Genetic impact of methylenetetrahydrofolate reductase (\textit{MTHFR}) polymorphism on the susceptibility to colorectal polyps: a meta-analysis

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Abstract

**Background:** There are several studies with inconsistent conclusions regarding the association between the rs1801133 and rs1801131 polymorphisms within the \textit{MTHFR} (methylenetetrahydrofolate reductase) gene and colorectal polyp risk. This discrepancy led us to assess the genetic impact of the two polymorphisms on the susceptibility to colorectal polyps.

**Methods:** A meta-analysis was carried out for quantitative synthesis. According to the inclusion/exclusion criteria, we retrieved, screened and selected all published articles related to colorectal polyps and the \textit{MTHFR} rs1801133 and rs1801131 polymorphisms. The \textit{P} value of association test, RRs (risk ratios) and 95\% CIs (confidence intervals) were mainly produced.

**Results:** A total of twenty-three case-control studies were included from twenty-two eligible articles. Pooling the results of both rs1801133 and rs1801131 polymorphisms in the overall population suggested a nonsignificant association between colorectal polyp cases and controls, in that all \textit{P} values in the test of association were larger than 0.05. Nevertheless, pooling results in the “UK” subgroup of rs1801131, comprising five studies (1257 cases/1407 controls), indicated an elevated risk in colorectal polyp cases in comparison with controls, under the genetic models of CC vs. AA \((P=0.032, \text{RR}=1.27, 95\% \text{CIs}=1.02, 1.57)\) and CC vs. AA+AC \((P=0.036, \text{RR}=1.27, 95\% \text{CIs}=1.02, 1.60)\).

**Conclusion:** The C/C genotype of \textit{MTHFR} rs1801131 is more likely to be a genetic risk factor for colorectal polyps in the UK region, although this finding should be verified with a larger sample size.

**Keywords:** \textit{MTHFR}, Polymorphism, Colorectal polyps, Susceptibility

Background

Colorectal polyps exhibit different morphologic features with flat, depressed, serrated, sessile or pedunculated shapes and are often regarded as benign protrusions of the colon and rectum mucosa [1, 2]. There are many types of colorectal polyps, such as hyperplastic polyps and adenomatous polyps [2, 3]. Despite the low malignant potential, the possible malignant change in colorectal polyps is related to the presence of colorectal cancer (CRC). For instance, some colonic polyps exist in patients with familial adenomatous polyposis (FAP) who are prone to cancer [4].

The 5,10-methylenetetrahydrofolate reductase (\textit{MTHFR}) gene is essential for the folate cycle and homocysteine metabolism [5]. rs1801133 (C677T) and rs1801131 (A1298C) are two common functional polymorphisms within the \textit{MTHFR} gene [6, 7]. \textit{MTHFR} rs1801133 and rs1801131 polymorphisms were reportedly associated with an enhanced risk of colorectal adenomatous polyp patients in
the Korean population [8]. However, no association between the MTHFR rs1801133 polymorphism and colorectal adenomatous polyp susceptibility was reported in the Dutch [9] or Japanese population [10]. These findings merit a comprehensive evaluation.

To the best of our knowledge, only one reported meta-analysis [6] of the association between MTHFR rs1801131 and colorectal adenoma and three meta-analyses [6, 11, 12] of MTHFR rs1801133 and colorectal adenoma were found during the database searching. However, the conclusion remains inconsistent. Additionally, we failed to retrieve a meta-analysis specific for the association between MTHFR polymorphisms and the susceptibility to both hyperplastic/adenomatous polyps. Herein, we have made an attempt to better investigate the potential genetic role of MTHFR rs1801133 and rs1801131 polymorphisms in the risk of colorectal polyps through an updated meta-analysis.

Methods

Database searching and screening process

Two authors (MS and JZ) gathered the relative records through searching the databases, namely, PubMed, WOS (Web of Science), and EMBASE (Excerpta Medica Database), prior to March 2018. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed [13]. The search terms used with the databases are shown in Additional file 1: Table S1. We independently excluded duplicate and ineligible records based on the following criteria: reviews, mouse data, case reports or trials, meta-analyses, meeting or conference abstracts, other genes, non-SNP or nonpolyp data, or missing genotype data for rs1801133 or rs1801131. Then, the remaining studies were included as eligible case-control studies.

