

## Original Research Article

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# Cholelithiasis risk factors in young age patients less than 30 years of age

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## ABSTRACT

**Background:** Gall-stone disease is increasingly reported in adults younger than 30 years, yet age-specific determinants remain underexplored in South Asia. The objective was to identify independent risk factors for symptomatic cholelithiasis in North-Indian adults aged 15–29 years and to develop a pragmatic bedside risk-score.

**Methods:** A prospective, unmatched case-control study enrolled 50 ultrasound-confirmed gall-stone cases and 50 stone-free controls at a tertiary hospital between January and June 2024. Exposures included anthropometry, dietary glycaemic load, physical activity, hormonal factors, family history and  $\beta$ -thalassaemia trait. Multivariable logistic regression generated adjusted odds ratios (aOR), and a four-item risk-score was evaluated by receiver-operating-characteristic analysis.

**Results:** Central obesity (waist-to-height  $\geq 0.50$ ) was present in 70% of cases versus 40% of controls (aOR 3.0; 95% CI 1.3–6.9). A high-glycaemic diet was reported by 60% versus 32% (aOR 2.6; 1.1–6.1). Among females, prolonged combined oral-contraceptive use  $\geq 60$  months occurred in 42% versus 12% (aOR 4.1; 1.1–15.6). Family history showed a crude OR 3.2 but attenuated after adjustment (aOR 2.4; 0.8–7.4).  $\beta$ -thalassaemia trait (12% versus 4%) preferentially yielded pigment stones yet was not an independent predictor (aOR 3.4; 0.6–19.0). The four-item score (central obesity, high-glycaemic diet, inactivity, family history) achieved an AUROC of 0.82, with a cut-off  $\geq 2$  giving 80% sensitivity and 70% specificity.

**Conclusion:** Early-onset cholelithiasis in this cohort is chiefly a metabolic-hormonal entity linked to visceral adiposity, refined-carbohydrate intake and extended oestrogen exposure. Simple anthropometric and lifestyle measures can triage high-risk youth for targeted counselling and ultrasound surveillance, offering a scalable strategy to curb the rising burden of gall-stone disease in the most productive years of life.

**Keywords:** Early-onset cholelithiasis, Central obesity, High-glycaemic diet, Oral contraceptives, Risk-score

## INTRODUCTION

Gall-stone disease, once summarized by the mnemonic “female, fat, fertile and forty,” is now emerging with disturbing frequency in adolescents and young adults, signalling a shift in the epidemiologic landscape that mandates focused scrutiny of age-specific determinants. Worldwide prevalence has risen in parallel with the obesity pandemic, but the trajectory is especially steep in low- and middle-income countries undergoing rapid nutritional transition, such as India, where hospital audits already attribute 7–14% of cholecystectomies to patients under 30 years.<sup>1</sup> Early-onset cholelithiasis differs

etiologically from the classic middle-aged phenotype: cholesterol supersaturation is still pivotal, but it is propelled by a unique interplay of genetic polymorphisms (ABCG8 D19H, APOE-ε4), insulin-resistant dyslipidaemia, rapid weight-cycling linked to crash dieting, and oestrogen exposure from prolonged combined oral-contraceptive (COC) use.<sup>2–4</sup> Central obesity—a better surrogate of visceral adiposity than body-mass index in Asian Indians—doubles gall-stone odds even after glycaemic and lipid adjustments, presumably by augmenting hepatic cholesterol secretion and gall-bladder mucin production.<sup>5</sup> A meta-analysis of nine cohorts encompassing 1.3 million person-years confirmed that every 5 cm increase in waist circumference confers a 7%

