The relationship between serum lipid levels and colorectal serrated lesions: A systematic review and meta-analysis

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Objective: To clarify the relationship between colorectal serrated lesions and serum lipid levels, and provide a scientific basis for the identification and early clinical prevention and treatment of populations that are at risk for colorectal serrated lesions.

Methods: Studies comparing serum lipid levels in patients with colorectal serrated lesions and controls were searched in PubMed, Embase, Web of Science, the Cochrane Library, China Biomedical Literature Database, CNKI, Wanfang Database, and VIP Database. Relevant literature was screened according to the inclusion and exclusion criteria. The mean and standard deviation of the serum lipid levels in patients and controls were extracted from the included literature. The combined weighted mean difference (WMD) and 95% confidence intervals (CIs) were calculated using Review Manager 5.0 software to evaluate the relationship between serum lipid levels and colorectal serrated lesions. Publication bias of the included studies was evaluated by the Egger test.

Results: Twenty-three studies were included, comprising 2,063 patients and 63,909 controls. The serum high-density lipoprotein cholesterol (HDL-C) levels in the case group was significantly lower than in the control group (WMD = −0.122 mmol/L, 95% CI: 0.170−0.073). Total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and serum triglyceride levels in the case group were significantly higher than in the control group, and the WMDs were 0.180 mmol/L (95% CI: 0.061−0.299), 0.155 mmol/L (95% CI: 0.038−0.273), and 0.241 mmol/L (95% CI: 0.181−0.302), respectively.

Conclusion: Colorectal serrated lesions may be related to blood lipid levels. Hyperlipidemia might be a risk factor for colorectal serrated lesions.

KEYWORDS
colorectal polyp, sessile serrated adenoma, meta-analysis, lipid, colorectal serrated lesions
Lipid levels may be associated with the risk of colorectal serrated lesions, but the results of existing studies are inconsistent. Tabuchi et al. (Tabuchi et al., 2006) found that there were no significant differences in serum total cholesterol (TC) and triglyceride (TG) between patients with colorectal serrated lesions and those without serrated lesions. Pyo et al. (Pyo et al., 2018) found that the serum TG level was an independent risk factor for TSA. A study by Fliss-Isakov et al. suggested that serum high-density lipoprotein cholesterol (HDL-C) was significantly decreased in female patients with colorectal serrated lesions (Fliss-Isakov et al., 2017). Therefore, the relationship between colorectal serrated lesions and the level of blood lipids needs evidence-based analysis. The present study was a systematic review and meta-analysis of the relationship between colorectal serrated lesions and serum lipid levels. It provided reliable evidence and a scientific basis for identifying high risk populations with colorectal serrated lesions and the early clinical prevention and treatment of CRC.

**Methods**

**Search strategy**

We conducted the standard method according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Two independent authors (XW and YZ) searched PubMed, Embase, Web of Science, the Cochrane Library, China Biomedical Literature Database, CNKI, Wanfang Database, and VIP Database for related studies comparing serum lipid levels in controls and patients suffering from colorectal serrated lesions. The keywords included lipoprotein, cholesterol, triglyceride, hyperlipidemia, dyslipidemia, intestinal polyph, adenomatous polyph, sessile serrated adenoma, sessile serrated polyph, and traditional serrated adenoma. Boolean logic operator “OR” was used to connect the search terms related to blood lipid level and the search terms related to serrated lesions, while “AND” was used to connect the search terms related to blood lipid level and serrated lesions. For example, the search strategy in the PubMed database was (“cholesterol” [Title/Abstract] OR “lipoprotein” [Title/Abstract] OR “triglyceride” [Title/Abstract] OR “hyperlipidemia” [Title/Abstract] OR “dyslipidemia” [Title/Abstract]) AND (“intestinal polyph” [Title/Abstract]) OR “adenomatous polyph” [Title/Abstract] OR “sessile serrated adenoma” [Title/Abstract] OR “sessile serrated polyph” [Title/Abstract] OR “traditional serrated adenoma” [Title/Abstract]). According to the different requirements of the different databases, the connectives were adjusted. In addition, manually retrieved references from the review articles and meta-analyses to supplement the literature were included in this study.
Inclusion criteria and exclusion criteria

Inclusion criteria were the following: 1) the subject was human; 2) the patients were diagnosed with polyps or adenomas of the colon and/or rectum; and 3) serum lipid levels included at least one of TC, TG, HDL-C, and low-density lipoprotein cholesterol (LDL-C).

Exclusion criteria were the following: 1) the published literature had been repeated or had a potential duplicate publication; 2) the article type was a review, conference abstract, editorial, note, or case report; 3) the language was not Chinese or English; 4) there was no case group or control group; 5) the results did not contain blood lipid concentration or had missing sample size data; and 6) the data for serrated lesions were not listed separately, or the data for non-serrated lesions could not be removed.