Data extraction and quality assessment

We carefully extracted the data from the above selected studies. The chi-squared test was applied for the calculation of the $P$ value of HWE (Hardy-Weinberg Equilibrium). The included studies should provide the genotype frequency data of the control group, which also must be in line with the requirement of HWE. We summarized the main features of the included studies, such as first author name, publication year, polymorphism genotype frequency, country, ethnicity, genotyping assay, and $P$ value of HWE. We also utilized quality assessment (Newcastle-Ottawa Scale, NOS) to determine the quality score of the enrolled studies. Studies with poor quality (NOS score less than five) were excluded.

Association test

We obtained the $P_{\text{association}}$, risk ratios (RRs) and 95% confidence intervals (CIs) through the association test. The $P_{\text{heterogeneity}}$ value of Cochran's Q statistic $> 0.1$ or $I^2$ value $< 50\%$ led us to use a fixed-effects model. Six genetic models were used: allele T vs. allele C for rs1801133, allele C vs. allele A for rs1801131 (allele); TT vs. CC, CC vs. AA (homozygote); CT vs. CC, AC vs. AA (heterozygote); CT + TT vs. CC, AC + CC vs. AA (dominant); TT vs. CC + CT, CC vs. AA + AC (recessive); carrier T vs. carrier C, carrier C vs. carrier A (carrier).

Heterogeneity source analysis

We also carried out a sensitivity analysis and subgroup analyses for all genetic models to evaluate the data stability and source of heterogeneity. Briefly, we omitted each included study in turn to acquire a group of meta-analysis estimations. The omitted study was regarded as the probable heterogeneity source if we detected an obvious alteration of RR and 95% CI value. Subgroup analyses were also carried out, taking the factors of country, ethnicity (Caucasian/Asian) and disease type (hyperplastic polyps/adenomatous polyps) into consideration.

Publication bias analysis

We conducted both Begg's test (Begg's funnel plot) and Egger's test (Egger's publication bias plot) to evaluate possible publication bias. The absence of a large publication bias was considered when the $P$ values of Begg's test and Egger's test were $> 0.05$. STATA/SE software (Stata-Corp, USA) was utilized for all the above tests.