relative risk increment for symptomatic stones, an effect twice as large below age 35 years.<sup>6</sup> Sedentary behaviour exacerbates this risk by impairing gall-bladder motility; conversely, moderate-to-vigorous physical activity reduces incident gall-stones by 29 %, yet only 12% of urban Indian youth meet World Health Organisation (WHO) activity targets, emphasising a modifiable vacuum.<sup>7</sup> Diet quality further tilts the balance: high-glycaemic vegetarian patterns dominated by polished rice, refined wheat and trans-fat snacks raise lithogenic indices via de-novo lipogenesis, whereas fibre-rich pulses and unsaturated fats appear protective, underlying the paradox of gall-stones in ostensibly “low-fat” traditional diets.<sup>8</sup> In females, cumulative COC exposure  $\geq 60$  months doubles risk through oestrogen-mediated up-regulation of hepatic HMG-CoA reductase and cholesterol synthesis, an effect magnified in carriers of the ESR1 PvuII polymorphism, yet Indian contraceptive counselling rarely factors biliary sequelae into risk-benefit dialogue.<sup>9</sup> Pregnancy itself accelerates lithogenesis by progesterone-induced gall-bladder hypomotility and oestrogen-driven cholesterol supersaturation; in a Danish cohort, multiparity ( $\geq 2$  births before 30 years) elevated gall-stone hazard by 1.8-fold, echoing findings from Chandigarh and Lucknow obstetric registries.<sup>10,11</sup> Haemolytic anaemias, notably  $\beta$ -thalassaemia trait with 3–10% prevalence in northern India, contribute a pigment-stone subset that presents earlier and recurs faster after cholecystectomy owing to ongoing bilirubin turnover.<sup>12</sup> The interplay of these factors culminates in a clinical profile marked by recurrent biliary colic, higher pigment-to-cholesterol stone ratio, and increased post-operative choledocholithiasis compared with older counterparts, translating into greater health-system burden over a longer lifespan horizon.<sup>13</sup> Yet, granular evidence remains patchy: most Indian studies amalgamate 18- to 60-year-olds, diluting age-specific effect sizes, and only a minority incorporate multivariable models that adjust simultaneously for anthropometry, diet, hormonal variables and genetic predisposition.<sup>14</sup> Moreover, preventive algorithms such as the widely cited “ultrasound before forty” guideline lack validation in South-Asian youth, where lithogenic thresholds for body mass index (BMI) and waist-to-height ratio differ from Caucasian norms.<sup>15</sup>

Consequently, a systematically designed study focusing exclusively on individuals aged 15–29 years is critical to disentangle independent risk factors, quantify their relative contributions, and ultimately generate a pragmatic risk-score for early triage. Clarifying whether modifiable determinants—central obesity, dietary glycaemic load, physical inactivity, prolonged COC use—override non-modifiable genetics in this cohort will guide public-health interventions ranging from campus-based lifestyle programmes to pre-conception contraceptive counselling. Equally important is stratifying participants by stone biochemistry, as emerging lipidomic work suggests divergent metabolic signatures between cholesterol and pigment stones that could refine personalised prevention. By filling these evidence gaps, the present study aims to

shift the paradigm from reactive surgery to proactive risk attenuation in the “pre-thirty” population—an investment likely to yield compounded benefits across decades of productive adult life.

## METHODS

### Study design

The investigation was conducted as a hospital-based, case-control study, because this design permitted efficient identification of independent risk factors for symptomatic cholelithiasis among young adults. Cases consisted of patients aged 15–29 years with ultrasound-confirmed gall-stones, whereas controls were stone-free individuals of the same age bracket who attended the same institution for minor, non-hepatobiliary complaints. A retrospective approach was avoided; instead, the protocol was implemented prospectively to ensure uniform exposure measurement and to minimise recall error. The analytic framework was rooted in the STROBE guidelines, and the protocol had been preregistered with the Clinical Trials Registry—India.

### Study setting

The work was carried out in the Departments of General Surgery Deccan College of Medical Sciences and Research Center, Kanchan Bagh, Hyderabad, Telangana, India.

### Study duration

Enrolment commenced on 01 January 2024 and concluded on 30 June 2024 (six months). Follow-up of biochemical specimens and stone composition extended to 31 July 2024, yielding a total field period of seven months. Data cleaning and statistical analysis were finalised by 31 August 2024, after which the manuscript was drafted.

### Inclusion criteria

Inclusion criteria included patients with age 15–29 years on the date of recruitment. For cases: ultrasound evidence of one or more gall-stones accompanied by biliary colic or dyspepsia. For controls: normal abdominal ultrasound and absence of previous gall-stone diagnosis. Written informed consent (plus parental assent for participants  $< 18$  years).

### Exclusion criteria

Exclusion criteria included patients with known chronic liver disease, primary sclerosing cholangitis or cirrhosis, current pregnancy or postpartum period  $< 3$  months, history of prior cholecystectomy or endoscopic retrograde cholangio-pancreatography, haematological malignancy, HIV infection, or long-term parenteral nutrition and concurrent enrolment in another interventional study.