Two independent authors (XW and YZ) screened all the literature included in this study by title, abstract, and full text. The literature meeting the inclusion and exclusion criteria were finally determined. A third author (RZ) made the final decision for any discrepancy.

Data extraction and literature quality evaluation

Data were extracted independently by the two authors (XW and YZ), and conflicts were resolved by the third author (RZ). The extracted data included the first author, year of publication, the state of the author, research type, colonoscopy time, type of serrated lesion, definition of the control group, a family history of CRC and colorectal polyps, history of inflammatory bowel disease, history of colorectal polyp, history of CRC, history of colorectal surgery, lipid-lowering drug-taking, the odds ratio (OR) of smoking and drinking, and the age and sex of the subjects. In addition, the mean, median, and standard deviation of serum lipid levels (TC, TG, HDL-C, and LDL-C) in the case and control groups were extracted. The mean variance estimation (hkbu.eu.hk) was used to transform the median data into mean and standard deviation.

Although some studies divided the subjects into a case group and control group, the temporal sequence of the colonoscopy and lipid level measurement was not clearly clarified. An article was classified as a cohort study when it investigated the incidence or prevalence of disease based on population characteristics or measurement parameters, while articles were classified as a case-control study when they grouped subjects before measuring the lipid levels. Otherwise, articles were classified as a cross-sectional study.

The Newcastle-Ottawa scale (NOS) was used to evaluate the quality of a case-control study or a cohort study. When the score was >7, the study was considered to be of high quality. The Agency for Healthcare Research and Quality (AHRQ) scale was used to evaluate the quality of the cross-sectional studies. When the score was >8, the study was considered to be of high quality.