Results

Identification of eligible studies

We initially identified a total of 153 records by searching three databases, namely, PubMed ($n = 22$), WOS ($n = 83$), and EMBASE ($n = 48$). After excluding duplicate records, a total of 115 records were filtered by our criteria. The following 88 records were excluded: reviews ($n = 31$), mouse data ($n = 4$), case reports or trials ($n = 7$), meta-analyses ($n = 6$), meeting or conference abstracts ($n = 8$); other genes ($n = 9$), non-SNP or nonpolyp data ($n = 23$). Subsequently, twenty-seven full-text articles were evaluated for eligibility. Five articles lacked control or T/T genotype data. Finally, a total of twenty-two articles [8–10, 14–32] were selected. We listed the characteristics of eligible studies in the meta-analysis (Table 1). The genotype contributions of all controls in the studies fulfilled the principle of HWE. We found that one article contained two case-control studies, namely, the genotype distribution data in both adenomatous and hyperplastic polyps. In total, twenty-three case-control studies were ultimately included for the overall meta-analysis of MTHFR rs1801133, and ten case-control studies were included for that of MTHFR rs1801131. In addition, one
| First author   | Year | NOS | Polymorphism | Case Disease type | Control Disease type | Country | Ethnicity | Genotyping assay | \( P_{\text{HWE}} \) |
|---------------|------|-----|--------------|------------------|----------------------|---------|-----------|------------------|-----------------|
| Al-Ghnimaniem [14] | 2007 | 7   | rs1801133    | adenomatous polyps | 41 A/A, 29 A/B, 6 B/B | UK      | Caucasian | PCR-RFLP         | 0.784           |
|               |      |     | rs1801133    | hyperplastic polyps | 41 A/A, 29 A/B, 6 B/B | UK      | Caucasian | PCR-RFLP         | 0.784           |
|               |      |     | rs1801131    | adenomatous polyps | 47 A/A, 26 A/B, 3 B/B | UK      | Caucasian | PCR-RFLP         | 0.799           |
|               |      |     | rs1801131    | hyperplastic polyps | 47 A/A, 26 A/B, 3 B/B | UK      | Caucasian | PCR-RFLP         | 0.799           |
| Ashktorab [15] | 2007 | 6   | rs1801133    | colorectal polyps  | 30 A/A, 5 A/B, 0 B/B | USA     | Caucasian | PCR-RFLP         | 0.649           |
| Beckett [16]   | 2015 | 5   | rs1801133    | adenomatous polyps | 88 A/A, 91 A/B, 18 A/B | Australia | Caucasian | PCR-RFLP         | 0.421           |
|               |      |     | rs1801131    | adenomatous polyps | 101 A/A, 83 A/B, 13 A/B | Australia | Caucasian | PCR-RFLP         | 0.460           |
| Chen [17]      | 1998 | 8   | rs1801133    | adenomatous polyps | 323 A/A, 324 A/B, 66 A/B | USA     | Caucasian | PCR-RFLP         | 0.234           |
| Chiang [18]    | 2015 | 7   | rs1801133    | adenomatous polyps | 91 A/A, 73 A/B, 18 A/B | China   | Asian     | PCR-RFLP         | 0.553           |
| de Vogel [19]  | 2011 | 6   | rs1801133    | adenomatous polyps | 4463 A/A, 3563 A/B, 708 A/B | Norway  | Caucasian | Real-time PCR    | 0.933           |
| Delgado [20]   | 2001 | 8   | rs1801133    | adenomatous polyps | 34 A/A, 52 A/B, 24 A/B | Mexico  | Caucasian | PCR-RFLP         | 0.625           |
| Giovannucci [21] | 2003 | 6   | rs1801133    | adenomatous polyps | 299 A/A, 325 A/B, 101 A/B | USA     | Caucasian | PCR-RFLP         | 0.401           |
|               |      |     | rs1801131    | adenomatous polyps | 369 A/A, 299 A/B, 57 A/B | USA     | Caucasian | PCR-RFLP         | 0.740           |
| Goode [22]     | 2004 | 7   | rs1801133    | adenomatous polyps | 259 A/A, 238 A/B, 67 A/B | USA     | Caucasian | PCR-RFLP         | 0.281           |
| Hazra [23]     | 2007 | 7   | rs1801133    | adenomatous polyps | 229 A/A, 232 A/B, 64 A/B | USA     | Caucasian | NA              | 0.658           |
|               |      |     | rs1801131    | adenomatous polyps | 264 A/A, 219 A/B, 46 A/B | USA     | Caucasian | NA              | 0.951           |
| Hirose [24]    | 2005 | 8   | rs1801133    | adenomatous polyps | 399 A/A, 496 A/B, 155 A/B | Japan   | Asian     | PCR-RFLP         | 0.966           |
| Yi [8]         | 2006 | 6   | rs1801133    | adenomatous polyps | 2 A/A, 4 A/B, 0 A/B | Korea   | Asian     | PCR-RFLP         | 0.221           |
|               |      |     | rs1801131    | adenomatous polyps | 3 A/A, 3 A/B, 0 A/B | Korea   | Asian     | PCR-RFLP         | 0.414           |
| Levine [25]    | 2000 | 7   | rs1801133    | adenomatous polyps | 263 A/A, 198 A/B, 49 A/B | USA     | Caucasian | PCR-RFLP         | 0.193           |
| Lightfoot [26] | 2008 | 8   | rs1801133    | adenomatous polyps | 130 A/A, 139 A/B, 27 A/B | UK      | Caucasian | Taqman drug metabolizing genotyping assays | 0.238 |
|               |      |     | rs1801131    | adenomatous polyps | 140 A/A, 130 A/B, 26 A/B | UK      | Caucasian | Taqman drug metabolizing genotyping assays | 0.590 |
| Marugame [10]  | 2000 | 8   | rs1801133    | adenomatous polyps | 89 A/A, 105 A/B, 26 A/B | Japan   | Asian     | PCR-RFLP         | 0.555           |
| Mitrou [27]    | 2006 | 7   | rs1801133    | adenomatous polyps | 402 A/A, 407 A/B, 89 A/B | UK      | Caucasian | PCR-RFLP         | 0.340           |
|               |      |     | rs1801131    | adenomatous polyps | 415 A/A, 380 A/B, 88 A/B | UK      | Caucasian | PCR-RFLP         | 0.941           |
Table 1 Main features of eligible studies for pooled analysis (Continued)