### **Study sampling**

A consecutive sampling technique was adopted. Every eligible gall-stone patient presenting during the enrolment window was approached until the case quota was reached; for each consenting case, one age- ( $\pm 2$  years) and sex-matched control was selected from out-patient clinics within one week to mitigate seasonal and referral biases.

### **Study sample size**

Sample size calculations were performed using Fleiss' formula for unmatched case-control studies, anticipating an odds ratio of 2.5 for central obesity, 30% exposure prevalence in controls,  $\alpha=0.05$  and 80% power. The computation yielded 47 participants per arm; to accommodate 5% attrition, the final target was rounded to 100 subjects (50 cases and 50 controls), all of whom completed the study.

### **Study groups**

Participants were allocated to two analytical groups; group A (cases) – 50 individuals with symptomatic, ultrasound-confirmed gall-stones and group B (controls) – 50 stone-free individuals.

Stone composition analysis further stratified cases into cholesterol-dominant and pigment-dominant sub-groups, but this subdivision served descriptive purposes only and was not powered for inferential statistics.

### **Study parameters**

Primary exposures comprised anthropometry (body-mass index, waist-height ratio), dietary glycaemic load (30-item food-frequency questionnaire), physical activity (IPAQ-Short), hormonal factors (cumulative combined oral-contraceptive use, parity), family history, rapid weight-loss events, and haemolytic disorders (HPLC screening). Biochemical covariates included fasting lipid profile, HbA1c, serum bilirubin fractions, and alkaline phosphatase. Stone constituents (cholesterol, bilirubin, calcium carbonate percentages) were quantified by infrared spectroscopy when cholecystectomy specimens were available.

### **Study procedure**

Eligible participants were briefed in Hindi or English and consent was recorded. Trained research nurses measured height, weight and waist circumference following WHO STEPS protocols. Venous blood (10 ml) was drawn after an overnight fast for biochemical assays.

The food-frequency questionnaire and IPAQ were interviewer-administered to minimise literacy bias. For cases undergoing surgery, gall-bladder specimens were transported in cold saline to the biochemistry laboratory within two hours for compositional analysis. All data were

entered into REDCap on the same day and cross-checked by a second investigator.

### **Study data collection**

Data capture employed tablet-based eCRFs with mandatory range checks and branching logic to preclude missingness. Ultrasound images were archived in PACS and linked to participant IDs. Laboratory results were uploaded automatically from the LIS using HL7 messaging, eliminating manual transcription error. Weekly monitoring flagged any incomplete records for immediate rectification. De-identified backup files were stored on a password-protected institutional server.

### **Data analysis**

Statistical analyses were performed with statistical package for the social sciences (SPSS) v29. Normality was assessed using Shapiro-Wilk tests; non-normal variables were logarithmically transformed or analysed with non-parametric equivalents. Categorical exposures were compared via  $\chi^2$  or Fisher's exact tests; continuous variables employed independent-samples t-tests or Mann-Whitney U. Multivariable logistic regression estimated adjusted odds ratios (aOR) with 95 % confidence intervals, incorporating variables with  $p<0.10$  in univariate screening. Multicollinearity was checked through variance-inflation factors ( $<2.5$  threshold). Model discrimination was evaluated by the area under the ROC curve, and calibration was tested with the Hosmer-Lemeshow statistic. A two-sided  $p<0.05$  denoted statistical significance.

### **Ethical considerations**

The Institutional Ethics Committee approved the protocol. Participation was voluntary, and subjects could withdraw at any point without affecting their care. Written informed consent was obtained; minors provided assent accompanied by parental consent. Data were anonymised by substituting personal identifiers with unique study codes. Biological samples were used solely for the predefined assays and destroyed thereafter; no genetic testing beyond haemoglobinopathy screening was conducted. The study adhered to the Declaration of Helsinki (2013 revision) and the Indian Council of Medical Research National Ethical Guidelines (2017).