Statistical analysis

The extracted data were transformed. Lipid unit conversion (medsci.cn) was used to convert the lipid concentration units to mmol/L. The combined means and SDs (cuhk.edu.HK) were used to merge each group's mean and standard deviation.
| First author and year of publication | Country | Design          | Year(s) of colonoscopy | Sample size (case/control) | Age (year) | Male (%) | Pathologic types | Definition of controls (Polyp-free) | Serum lipids | confounding factor for adjustment | Quality score |
|--------------------------------------|---------|-----------------|-------------------------|-----------------------------|------------|----------|-----------------|------------------------------------|--------------|-------------------------------|---------------|
| Ding et al. (2015)                   | China   | Case-control    | 2014–2014               | 31/726                      | 48.04 ± 7.97 | 67.24    | hyperplastic polyps | Normal                            | TC, TG, HDL-C, LDL-C | None                          | 5             |
| Zhu (2017)                           | China   | Case-control    | 2015–2016               | 40/318                      | 50.80 ± 14.25* | 40.88*   | TSA                          | Normal                            | TG            | None                          | 5             |
| Wang et al. (2005)                   | China   | Cross-sectional | 2001–2002               | 138/4122                    | 48.53 ± 11.47 | 54.3     | hyperplastic polyps | Normal                            | TG, HDL-C    | None                          | 3             |
| Liu et al. (2010)                    | China   | Cross-sectional | 2006–2008               | 341/3062                    | 48.53 ± 11.47 | 55.19    | hyperplastic polyps | Normal                            | TC, TG, HDL-C | AGE                          | 7             |
| Fliss-Isakov et al. (2017)           | Israel  | Case-control    | 2010–2015               | 75/407                      | 57.71 ± 6.71 | 46.27    | hyperplastic polyps, TSA | Normal                            | TG, HDL-C    | AGE, SEX                       | 7             |
| Xie et al. (2019)                    | China   | Cohort          | 2015–2017               | 14/48                       | 44.81 ± 11.17* | 50*      | hyperplastic polyps | Normal                            | TC, TG, HDL-C, LDL-C | None                          | 6             |
| Pyo et al. (2018)                    | Korea   | Case-control    | 2002–2012               | 395/34730                   | 48.55 ± 9.31 | 50.35*   | SSA/P, TSA                   | Normal                            | TC, TG, HDL-C, LDL-C | SEX                          | 5             |
| Anderson et al. (2011)               | USA     | Case-control    | 2007–2010               | 90/200                      | N           | 39.66    | SSA/P                      | Normal                            | TC, TG        | None                          | 5             |
| Kim et al. (2019)                    | Korea   | Cross-sectional | 2012–2017               | 423/18277                   | 47.03 ± 10.61 | 40.86    | SSA/P, TSA                   | Normal                            | TC, TG, HDL-C, LDL-C | SEX                          | 5             |
| Wen and Wang (2018)                  | China   | Case-control    | 2016–2017               | 32/50                       | 46.7*        | 54*      | hyperplastic polyps | Normal                            | TC, TG, HDL-C, LDL-C | AGE, SEX                      | 7             |
| Zheng et al. (2018)                  | China   | Case-control    | 2016–2018               | 5/60                        | 54.37 ± 12.96* | 38.33*   | hyperplastic polyps | Normal                            | TC, TG, HDL-C, LDL-C | None                          | 5             |
| Lin et al. (2014)                    | China   | Case-control    | 2011–2012               | 33/138                      | 49.3 ± 12.4* | 61.39*   | hyperplastic polyps | No polyps                          | TC, TG, LDL-C | AGE, SEX                       | 7             |
| Cao et al. (2015)                    | China   | Case-control    | 2012–2015               | 59/153                      | 62.3*        | 54.9*    | hyperplastic polyps | Normal                            | TC, TG, LDL-C | AGE, SEX                       | 7             |
| Yang et al. (2019)                   | China   | Case-control    | 2014–2015               | 81/628                      | 45.34 ± 10.05 | 61.92    | hyperplastic polyps | Normal                            | TC, TG, LDL-C | None                          | 5             |
| Zhang (2015)                         | China   | Case-control    | 2011–2014               | 25/120                      | 50 ± 12*     | 63.33*   | hyperplastic polyps | No polyps                          | TC, TG, LDL-C | AGE, SEX                       | 7             |
| Zhou et al. (2015)                   | China   | Case-control    | 2012–2014               | 30/112                      | 57 ± 14*     | 57.14*   | hyperplastic polyps | No polyps                          | TC, TG, LDL-C | AGE, SEX                       | 7             |
| Pan (2019)                           | China   | Case-control    | 2018–2018               | 11/104                      | 54.06 ± 19.57* | 59.62*   | hyperplastic polyps | Normal                            | TC, TG, HDL-C, LDL-C | AGE, SEX                      | 7             |
| Yang (2021)                          | China   | Case-control    | 2019–2020               | 19/82                       | 60.42 ± 3.43* | 62.2*    | hyperplastic polyps | Normal                            | TC, TG, HDL-C, LDL-C | None                          | 5             |
| Dui et al. (2017)                    | China   | Case-control    | 2012–2015               | 100/103                     | 46.55 ± 12.79 | 61.58    | hyperplastic polyps, SSA/ P, TSA | Normal                            | TC, TG, HDL-C, LDL-C | None                          | 5             |
| Ning (2018)                          | China   | Case-control    | 2016–2017               | 26/177                      | 58.31 ± 12.22* | 59.32*   | hyperplastic polyps | Normal                            | TC, TG, HDL-C, LDL-C | AGE, SEX                      | 7             |
| Wu et al. (2021)                     | China   | Case-control    | 2019–2020               | 34/80                       | 46.8 ± 13.4* | 43.75*   | hyperplastic polyps | Normal                            | TC, TG, HDL-C, LDL-C | None                          | 5             |
| Zhang and Li (2014)                  | China   | Case-control    | 2013–2014               | 45/164                      | 46.7 ± 9.8*  | 62.8*    | hyperplastic polyps | No polyps                          | TC, TG, HDL-C, LDL-C | AGE, SEX                      | 7             |
| Gong (2018)                          | China   | Case-control    | 2017–2018               | 16/48                       | 44.81 ± 11.17* | 50*      | hyperplastic polyps | Normal                            | TC, TG, HDL-C, LDL-C | None                          | 5             |

*Data related to controls only.
Review Manager 5.0 was used for statistical analysis. Weighted mean differences (WMDs) and 95% confidence intervals (CIs) were computed. I-squared ($I^2$) was used to assess the heterogeneity of the results. When $I^2 < 50\%$, a fixed-effect model was used for the meta-analysis. When $50\% \leq I^2 < 75\%$, a random-effect model was used for the meta-analysis. When $I^2 \geq 75\%$, the source of the heterogeneity should be analyzed. Subgroup analyses and meta-regression analyses were performed to identify the potential sources of the heterogeneity. The moderators selected for this study included the subjects’ baseline characteristics and pathological types, risk factors for colorectal serrated lesions, factors influencing the diagnosis of colorectal serrated lesions, and factors influencing lipid levels. Sensitivity analysis was performed by one-by-one elimination to assess the stability of the results. The Egger test was used to evaluate the publication bias.

**Results**

**Literature selection and exclusion**

A total of 7,888 articles were searched out. There were 2,913 repeat studies. Then, 4,590 articles were excluded according to the title and abstract, and 362 articles were excluded after reading the full text. Finally, 23 articles were included. The flowchart of the literature selection and exclusion are shown in Figure 1.

**Characteristics of the included literatures**

The characteristics of the included literature are shown in Table 1. A total of 65,972 subjects were included, including 2,063 cases with colorectal serrated lesions and 63,909 controls. Most of the subjects were from Asia, and most of the serrated lesions were hyperplastic polyps. The 23 studies included 19 case-control studies, one cohort study, and three cross-sectional studies.

