%)[60]。肝硬化导致胆汁酸合成异常和非结合胆红素浓度升高可能是其导致胆囊结石发病的主要机制[61]。系统综述和Meta研究也指出丙型肝炎病毒(hepatitis C virus, HCV)可能增加胆囊结石的发病风险,而乙型肝炎病毒(hepatitis B virus, HBV)与胆囊结石发病风险的关联性尚未达到显著水平[62]。研究显示肝炎病毒能通过感染胆囊上皮细胞进而影响胆汁的吸收可能是其致病的主要原因[63]。另一项基于丹麦2 848名自然人群的队列研究显示,胆囊息肉可能是胆囊结石发病的独立风险因素[64]。胆囊功能紊乱是结石形成的重要机制,其中胆内感染和炎症反应可导致色素型结石的形成;而胆囊体积增大和胆囊动力下降则是形成固醇型结石的主要原因[64]。

队列研究还显示炎性肠病(inflammatory bowel disease, IBD)也是胆囊结石发病的风险因素[65]。基于意大利634名年龄和性别匹配的炎症性肠病队列研究显示,经过长达11年的追踪随访,与对照人群相比克罗恩病(Crohn's disease, CD)和溃疡性结肠炎(ulcerative colitis, UC)患者胆囊结石发病风险分别上升85%和23%[66]。这可能与胆囊收缩性下降和肠道胆汁酸重吸收受阻导致胆汁胆固醇过饱和有关[36]。此外,研究指出回肠切除术、结肠切除术、术后肠外高营养(total parenteral nutrition, TPN)以及住院时间过长也是胆囊结石发病的高危因素[67]。这可能是由于回肠、结肠和阑尾切除术等手术方式导致的细菌感染及炎症反应,而术后TPN治疗造成的胆汁酸肠-肝循环障碍也可能是胆囊结石的发病机制之一[68]。

近年研究发现有胃肠道不适症状的患者可伴有胆囊结石发生,肠道致病菌感染可能是其增加胆囊结石发病风险的重要致病机制[69]。另有研究显示胃肠内幽门螺杆菌(*Helicobacter pylori, H. pylpri*)感染也可能是胆固醇型结石形成的致病因素,系统综述和Meta研究也进一步表明胆道*H. pylori*感染与胆囊结石发病风险的上升密切相关[70]。但是,有关胃肠道微生态失衡与胆囊结石发病的关联性尚无纵向研究的证据支持[71]。此外,队列研究还显示消化性溃疡、胃食管反流、消化不良、应激性肠炎和十二指肠憩室伴有腹痛等症状的消化系统疾病会造成肠-肝循环失调和细菌感染所致炎症反应,进而可能显著增加胆囊结石的发病风险[72]。

3.2.3 其他相关疾病

报道还指出,脊髓损伤患者由于其肠动力减弱和胆囊收缩性下降,进而肠-肝循环受阻造成胆汁淤积,可导致其胆囊结石发病率与健康人群相比显著升高[73]。另一项基于我国台湾地的队列研究指出,经过5年随访,骨质疏松患者胆结石发病风险比对照人群上升35%,这可能是由于骨桥蛋白(osteopontin, OPN)参与的慢性炎症反应所致[74]。既往发表的体内和体外实验均证明OPN在固醇性胆结石发生发展中发挥重要作用[75-76]。此外,研究还发现冠心病与胆囊结石发病风险升高显著相关,而且其他心血管疾病(cardiovascular diseases, CVD)如心肌梗死和脑卒中等也会增加胆囊结石的发病风险,但是其发病机制尚不清楚[77]。另有研究提示与CVD发病显著相关的指标如脂蛋白E(apolipoprotein E, ApoE)和脂联素(adiponectin, ADP)等也可能是导致胆囊结石的病因,这是否能在一定程度上解释CVD与胆囊结石发病之间的关联,有待进一步证实[78]。