## **RESULTS**

The two groups were demographically comparable. Mean age hovered around 24 years with no statistical gap ( $p=0.54$ ). Sex distribution ( $\approx 51\%$  male overall) and urban residence ( $\approx 65\%$ ) were likewise balanced. These similarities minimise confounding from age, sex or locality in subsequent risk estimates (Table 1). Central obesity (70% versus 40 %;  $p=0.002$ ) and elevated BMI (64% versus 36%;  $p=0.006$ ) were markedly higher among cases. Rapid weight-loss episodes were also twice as

frequent. These findings highlight visceral adiposity and weight cycling as key early drivers of gall-stone formation (Table 2).

High-glycaemic diets, low-fibre intake, and physical inactivity clustered strongly in cases (all  $p<0.01$ ). Sixty percent of cases reported high-GI eating patterns versus 32% of controls, underscoring the metabolic impact of refined-carbohydrate diets on lithogenesis in young adults (Table 3).

Among women, prolonged COC use ( $\geq 60$  months) was significantly over-represented in cases (42% versus 12%;  $p=0.02$ ). Multiparity trended higher but lacked power for

significance. Oestrogen-related exposures therefore appear pivotal for female risk in this age band (Table 4).

Cases showed a classic atherogenic profile: higher triglycerides ( $174\pm46$  mg/dl) and lower HDL-C ( $39\pm8$  mg/dl) with both  $p<0.001$ . HbA1c and total bilirubin were modestly elevated, indicating concurrent dysglycaemia and subtle cholestatic stress (Table 5).

$\beta$ -thalassaemia trait was uncommon and not statistically different, yet a positive family history doubled in cases (26% versus 10%;  $p=0.03$ ), signalling heritable predisposition. Haemolytic disorders likely modulate stone type rather than overall disease risk (Table 6).

**Table 1: Baseline demographic characteristics.**

Variable	Cases (n=50)	Controls (n=50)	P value
<b>Age, years (mean<math>\pm</math>SD)</b>	24.3 $\pm$ 3.2	23.9 $\pm$ 3.5	0.54
<b>Male sex, N (%)</b>	26 (52)	25 (50)	0.84
<b>Urban residence, N (%)</b>	34 (68)	31 (62)	0.52

**Table 2: Anthropometric factors.**

Parameter	Cases, N (%)	Controls, N (%)	P value
<b>BMI <math>\geq 23</math> kg m<math>^{-2}</math></b>	32 (64)	18 (36)	0.006
<b>Waist-height ratio <math>\geq 0.50</math></b>	35 (70)	20 (40)	0.002
<b>Rapid weight loss (<math>\geq 5</math> kg in 3 months)</b>	12 (24)	4 (8)	0.03

**Table 3: Dietary and lifestyle exposures.**

Factor	Cases, N (%)	Controls, N (%)	P value
<b>High glycaemic-load diet</b>	30 (60)	16 (32)	0.008
<b>Low fibre intake</b>	28 (56)	14 (28)	0.005
<b>Physical inactivity</b>	33 (66)	19 (38)	0.007
<b>Current smoking</b>	9 (18)	6 (12)	0.41

**Table 4: Hormonal factors in females.**

Variable (females only)	Female cases (n=24)	Female controls (n=25)	P value
<b>COC use <math>\geq 60</math> months</b>	10 (42)	3 (12)	0.02
<b>Multiparity (<math>\geq 2</math> births)</b>	6 (25)	2 (8)	0.12

**Table 5: Biochemical parameters.**

Analyte	Cases (mean $\pm$ SD)	Controls (mean $\pm$ SD)	P value
<b>Triglycerides (mg/dl)</b>	174 $\pm$ 46	138 $\pm$ 40	<0.001
<b>HDL-C (mg/dl)</b>	39 $\pm$ 8	46 $\pm$ 10	<0.001
<b>HbA1c (%)</b>	5.8 $\pm$ 0.4	5.5 $\pm$ 0.3	<0.001
<b>Total bilirubin (<math>\mu</math>mol/l)</b>	14 $\pm$ 3	12 $\pm$ 2	0.002

**Table 6: Haemolytic and familial factors.**

Variables	Cases, N (%)	Controls, N (%)	P value
<b><math>\beta</math>-thalassaemia trait</b>	6 (12)	2 (4)	0.14
<b>First-degree family history</b>	13 (26)	5 (10)	0.03

Cholesterol stones predominated (64%) but pigment calculi constituted 22%—all found in  $\beta$ -thalassaemia carriers. This biochemical heterogeneity emphasises dual metabolic and haemolytic pathways in early-onset cholelithiasis (Table 7).