As shown in Figure 2, 17 studies reported an association between serum HDL-C and colorectal serrated lesions in a population of 1,735 patients and 62,352 controls. The meta-analysis showed that the serum HDL-C level was lower in patients with colorectal serrated lesions than in the controls (WMD = $-0.122$ mmol/L, 95% CI = $-0.170$ to $-0.073$, $p < 0.001$). Because the heterogeneity test result showed $I^2 = 85.6\%$ ($p < 0.001$), suggesting high heterogeneity, a meta-regression and subgroup analysis were performed to explore the source of the heterogeneity. The results suggested that the undefined healthy subjects in the control group were the main source of the heterogeneity. Fifteen studies showed lower HDL-C levels in the case group, suggesting that the population with colorectal serrated lesions may have had lower HDL-C levels (Table 2).

As shown in Figure 3, 18 studies reported an association between serum LDL-C and colorectal serrated lesions in a population of 1,735 patients and 62,352 controls. The meta-analysis showed that the serum LDL-C level was higher in patients with colorectal serrated lesions than in the controls (WMD = $0.155$ mmol/L, 95% CI = $0.038$ to $0.273$, $p = 0.010$). The result of the heterogeneity test showed $I^2 = 78.4\%$ ($p < 0.001$),
TABLE 2 Heterogeneity source analyses for mean difference of HDL-C.

| Variables                              | NO. of studies | WMD(95%CI) (mmol/L) | Heterogeneity | Meta-regression p |
|-----------------------------------------|----------------|---------------------|---------------|-------------------|
|                                         |                |                     | $I^2$ (%)      | $p$               |
| Chinese                                 |                |                     |               |                   |
| Yes                                     | 14             | -0.138 (-0.201, -0.075) | 86.1          | <0.001 | 0.623 |
| No                                      | 3              | -0.082 (-0.148, -0.015) | 82.0          | 0.004  |       |
| Case-control study                      |                |                     |               |                   |
| Yes                                     | 13             | -0.150 (-0.228, -0.073) | 88.6          | <0.001 | 0.540 |
| No                                      | 4              | -0.086 (-0.118, -0.054) | 45.0          | 0.142  |       |
| Hyperplastic polyps                     |                |                     |               |                   |
| Yes                                     | 14             | -0.148 (-0.211, -0.085) | 86.5          | <0.001 | 0.393 |
| No                                      | 3              | -0.045 (-0.072, -0.019) | 0.0           | 0.890  |       |
| Normal control                          |                |                     |               |                   |
| Yes                                     | 15             | -0.096 (-0.127, -0.064) | 64.0          | <0.001 | 0.166 |
| No                                      | 2              | -0.367 (-1.170, 0.437) | 98.6          | <0.001 |       |
| Excluded subjects with family history of CRC |    |                     |               |                   |
| Yes                                     | 4              | -0.071 (-0.113, -0.028) | 61.5          | 0.050  | 0.612 |
| No                                      | 13             | -0.143 (-0.213, -0.074) | 87.3          | <0.001 |       |
| Excluded subjects with family history of CRA |            |                     |               |                   |
| Yes                                     | 3              | -0.103 (-0.170, -0.036) | 45.5          | 0.160  | 0.840 |
| No                                      | 14             | -0.127 (-0.184, -0.069) | 87.9          | <0.001 |       |
| Excluded subjects with history of inflammatory bowel | |                     |               |                   |
| Yes                                     | 12             | -0.142 (-0.210, -0.075) | 89.1          | <0.001 | 0.527 |
| No                                      | 5              | -0.091 (-0.144, -0.037) | 59.0          | 0.045  |       |
| Excluded subjects with history of CRA   |                |                     |               |                   |
| Yes                                     | 7              | -0.109 (-0.156, -0.062) | 71.8          | 0.002  | 0.865 |
| No                                      | 10             | -0.130 (-0.218, -0.042) | 90.0          | <0.001 |       |
| Excluded subjects with history of CRC   |                |                     |               |                   |
| Yes                                     | 16             | -0.131 (-0.184, -0.078) | 85.5          | <0.001 | 0.613 |
| No                                      | 1              | -0.040 (-0.076, -0.004) | —             | —      |       |
| Excluded subjects with history of colorectal surgery | |                     |               |                   |
| Yes                                     | 3              | -0.083 (-0.125, -0.040) | 0.0           | 0.843  | 0.558 |
| No                                      | 14             | -0.135 (-0.192, -0.077) | 88.3          | <0.001 |       |
| Excluded subjects taking lipid-lowering drugs |          |                     |               |                   |
| Yes                                     | 10             | -0.176 (0.277, -0.076) | 90.2          | <0.001 | 0.364 |
| No                                      | 7              | -0.083 (-0.118, -0.048) | 60.1          | 0.020  |       |
| The OR of smoking >1                    |                |                     |               |                   |
| Yes                                     | 4              | -0.076 (-0.130, -0.023) | 73.1          | 0.011  | 0.504 |
| No                                      | 13             | -0.146 (-0.214, -0.079) | 87.1          | <0.001 |       |
| The OR of drinking >1                   |                |                     |               |                   |
| Yes                                     | 3              | -0.045 (-0.072, -0.019) | 0.0           | 0.890  | 0.393 |
| No                                      | 14             | -0.148 (-0.211, -0.085) | 86.5          | <0.001 |       |
| Comparable in age                       |                |                     |               |                   |
| Yes                                     | 7              | -0.079 (-0.118, -0.039) | 92.2          | <0.001 | 0.397 |
| No                                      | 10             | -0.192 (-0.309, -0.075) | 65.9          | 0.002  |       |
| Comparable in sex                       |                |                     |               |                   |
| Yes                                     | 8              | -0.160 (-0.255, -0.065) | 92.3          | <0.001 | 0.647 |
| No                                      | 9              | -0.094 (-0.135, -0.052) | 58.9          | 0.013  |       |
suggesting high heterogeneity. The results of a meta-regression and subgroup analysis suggested that the undefined healthy subjects in the control group and the unexcluded subjects with a family history of CRC were the main source of the heterogeneity. Thirteen studies showed higher LDL-C levels in the case group, suggesting that the population with colorectal serrated lesions may have had higher LDL-C levels (Table 3).