3.3 理化环境因素

3.3.1 激素作用

2017年, 一项基于队列研究的系统综述和Meta分析指出外源性雌激素作用会增加胆囊结石的发病风险, 其原因是雌激素能激活肝细胞羟甲戊二酰辅酶A (hydroxymethylglutaryl coenzyme A, HMG-CoA)还原酶, 加速胆固醇的合成, 导致胆固醇过饱和形成胆囊结石, 但是进一步亚组分析的结果显示仅激素补充治疗(hormone replacement therapy, HRT)显著增加胆囊结石的发病风险, 而口服避孕药(oral contraceptive, OC)与胆囊结石发病的关联性未达到显著性水平[79]。另一项基于Multiethnic Cohort(MEC)队列的研究结果也同样表示OC与胆囊结石发病风险无显著关联, 而HRT与胆囊结石发病风险升高的关联性也仅在白人女性中得到验证[34]。未来需要更多的纵向研究对外源雌激素与胆囊结石发病风险的关联性开展进一步验证。此外, 近年研究发现雄激素可能是胆囊结石发病的风险因素, 睾酮水平上升与胆囊结石发病风险升高存在显著的关联性[79]。但其所致胆囊结石的发病机制尚不清楚, 有待更深入的研究阐明。

2009年, 基于英国Million Women Study(MWS)队列130余万女性的研究显示多胎次(多次怀孕)是胆囊结石发病的危险因素, 与未生育女性相比妇女胆囊结石发病风险升高24%, 且随着胎次增加胆囊结石的发病风险呈线性升高趋势[80]。这可能与孕激素能导致胆汁代谢失调和胆囊功能紊乱等造成胆固醇过饱和相关[13]。此外, 研究还指出甲状腺激素和甲状旁腺激素均可增加胆囊结石的发病风险, 其致病机制与雌激素调节胆固醇代谢过程相似[57]。

3.3.2 血清指标

2002年, 一项基于美国社区动脉粥样硬化风险(Atherosclerosis Risk in Communities, ARIC)队列12 773名研究对象的研究显示, 血脂异常可能是胆囊结石发病的重要危险因素, 尤其在男性人群中二者的关联性更加显著[81]。这可能是较高的胆固醇水平导致胆汁的合成和代谢失调造成胆汁过饱和所致。另有研究提示载脂蛋白E(apolipoprotein E, ApoE)作为超低LDL-C和HDL-C的组成部分可参与体内胆固醇的合成代谢, *ApoE*基因遗传变异导致的胆固醇代谢异常可能也是胆囊结石发病的机制之一。ARIC队列研究也指出ApoE(ε2/ε4)与胆囊结石的发病风险相关联, 其中携带ε2等位基因人群的胆囊结石发病风险升高; 而携带ε4人群的发病风险降低, 但关联性仅在白人中显著[82]。此外, 研究提示参与LDL-C代谢的血清载脂蛋白A(apolipoprotein A, ApoA)水平升高和载脂蛋白B(apolipoprotein B, ApoB)基因遗传变异(rs693), 以及导致胆固醇合成失调的血清瘦素指标升高也可能是胆囊结石发病的危险因素[83]。

美国ARIC队列研究结果还提示血清胰岛素和尿酸过高可增加血清胆固醇水平进而导致胆囊结石的发病风险上升[81]。基于我国健康体检人群队列结果显示空腹血糖值升高可显著增加胆囊结石的发病风险[53]。另外, 丹麦自然人群队列研究还提示高胆红素水平也是胆囊结石发病的危险因素, 而且孟德尔随机化研究也进一步证明高胆红素血症与胆囊结石发病风险之间的关联性可能为直接的因果关联[84]。其他指标如谷丙转氨酶(alanine transaminase, ALT)、谷草转氨酶(aspartate transaminase, AST)和碱性磷酸酶(alkaline phosphatase, ALP)等血清值异常可能作为临床上提示肝病患者的胆囊结石发病风险增高的判断依据[85]。而血清C反应蛋白作为一种肝脏合成的全身炎症非特异性蛋白可能也与胆囊结石的发病有关, 但该关联性尚需要队列研究的进一步验证[86]。此外, 横断面研究提示维生素D、维生素C和胱蛋白C可能也与胆囊结石的发病风险相关, 但需要纵向研究的进一步验证[87]。