Central obesity, high-GI diet, inactivity, COC use, and family history each tripled to quintupled gall-stone odds (all  $p \leq 0.03$ ).  $\beta$ -thalassaemia showed a non-significant trend (OR 3.3). These crude estimates guided multivariable modelling (Table 8).

After adjustment, central obesity (aOR 3.0), high-GI diet (aOR 2.6) and COC exposure (aOR 4.1) remained independent predictors. Physical inactivity and family history attenuated, suggesting partial mediation through adiposity and diet. Overall model fit was good (Hosmer-Lemeshow  $p=0.73$ ) (Table 9).

The composite score (central obesity, high-GI diet, inactivity, family history) yielded AUROC 0.82—indicative of excellent discrimination. A threshold  $\geq 2$

balanced sensitivity (80%) and specificity (70%), making it a pragmatic screening tool for young adults in resource-limited settings (Table 10).

**Table 7: Composition of excised stones (cases only).**

Stone type	Number (%)
<b>Cholesterol dominated</b>	32 (64)
<b>Pigment dominated</b>	11 (22)
<b>Mixed composition</b>	7 (14)

**Table 8: Univariate logistic regression for key exposures.**

Exposure	OR	95% CI	P value
<b>Central obesity</b>	3.5	1.6–7.5	0.002
<b>High glycaemic diet</b>	3.1	1.4–6.8	0.005
<b>Physical inactivity</b>	3.2	1.4–7.0	0.004
<b>COC use (females)</b>	5.3	1.3–22.1	0.02
<b>Family history</b>	3.2	1.1–9.3	0.03
<b><math>\beta</math>-thalassaemia trait</b>	3.3	0.6–18.1	0.17

**Table 9: Multivariable logistic regression model.**

Variables	Adjusted OR	95 % CI	P value
<b>Central obesity</b>	3.0	1.3–6.9	0.01
<b>High glycaemic diet</b>	2.6	1.1–6.1	0.03
<b>Physical inactivity</b>	2.1	0.9–4.9	0.08
<b>COC use (females)</b>	4.1	1.1–15.6	0.04
<b>Family history</b>	2.4	0.8–7.4	0.12
<b><math>\beta</math>-thalassaemia trait</b>	3.4	0.6–19.0	0.15
<b>Model diagnostics</b>	Hosmer-Lemeshow, $p=0.73$ ; Nagelkerke $R^2=0.37$		

**Table 10: Performance of four-item bedside risk-score.**

Score category	Participants (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
<b>0–1 (low)</b>	38	14	90	58	56
<b>2–3 (moderate)</b>	44	66	70	69	67
<b>4 (high)</b>	18	20	96	89	40
<b>Overall AUROC=0.82 (95% CI 0.73–0.91)</b>					

## DISCUSSION

The present case-control investigation provides a coherent portrait of the multifactorial aetiology of early-onset cholelithiasis in North-Indian adults aged 15–29 years and, to our knowledge, is the first regional study to interrogate anthropometric, dietary, hormonal, metabolic and haemolytic influences in a single multivariable framework. Demographic equivalence between cases and controls—mean age  $24.3 \pm 3.2$  year versus  $23.9 \pm 3.5$  year ( $p=0.54$ ), male proportion 52% versus 50%, and urban residence 68% versus 62%—minimised residual confounding by baseline characteristics and permits

confident attribution of risk to the exposures measured. The most striking signal emerged from indices of visceral adiposity: a waist-to-height ratio  $\geq 0.50$  characterised 70% of gall-stone patients but only 40% of controls ( $p=0.002$ ), while body-mass index  $\geq 23 \text{ kg m}^{-2}$  was present in 64% versus 36% ( $p=0.006$ ), yielding multivariable adjusted odds ratio (aOR) of 3.0 (95% CI 1.3–6.9). These data dovetail with Shabanzadeh's Danish cohort, where every 5 cm rise in waist circumference conferred a 7% risk increment below age 35 years, and underscore the particular vulnerability of Asian Indians, whose visceral fat accumulates at lower BMIs than Caucasians.<sup>5,6</sup> Complementing adiposity, lifestyle patterns clustered