As shown in Figure 4, 20 studies reported an association between serum TC and colorectal serrated lesions in a population of 1,810 patients and 59,062 controls. The meta-analysis showed that the serum TC level was higher in patients with colorectal serrated lesions than in controls (WMD = 0.180 mmol/L, 95% CI = 0.061–0.299, p < 0.001). The result of the heterogeneity test showed $I^2 = 78.3\%$ (p < 0.001), suggesting high heterogeneity. The meta-regression and subgroup analysis suggested that the unexcluded subjects taking lipid-lowering drugs and other drugs that affect blood lipid levels were the main source of the heterogeneity. Sixteen studies showed higher TC levels in the case group, suggesting that the population with colorectal serrated lesions may have had higher TC levels (Table 4).

As shown in Figure 5, 23 studies reported an association between serum TG and colorectal serrated lesions in a population of 2,063 patients and 63,909 controls. Since the result of the heterogeneity test showed $I^2 = 57.9\%$ (p < 0.001), a random effect model was used for the meta-analysis. The meta-analysis showed that the serum TG level was higher in patients with colorectal serrated lesions than in the controls (WMD = 0.241 mmol/L, 95% CI = 0.181–0.302, p < 0.001).

**Sensitivity analysis and publication bias**

The sensitivity analysis results showed good stability of the meta-analysis results on the relationship between the four blood lipid indexes (TC, TG, HDL-C and LDL-C) and colorectal serrated lesions (Table 5). The Egger test showed that there was no obvious publication bias in the literature included in the meta-analysis on the relationship between TC, HDL-C, LDL-C ($p = 0.108$) and colorectal serrated lesions. However, there might be a publication bias in the literature included in the meta-analysis of TG and colorectal serrated lesions (Table 6).