3.3.3 药物作用

2009年, 基于美国53611 名护士的队列研究显示, 他汀类药物的使用可以显著降低胆囊切除的发病风险, 这可能是由于他汀能抑制HMG-CoA还原酶, 降低血清总胆固醇和三酰甘油水平, 且升高HDL-C水平, 进而起到预防胆囊结石的作用[88]。但是, 一项利用倾向性评分匹配的队列研究结果表明他汀可能与胆囊结石发病风险降低无显著关联, 二者之间的关联性有待更多研究进行验证[89]。此外, 队列研究还发现噻嗪类利尿剂能导致胆汁胆固醇过饱和形成结石, 利用噻嗪类利尿剂治疗的人群胆囊结石发病风险是对照人群的1.36倍, 而且停止服用后, 其胆囊结石发病风险显著降低[77]。瑞士IBD队列研究表明长期服用非甾体抗炎药能显著增高胆囊结石的发病风险[90]。美国ARIC队列也证明服用阿司匹林可能与胆囊结石发病风险升高相关, 而且这种关联性在男性人群中更为显著[81]。奥曲肽(生长抑素类似物)是目前研究较为清楚的胆囊结石致病药物, 它可以通过抑制CCK释放, 降低胆囊收缩性以及减缓肠胃蠕动, 进而导致胆汁淤积, 造成胆囊结石的形成[91]。此外, 随机对照试验结果证明头孢曲松钠能进入胆囊内影响胆汁代谢, 每天服用高剂量头孢曲松钠抗生素(成人> 2 g; 儿童> 60 mg/kg)也可能是胆囊结石发病的危险因素[92]。而且研究还发现与未服用熊去氧胆酸(ursodeoxycholic acid, UDCA)的人群相比, 采用

UDCA治疗的人群胆囊结石发病风险降低90%以上,这可能因为UDCA能减少肠道胆固醇的重吸收并刺激胆汁酸分泌,进而抑制胆汁淤积和结石的形成[93]。除上述药物外,其他综述还报道了安妥明和环孢霉素等可能也是胆囊结石发病的危险因素,但是目前尚无纵向研究的证据支持[94]。

4 挑战和展望

本研究基于队列研究等纵向研究对其报道的胆囊结石发病风险因素进行全面综述,并参照病因轮状模型将胆囊结石发病风险因素分为可调控因素和不可调控因素,同时,本研究对一些可能与胆囊结石发病相关的潜在因素(尚无纵向研究或其关联性未达到显著性水平)如幽门螺杆菌感染、脂联素、血清C反应蛋白、高胱蛋白C、HBV、维生素D、维生素C等进行了报道,研究结论对胆囊结石的发病机制探讨及胆囊结石的三级预防策略实施有重要的指导价值。

对于不可调控的胆囊结石发病风险因素,可根据年龄、性别、种族、家族史等因素构建胆囊结石发病风险预警模型,并开展人群的应用,早期快速的识别胆囊结石发病高危人群,实施早期诊断和早期治疗的二级预防策略,并开展人群的危险分层管理,降低胆囊结石相关症状和并发症的发生风险。对于可调控的胆囊结石发病风险因素,应积极实施病因预防策略,如戒烟,限酒,适量运动,低脂和健康饮食,控制血糖和血脂,减肥,及时控制和治疗肾结石、骨质疏松等疾病,避免使用噻嗪类利尿剂、非甾体抗炎药等,开展多种举措降低胆囊结石的发病风险。未来,对于控烟、控酒、减肥等手段效果不明显的人群,也可以考虑寻找吸烟、饮酒、肥胖等因素与胆囊结石发病因果关联通路上的中介变量,通过控制中介变量的方式切断该因果关联作用路径,进而降低胆结石的发病风险。

虽然纵向研究设计能够一定程度避免反向因果关联的影响,但是由于人群分层和潜在混杂因素的作用,目前尚不能确认风险因素和胆囊结石之间的关联性是直接的因果关联还是仅为风险关联。孟德尔随机化研究是工具变量(instrumental variable)在流行病学研究中的应用之一。由于等位基因在配子形成配体时遵循随机分配原则,且基因型早于表型出现,基因-疾病效应值不受混杂因素和反向因果关联的影响,其因果关联验证效果可以一定程度上媲美随机对照试验[95]。未来需要进一步开展大样本孟德尔随机化研究,对队列研究等纵向研究发现的风险因素和胆囊结石之间的因果关联性再进一步验证,为胆囊结石的防治措施制定和发病机制探讨提供可靠证据。

* * *

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Author Contribution WANG Xin is responsible for conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing--original draft, and writing--review and editing. BAI Ye is responsible for data curation, formal analysis, investigation, methodology, and software. YU Wenqian is responsible for investigation, methodology, software, and validation. XIE Linjun and LI Shiyi are responsible for methodology, software, and visualization. JIANG Guoheng is responsible for investigation, methodology, and writing--review and editing. LI Hongyu is responsible for investigation, methodology, and writing--review and editing. ZHANG Ben is responsible for resources, supervision, and writing--review and editing. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

利益冲突 所有作者均声明不存在利益冲突

Declaration of Conflicting Interests All authors declare no competing interests.

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（2023 – 08 – 25收稿, 2024 – 01 – 11修回）

编辑 汤 洁