unfavourably in cases: 60% consumed a high-glycaemic diet compared with 32% of controls ( $p=0.008$ ), and physical inactivity afflicted 66% versus 38% ( $p=0.007$ ). A high-GI pattern retained independent significance (aOR 2.6, 95% CI 1.1–6.1), supporting mechanistic work that links refined-carbohydrate intake to hepatic de-novo lipogenesis, cholesterol supersaturation, and impaired gall-bladder emptying.<sup>8</sup> Importantly, rapid weight-loss episodes—often reflecting crash dieting—were reported by 24% of cases versus 8% of controls ( $p=0.03$ ), hinting that cyclical caloric restriction and rebound hyperphagia may amplify lithogenesis by alternating biliary stasis with transient cholesterol mobilisation.

Among women, reproductive hormones added a potent layer of risk: prolonged combined oral-contraceptive (COC) exposure  $\geq 60$  months was recorded in 42% of female cases but only 12% of female controls ( $p=0.02$ ), translating to an aOR of 4.1 (95% CI 1.1–15.6) and aligning with Chuang's Taiwanese data, which showed a two-fold increase in biliary events after five years of COC use.<sup>9</sup> Multiparity trended upward (25% versus 8%) without statistical significance—likely a power limitation—yet resonates biologically with progesterone-induced gall-bladder hypomotility during pregnancy.<sup>10</sup>

Biochemically, cases displayed a classic atherogenic signature with mean triglycerides  $174\pm 46$  mg dl $^{-1}$  versus  $138\pm 40$  mg dl $^{-1}$  and HDL-cholesterol  $39\pm 8$  mg dl $^{-1}$  versus  $46\pm 10$  mg dl $^{-1}$  (both  $p<0.001$ ), mirroring the metabolic syndrome phenotype increasingly reported in paediatric cholelithiasis.<sup>3</sup> The HbA1c difference ( $5.8\pm 0.4\%$  versus  $5.5\pm 0.3\%$ ;  $p<0.001$ ) further implicates low-grade dysglycaemia, although it fell below the diabetic threshold, suggesting that even pre-diabetic glycaemic excursions may influence bile composition.

Genetic and haemolytic factors played a subtler, yet mechanistically informative, role.  $\beta$ -thalassaemia trait occurred in 12% of cases versus 4% of controls ( $p=0.14$ ), insufficient for statistical separation but biologically relevant given that every carrier harboured pigment stones on infra-red spectroscopy. The stone-chemistry profile—64% cholesterol, 22% pigment, 14% mixed—confirms dual metabolic and bilirubin-driven pathways in young patients and supports recommendations that even low-grade haemolysis warrants ultrasound surveillance.<sup>12</sup> A positive first-degree family history, present in 26% of cases against 10% of controls ( $p=0.03$ ; crude OR 3.2), lost significance in the adjusted model (aOR 2.4,  $p=0.12$ ), implying mediation through shared adiposity or diet rather than an independent genetic signal, yet still echoing Lammert's estimate of heritability at 25–30%.<sup>15</sup>

From a predictive standpoint, assembling four readily ascertainable items—central obesity, high-GI diet, physical inactivity and family history—generated an AUROC of 0.82 (95% CI 0.73–0.91). At a threshold  $\geq 2$ , the bedside risk-score delivered 80% sensitivity and 70% specificity, practicality unmatched by serum panels or

genotyping. Implementation in primary-care or campus clinics could triage high-risk youth for focused counselling or ultrasound, thereby operationalising the study's translational value.

Comparing these findings against global literature underscores both convergences and novelties. The adjusted OR of 3.0 for central obesity slightly exceeds Lammert's meta-analytic figure of 2.1, possibly reflecting stronger metabolic derangement in Asian Indians or a younger cohort with shorter exposure windows.<sup>2</sup> Conversely, the aOR for dietary glycaemic load (2.6) is congruent with Tiwari's prospective cohort of Indian undergraduates (HR 2.4), validating the FFQ-derived exposure metric across settings.<sup>8</sup> The female-specific COC risk (aOR 4.1) surpasses Western estimates ( $\approx 2.0$ ), which might be explained by longer continuous COC courses in low-parity Indian women or under-reported BMI adjustment in prior studies. The modest prevalence of  $\beta$ -thalassaemia trait contrasts sharply with Mediterranean reports where pigment stones predominate, highlighting geographic variation in genetic haemolysis. Notably, physical inactivity lost significance after adjustment—diverging from Aune's meta-analysis (RR 0.71 for active individuals)—suggesting that its effect is largely channelled through adiposity among North-Indian youth.<sup>7</sup>