| First author    | Year | NOS  | Polymorphism     | Case            | Disease type              | Control          | Country | Ethnicity | Genotyping assay | $P_{\text{HWE}}$ |
|-----------------|------|------|------------------|-----------------|---------------------------|-----------------|---------|-----------|------------------|----------------|
| Pufulete [28]   | 2003 | 7    | rs1801133        | 20              | adenomatous polyps        | 41              | UK      | Caucasian | PCR-RFLP         | 0.784          |
|                 |      |      | rs1801131        | 18              | adenomatous polyps        | 47              | UK      | Caucasian | PCR-RFLP         | 0.799          |
| Ulrich [29]     | 1999 | 9    | rs1801133        | 258             | adenomatous polyps        | 303             | USA     | Caucasian | PCR-RFLP         | 0.260          |
|                 |      |      | rs1801131        | 98              | adenomatous polyps        | 297             | USA     | Caucasian | PCR-RFLP         | 0.192          |
| van den [9]     | 2005 | 7    | rs1801133        | 343             | adenomatous polyps        | 325             | USA     | Caucasian | PCR-RFLP         | 0.560          |
| Williams [31]   | 2013 | 7    | rs1801133        | 34              | adenomatous polyps        | 44              | UK      | Caucasian | PCR-RFLP         | 0.822          |
| Yamaji [32]     | 2009 | 6    | rs1801133        | 263             | adenomatous polyps        | 219             | Japan   | Asian     | TaqMan PCR       | 0.993          |
|                 |      |      | rs1801131        | 452             | adenomatous polyps        | 441             | Japan   | Asian     | TaqMan PCR       | 0.609          |

A/A C/C genotype of rs1801133, or A/A genotype of rs1801131, A/B C/T genotype of rs1801133, or A/C genotype of rs1801131, B/B T/T genotype of rs1801133, or C/C genotype of rs1801131, NA not available, PCR-RFLP polymerase chain reaction-restriction fragment length polymorphism, HWE Hardy-Weinberg Equilibrium, NOS Newcastle-Ottawa Scale

**FIG. 1** Flowchart of database searching and record screening process
### Table 2 Pooled analysis for the MTHFR rs1801133 polymorphism