**Discussion**

CRC, whose morbidity and mortality are high, can be a serious threat to human health. Colorectal adenomas are generally considered to be precancerous lesions of CRC. The early detection, diagnosis, and treatment of colorectal serrated lesions can effectively prevent CRC occurrence. However, colorectal serrated lesions are difficult to detect by fecal occult blood tests and CT colonic imaging because they do not easily bleed, are often sessile, and are flatter than traditional adenomas. In recent years, colorectal serrated lesions have gradually become an emerging research focus, and more attention has been paid to these lesions. Although colonoscopy can intuitively examine intestinal lesions, the fuzzy boundary and flat shape of serrated lesions increase the difficulty and false-negative rate.
| Variables                                      | NO. of studies | WMD(95%CI) (mmol/L) | Heterogeneity | Meta-regression p |
|-----------------------------------------------|----------------|---------------------|---------------|------------------|
|                                              |                | F(%) | p     |                  |
|                                              |                |      |       |                  |
| Chinese                                      |                |      |       |                  |
| Yes                                          | 16             | 0.193 (0.030, 0.355)| 77.5          | <0.001           | 0.438 |
| No                                           | 2              | 0.025 (−0.063, 0.114)| 58.7          | 0.120            |       |
| Case-control study                           |                |      |       |                  |
| Yes                                          | 16             | 0.160 (0.023, 0.297)| 77.7          | <0.001           | 0.972 |
| No                                           | 2              | 0.196 (−0.315, 0.706)| 80.3          | 0.024            |       |
| Hyperplastic polyps                          |                |      |       |                  |
| Yes                                          | 15             | 0.194 (0.019, 0.369)| 79.0          | <0.001           | 0.543 |
| No                                           | 3              | 0.042 (−0.047, 0.132)| 49.8          | 0.136            |       |
| Normal control                               |                |      |       |                  |
| Yes                                          | 14             | 0.158 (0.062, 0.255)| 56.9          | 0.004            | 0.288 |
| No                                           | 4              | 0.005 (−0.526, 0.529)| 93.8          | <0.001           |       |
| Excluded subjects with family history of CRC |                |      |       |                  |
| Yes                                          | 4              | 0.077 (−0.042, 0.197)| 63.6          | 0.041            | 0.878 |
| No                                           | 14             | 0.176 (−0.004, 0.356)| 79.7          | <0.001           |       |
| Excluded subjects with family history of CRA |                |      |       |                  |
| Yes                                          | 3              | 0.246 (0.067, 0.424)| 0.0           | 0.398            | 0.521 |
| No                                           | 15             | 0.134 (0.003, 0.265)| 80.9          | <0.001           |       |
| Excluded subjects with history of inflammatory bowel |            |      |       |                  |
| Yes                                          | 13             | 0.126 (−0.040, 0.291)| 83.0          | <0.001           | 0.394 |
| No                                           | 5              | 0.209 (0.043, 0.376)| 44.9          | 0.123            |       |
| Excluded subjects with history of CRA         |                |      |       |                  |
| Yes                                          | 6              | 0.168 (0.001, 0.335)| 71.0          | 0.004            | 0.942 |
| No                                           | 12             | 0.132 (−0.060, 0.323)| 80.9          | <0.001           |       |
| Excluded subjects with history of CRC         |                |      |       |                  |
| Yes                                          | 17             | 0.171 (0.028, 0.313)| 79.6          | <0.001           | 0.724 |
| No                                           | 1              | 0.070 (−0.009, 0.149)| _             | _                |       |
| Excluded subjects with history of colorectal surgery |      |      |       |                  |
| Yes                                          | 3              | 0.313 (0.112, 0.515)| 0.0           | 0.430            | 0.289 |
| No                                           | 15             | 0.123 (−0.004, 0.251)| 80.5          | <0.001           |       |
| Excluded subjects taking lipid-lowering drugs |                |      |       |                  |
| Yes                                          | 12             | 0.215 (−0.004, 0.433)| 81.2          | <0.001           | 0.512 |
| No                                           | 6              | 0.059 (−0.033, 0.152)| 50.7          | 0.072            |       |
| The OR of smoking >1                         |                |      |       |                  |
| Yes                                          | 4              | 0.024 (−0.061, 0.109)| 45.0          | 0.141            | 0.277 |
| No                                           | 14             | 0.221 (0.037, 0.405)| 78.0          | <0.001           |       |
| The OR of drinking >1                        |                |      |       |                  |
| Yes                                          | 4              | 0.024 (−0.061, 0.109)| 45.0          | 0.141            | 0.277 |
| No                                           | 14             | 0.221 (0.037, 0.405)| 78.0          | <0.001           |       |
| Comparable in age                            |                |      |       |                  |
| Yes                                          | 8              | 0.146 (−0.113, 0.404)| 86.2          | <0.001           | 0.813 |
| No                                           | 10             | 0.117 (0.007, 0.228)| 58.3          | 0.010            |       |
| Comparable in sex                            |                |      |       |                  |
| Yes                                          | 10             | 0.114 (−0.038, 0.267)| 85.4          | <0.001           | 0.417 |
| No                                           | 8              | 0.224 (0.033, 0.415)| 55.4          | 0.028            |       |
by microscopic detection. Therefore, identifying populations at high risk for colorectal serrated lesions is of great significance.

Obesity, dietary fat, and total energy intake, which are closely related to hyperlipemia, have been proven to be associated with an increased risk of colorectal serrated lesions. Moreover, at present, many scholars regard dyslipidemia as one of the potential risk factors for colorectal cancer. Macarie M et al. found increased triglycerides levels were associated with the risk of sessile serrated lesions, which is important in the pathogenesis of colorectal carcinoma (Macarie et al., 2020). The relationship also had been proved in Japanese men (Tabuchi et al., 2006). The mechanisms include the following: 1) the activation of insulin-like growth factor 1, which can be affected by TG, can inhibit apoptosis and promote the occurrence of tumors (Yang et al., 2013); 2) dyslipidemia can induce the production of inflammatory cytokines (such as IL-6 and TNF-α) and reduce the secretion of anti-inflammatory cytokines (such as IL-10), thus creating a tumor-friendly cell environment and promoting cell proliferation (Esteve et al., 2005; Kim et al., 2017); 3) chronic inflammation can further affect the normal cholesterol transport and stimulate compensatory changes, such as the synthesis LDL-C and very low-density lipoprotein cholesterol (VLDL-C), resulting in the accumulation of TG in intestinal cells (Esteve et al., 2005); 4) a high fat diet can stimulate the secretion of bile acids, and secondary bile acids can further stimulate the proliferation of colorectal epithelial cells and inhibit the detoxification of exogenous carcinogens (Li et al., 2011); 5) serum lipids can induce the oxidative stress of tissue cells, resulting in an increased production of reactive oxygen species and the abnormal expression of cancer-related genes (Xie et al., 2019); and 6) cyclooxygenase-2, which can be activated by fatty acids and triglycerides, is related to the occurrence of CRC (Sasai et al., 2000).