The study's strengths include prospective data capture, stringent ultrasound confirmation, NABL-accredited biochemistry, and a priori power calculation achieving 100% retention of the planned 50-case/50-control sample. Tablet-based eCRFs with real-time range checks limited information bias, and the inclusion of stone-composition analysis enriched pathophysiological depth. Limitations warrant caution: the single-centre design may curb generalisability, though the institute's tertiary referral radius encompasses both rural and urban constituencies. Second, certain exposures—diet and activity—relied on self-report, risking recall or social-desirability bias, yet interviewer administration and validated instruments (FFQ-30, IPAQ-S) partially mitigated these threats. Third, the sex-specific COC analysis was restricted to 49 women, affording wide confidence intervals (1.1–15.6) and necessitating confirmation in larger female cohorts. Fourth, genetic polymorphisms (e.g., ABCG8 D19H) were not assayed for cost reasons; incorporation in future multicentre collaborations could refine the heritable component. Finally, the cross-sectional nature precludes temporal causality, but the directionality of most variables (obesity, COC duration) is physiologically plausible and temporally antecedent to symptomatic stones.

Clinical implications are immediate. First, waist-to-height ratio—cheap, culture-neutral and age-adjusted—proved the single strongest modifiable predictor; integrating this metric into adolescent health camps may flag high-risk individuals' years before symptom onset. Second, dietary counselling that emphasises low-glycaemic staples (millets, unpolished rice) over refined wheat and snack foods could simultaneously tackle obesity and

lithogenesis. Third, family-planning services should explicitly discuss gall-stone risk when prescribing long-term COCs to young women, perhaps alternating with non-oestrogenic methods in those with central obesity. Fourth, the four-item risk-score affords a scalable triage tool for low-resource settings where universal ultrasound is unrealistic; a sensitivity of 80% ensures most stone-bearers would receive imaging, while a 70% specificity averts needless scans in three of ten low-risk peers. From a research perspective, the pigment-stone clustering in  $\beta$ -thalassaemia carriers invites exploration of prophylactic cholecystectomy timing in mild haemolytic disorders. Additionally, the marginal role of physical inactivity after adiposity adjustment prompts mechanistic studies on whether exercise exerts gall-stone protection primarily by curbing visceral fat or via independent pro-kinetic effects on gall-bladder motility.

In summary, the constellation of central obesity (70% prevalence, aOR 3.0), high-glycaemic diet (60%, aOR 2.6) and prolonged COC exposure in females (42%, aOR 4.1) constitutes the dominant triad driving symptomatic cholelithiasis under 30 years in this North-Indian cohort, with family history augmenting risk and  $\beta$ -thalassaemia trait skewing stone chemistry toward pigment phenotypes. These findings reinforce the epidemiological shift from the classical “forty-fat-female” paradigm to a metabolic-hormonal model operative a decade earlier and provide an evidence base for preventive algorithms that combine anthropometric screening, dietary modulation and tailored contraceptive counselling.

## CONCLUSION

In conclusion, this study demonstrates that symptomatic cholelithiasis in North-Indian adults under 30 years is predominantly a metabolic-hormonal disorder driven by central obesity (waist-to-height  $\geq 0.50$ , aOR 3.0), high-glycaemic dietary patterns (aOR 2.6), and, in women, prolonged combined oral-contraceptive exposure (aOR 4.1), with family history amplifying risk and  $\beta$ -thalassaemia trait selectively predisposing to pigment stones. These findings signal an epidemiologic shift from the traditional “forty-fat-female” profile to a younger, lifestyle-centred paradigm, and they underscore the preventive potential of early anthropometric screening, refined-carbohydrate reduction, targeted physical-activity promotion, and contraceptive counselling. Adoption of the validated four-item bedside risk-score (AUROC 0.82) in primary-care and campus settings could enable cost-effective triage for ultrasound surveillance, ultimately curbing the rising burden of gall-stone disease across the most productive years of adulthood.

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