| Comparison                      | Subgroup     | Sample size | Studies | Case/control | RR (95% CI)                | Test of association |
|---------------------------------|--------------|-------------|---------|--------------|----------------------------|---------------------|
| allele T vs. allele C           | overall      | 23          | 8321/17731 | 0.98 (0.95, 1.01) | 1.42 | 0.156 |
|                                 | UK           | 6           | 1353/1517 | 0.99 (0.92, 1.07) | 0.14 | 0.886 |
|                                 | USA          | 8           | 2863/4343 | 1.00 (0.95, 1.05) | 0.14 | 0.890 |
|                                 | Japan        | 3           | 1369/1933 | 0.97 (0.91, 1.03) | 1.03 | 0.301 |
|                                 | Caucasian    | 18          | 6868/15610 | 0.99 (0.96, 1.02) | 0.86 | 0.391 |
|                                 | Asian        | 5           | 1453/2121 | 0.95 (0.90, 1.01) | 1.53 | 0.126 |
|                                 | hyperplastic polyps | 2        | 213/7022 | 0.99 (0.84, 1.16) | 0.13 | 0.897 |
|                                 | adenomatous polyps | 20         | 8086/16994 | 0.98 (0.95, 1.01) | 1.43 | 0.153 |
| TT vs. CC                       | overall      | 22          | 8317/17696 | 0.97 (0.90, 1.05) | 0.75 | 0.454 |
|                                 | UK           | 6           | 1353/1517 | 1.05 (0.85, 1.30) | 0.47 | 0.641 |
|                                 | USA          | 7           | 2841/4308 | 1.01 (0.89, 1.14) | 0.11 | 0.913 |
|                                 | Japan        | 3           | 1369/1933 | 0.95 (0.82, 1.11) | 0.61 | 0.540 |
|                                 | Caucasian    | 17          | 6846/15575 | 0.99 (0.91, 1.08) | 0.31 | 0.760 |
|                                 | Asian        | 5           | 1453/2121 | 0.92 (0.80, 1.07) | 1.06 | 0.291 |
|                                 | hyperplastic polyps | 2       | 213/7022 | 1.13 (0.77, 1.65) | 0.62 | 0.532 |
|                                 | adenomatous polyps | 20         | 8086/16994 | 0.97 (0.77, 1.15) | 0.88 | 0.377 |
| CT vs. CC                       | overall      | 23          | 8321/17731 | 0.97 (0.94, 1.00) | 1.77 | 0.077 |
|                                 | UK           | 6           | 1353/1517 | 0.96 (0.89, 1.04) | 0.93 | 0.351 |
|                                 | USA          | 8           | 2863/4343 | 0.99 (0.94, 1.04) | 0.44 | 0.663 |
|                                 | Japan        | 3           | 1369/1933 | 0.94 (0.88, 1.01) | 1.67 | 0.094 |
|                                 | Caucasian    | 18          | 6868/15610 | 0.98 (0.95, 1.01) | 1.11 | 0.269 |
|                                 | Asian        | 5           | 1453/2121 | 0.94 (0.87, 1.00) | 1.92 | 0.055 |
|                                 | hyperplastic polyps | 2       | 213/7022 | 0.88 (0.73, 1.07) | 1.27 | 0.205 |
|                                 | adenomatous polyps | 20         | 8086/16994 | 0.98 (0.95, 1.01) | 1.58 | 0.113 |
| CT + TT vs. CC                  | overall      | 23          | 8321/17731 | 0.98 (0.95, 1.00) | 1.76 | 0.079 |
|                                 | UK           | 6           | 1353/1517 | 0.98 (0.91, 1.06) | 0.66 | 0.511 |
|                                 | USA          | 8           | 2863/4343 | 0.99 (0.95, 1.04) | 0.33 | 0.743 |
|                                 | Japan        | 3           | 1369/1933 | 0.96 (0.91, 1.01) | 1.53 | 0.125 |
|                                 | Caucasian    | 18          | 6868/15610 | 0.98 (0.96, 1.01) | 1.08 | 0.280 |
|                                 | Asian        | 5           | 1453/2121 | 0.95 (0.90, 1.00) | 1.95 | 0.052 |
|                                 | hyperplastic polyps | 2       | 213/7022 | 0.94 (0.80, 1.09) | 0.82 | 0.414 |
|                                 | adenomatous polyps | 20         | 8086/16994 | 0.98 (0.95, 1.00) | 1.65 | 0.098 |
| TT vs. CC + CT                  | overall      | 22          | 8317/17696 | 0.99 (0.92, 1.07) | 0.19 | 0.847 |
|                                 | UK           | 6           | 1353/1517 | 1.09 (0.87, 1.36) | 0.78 | 0.436 |
|                                 | USA          | 7           | 2841/4308 | 1.02 (0.89, 1.16) | 0.23 | 0.822 |
|                                 | Japan        | 3           | 1369/1933 | 1.01 (0.86, 1.18) | 0.08 | 0.934 |
|                                 | Caucasian    | 17          | 6846/15575 | 1.00 (0.91, 1.09) | 0.07 | 0.944 |
|                                 | Asian        | 5           | 1453/2121 | 0.98 (0.83, 1.15) | 0.28 | 0.780 |
|                                 | hyperplastic polyps | 2       | 213/7022 | 1.23 (0.83, 1.84) | 1.04 | 0.299 |
|                                 | adenomatous polyps | 20         | 8086/16994 | 0.98 (0.91, 1.04) | 0.39 | 0.696 |
| carrier T vs. carrier C         | overall      | 23          | 8321/17731 | 0.99 (0.96, 1.01) | 0.99 | 0.322 |
|                                 | UK           | 6           | 1353/1517 | 0.99 (0.92, 1.07) | 0.21 | 0.831 |
|                                 | USA          | 8           | 2863/4343 | 1.00 (0.95, 1.05) | 0.15 | 0.883 |
|                                 | Japan        | 3           | 1369/1933 | 0.98 (0.91, 1.05) | 0.69 | 0.491 |
|                                 | Caucasian    | 18          | 6868/15610 | 0.99 (0.96, 1.02) | 0.64 | 0.523 |
|                                 | Asian        | 5           | 1453/2121 | 0.97 (0.90, 1.03) | 0.99 | 0.322 |
|                                 | hyperplastic polyps | 2       | 213/7022 | 0.98 (0.82, 1.16) | 0.26 | 0.793 |
|                                 | adenomatous polyps | 20         | 8086/16994 | 0.99 (0.96, 1.02) | 0.97 | 0.331 |