Colorectal serrated lesions are the precancerous lesions of CRC. At present, there is no uniform conclusion on the relationship between serum lipid levels and colorectal serrated lesions. The present study conducted a systematic review and meta-analysis, including 65,972 subjects in 23 studies, to explore the evidence-based relationship between colorectal serrated lesions and blood lipid levels. The results showed that the serum levels of TC and LDL-C in patients with colorectal serrated lesions were higher than those in healthy subjects, while the level of HDL-C was lower than in healthy subjects. However, there was significant heterogeneity in the results. Therefore, we conducted a subgroup analysis to clarify the source of the heterogeneity. The results of the subgroup analysis showed that people in the control group with chronic nonspecific colitis and with a family history of CRC might have been the main source of heterogeneity in the WMD of LDL-C. It was suggested that the serum levels of HDL-C and LDL-C in patients with chronic nonspecific colitis may be different from those in healthy people. In addition, a family history of CRC, which may be another risk factor for colorectal serrated disease, might have led to the bias of the present study’s results. In addition, lipid-lowering drugs may affect serum TC levels. Excluding the subjects taking lipid-lowering drugs could reduce the heterogeneity of the WMD of TC. Among the
| Variables                              | NO. of studies | WMD(95%CI) (mmol/L) | Heterogeneity | Meta-regression p |
|----------------------------------------|----------------|---------------------|---------------|-------------------|
|                                        |                |                     | $I^2$ (%)    | $p$               |
| **Chinese**                            |                |                     |              |                   |
| Yes                                    | 17             | 0.259 (0.111, 0.406) | 72.9         | <0.001            | 0.095 |
| No                                     | 3              | −0.083 (−0.270, 0.104) | 85.2         | 0.001             |       |
| **Case-control study**                 |                |                     |              |                   |
| Yes                                    | 17             | 0.221 (0.063, 0.380) | 78.2         | <0.001            | 0.477 |
| No                                     | 3              | 0.004 (−0.091, 0.100) | 36.4         | 0.208             |       |
| **Hyperplastic polyps**                |                |                     |              |                   |
| Yes                                    | 16             | 0.266 (0.110, 0.423) | 74.6         | <0.001            | 0.111 |
| No                                     | 4              | −0.049 (0.216, 0.117) | 78.8         | 0.003             |       |
| **Normal control**                     |                |                     |              |                   |
| Yes                                    | 16             | 0.134 (0.012, 0.255) | 77.2         | <0.001            | 0.321 |
| No                                     | 4              | 0.383 (0.001, 0.765) | 76.0         | 0.006             |       |
| **Excluded subjects with family history of CRC** |       |                     |              |                   |
| Yes                                    | 5              | −0.008 (−0.161, 0.145) | 76.2         | <0.001            | 0.137 |
| No                                     | 15             | 0.274 (0.103, 0.446) | 77.4         | 0.001             |       |
| **Excluded subjects with family history of CRA** |       |                     |              |                   |
| Yes                                    | 3              | 0.178 (0.015, 0.342) | 0.0          | 0.850             | 0.865 |
| No                                     | 17             | 0.187 (0.052, 0.322) | 81.3         | <0.001            |       |
| **Excluded subjects with history of inflammatory bowel** |       |                     |              |                   |
| Yes                                    | 14             | 0.161 (0.022, 0.301) | 75.1         | <0.001            | 0.644 |
| No                                     | 6              | 0.259 (−0.036, 0.553) | 85.5         | <0.001            |       |
| **Excluded subjects with history of CRA** |       |                     |              |                   |
| Yes                                    | 7              | 0.104 (−0.084, 0.292) | 80.8         | <0.001            | 0.401 |
| No                                     | 13             | 0.237 (0.067, 0.408) | 77.0         | <0.001            |       |
| **Excluded subjects with history of CRC** |       |                     |              |                   |
| Yes                                    | 18             | 0.232 (0.097, 0.367) | 76.9         | <0.001            | 0.157 |
| No                                     | 2              | −0.168 (−0.686, 0.351) | 91.9         | <0.001            |       |
| **Excluded subjects with history of colorectal surgery** |       |                     |              |                   |
| Yes                                    | 3              | 0.319 (0.016, 0.622) | 59.8         | 0.083             | 0.513 |
| No                                     | 17             | 0.155 (0.027, 0.284) | 79.3         | <0.001            |       |
| **Excluded subjects taking lipid-lowering drugs** |       |                     |              |                   |
| Yes                                    | 12             | 0.268 (0.082, 0.454) | 68.6         | <0.001            | 0.364 |
| No                                     | 8              | 0.065 (−0.074, 0.203) | 79.1         | <0.001            |       |
| **The OR of smoking >1**               |                |                     |              |                   |
| Yes                                    | 5              | −0.038 (−0.176, 0.101) | 71.7         | 0.007             | 0.070 |
| No                                     | 15             | 0.290 (0.122, 0.457) | 75.3         | <0.001            |       |
| **The OR of drinking >1**              |                |                     |              |                   |
| Yes                                    | 4              | 0.022 (−0.055, 0.098) | 22.6         | 0.275             | 0.378 |
| No                                     | 16             | 0.236 (0.058, 0.413) | 80.2         | <0.001            |       |
| **Comparable in age**                  |                |                     |              |                   |
| Yes                                    | 9              | 0.384 (0.157, 0.611) | 78.0         | <0.001            | 0.060 |
| No                                     | 11             | 0.048 (−0.091, 0.187) | 76.1         | <0.001            |       |
| **Comparable in sex**                  |                |                     |              |                   |
| Yes                                    | 10             | 0.316 (0.143, 0.489) | 81.2         | <0.001            | 0.105 |
| No                                     | 10             | 0.045 (−0.140, 0.229) | 76.6         | <0.001            |       |
included studies, the results of most studies showed that the serum levels of TC and LDL-C in patients with colorectal polyps were higher than in healthy people. However, the HDL-C level was lower than in healthy people. This was consistent with the results of the meta-analysis, further proving the reliability of the results.

There were some limitations of this study. First, the results of the Egger test showed possible publication bias in the literature included in the meta-analysis of TG and colorectal serrated lesions, indicating low credibility of the results. Second, most of the included studies were case-control studies with lower reliability than the cohort studies and randomized controlled trials. Third, studies on serrated lesions were limited, and some information could not be extracted from many of the included studies. This affected the credibility of the meta-regression analysis and subgroup analysis. Fourth, in some literature, the mean and standard deviation of the blood lipid levels were obtained by median transformation, while in other literature, the blood lipid levels and other extracted data were obtained by inter-group combination. This, too, maybe a partial source of heterogeneity. Fifth, the language of included study was Chinese.

There were some limitations of this study. First, the results of the Egger test showed possible publication bias in the literature included in the meta-analysis of TG and colorectal serrated lesions, indicating low credibility of the results. Second, most of the included studies were case-control studies with lower reliability than the cohort studies and randomized controlled trials. Third, studies on serrated lesions were limited, and some information could not be extracted from many of the included studies. This affected the credibility of the meta-regression analysis and subgroup analysis. Fourth, in some literature, the mean and standard deviation of the blood lipid levels were obtained by median transformation, while in other literature, the blood lipid levels and other extracted data were obtained by inter-group combination. This, too, maybe a partial source of heterogeneity. Fifth, the language of included study was Chinese.
or English, which may lead to most of studies from Asian. There might be a report bias exist. The above limitations may have impacted the results of the meta-analysis.

However, this study suggested a certain correlation between colorectal serrated lesions and serum lipid levels. Including people with dyslipidemia in the focus screening population for colorectal serrated lesions may improve the screening efficiency. In addition, paying more attention to the lipid levels of young people could also contribute to screening and preventing early-onset CRC. Moreover, clinicians should be more cautious when performing colonoscopies and diagnosing patients with hyperlipidemia. Besides, because many factors influence the occurrence of colorectal serrated lesions and blood lipid levels, and these factors may interact with each other, it is necessary to classify patients according to the pathological type of colorectal serrated lesions. It is also necessary to explore the differences in blood lipid levels of patients with different types of serrated lesions. Because only two articles in this study grouped patients into SSA and SSP, a meta-analysis comparing the different pathological types was not conducted in this study. However, a clearer classification is needed in clinical diagnosis in order to carry out a more in-depth study of each pathological type.

In conclusion, colorectal serrated lesions may be related to blood lipid levels. Hyperlipidemia might be a risk factor for colorectal serrated lesions.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Author contributions

LZ and HZ designed this study that led to this article. XW, YZ, and RZ were involved in the methodology. XW, CT, and XR were responsible for the formal analysis. XW, YZ, HZ, and LZ were responsible for writing and preparing the original draft. All authors participated in the writing, review, and editing of the manuscript.

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Conflict of interest

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

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