RRs: Risk ratios, CIs: Confidence intervals
study in which the TT genotype frequency of case and control groups for rs1801133 equaled zero was not included in the meta-analysis under the TT vs. CC (homozygote) and TT vs. CC + CT (recessive) models. The PRISMA-based analysis flowchart is shown in Fig. 1. None of the included studies exhibited poor quality (all NOS scores were larger than five).

**Pooled analysis for MTHFR rs1801133**

First, we carried out a meta-analysis to investigate the genetic relationship between *MTHFR* rs1801133 and colorectal polyp susceptibility. A total of twenty-three case-control studies with 8321 cases and 17,731 controls were included. As shown in Table 2, compared with the control group, no increased risk of colorectal polyps was detected in the case group under the six genetic models, namely, allele T vs. allele C ($P$ value in test of association =0.156); TT vs. CC ($P$ =0.454); CT vs. CC ($P$ =0.077); CT + TT vs. CC ($P$ =0.079); TT vs. CC + CT ($P$ =0.847); carrier T vs. carrier C ($P$ =0.322). We also conducted subgroup analyses by country, ethnicity (Caucasian/Asian) and disease type (hyperplastic polyps/adenomatous polyps). A similar nonsignificant genetic relationship was observed for all the models (all $P > 0.05$, Table 2). For example, there was no significant difference between the colorectal polyp cases and negative controls in the UK subgroup under the T vs. C allele (Table 2, $P$ =0.886); TT vs. CC ($P$ =0.641); CT vs. CC ($P$ =0.351); CT + TT vs. CC ($P$ =0.511); TT vs. CC + CT ($P$ =0.436); or carrier T vs. carrier C ($P$ =0.831). In the subgroup analysis of “adenomatous polyps”, we also did not observe a statistically significant association under the allele T vs. allele C (Table 2, $P$ =0.153); TT vs. CC ($P$ =0.377); CT vs. CC ($P$ =0.113); CT + TT vs. CC ($P$ =0.098); TT vs. CC + CT ($P$ =0.696); and carrier T vs. carrier C ($P$ =0.331). We show the forest plots of the subgroup analyses based on disease type under the allele T vs. allele C model in Fig. 2. These results revealed that *MTHFR* rs1801133 does not appear to be significantly linked to susceptibility to colorectal polyps.

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**Table 2**

| Study ID                  | rs1801133            | RR (95% CI)       | Weight |
|--------------------------|----------------------|-------------------|--------|
| **adenomatous polyps**   |                      |                   |        |
| Al-Ghanniemi (2007)      | allele T vs. allele C| 0.74 (0.43, 1.27) | 0.39   |
| Beckett (2015)           |                      | 0.94 (0.69, 1.28) | 0.85   |
| Chen (1998)              |                      | 1.13 (0.88, 1.46) | 3.86   |
| Chiang (2015)            |                      | 0.62 (0.42, 0.91) | 0.91   |
| de Vogel (2011)          |                      | 0.96 (0.91, 1.02) | 25.66  |
| Delgado (2001)           |                      | 1.13 (0.86, 1.50) | 0.68   |
| Giovannucci (2003)       |                      | 0.98 (0.87, 1.10) | 5.42   |
| Goode (2004)             |                      | 0.97 (0.85, 1.09) | 5.22   |
| Hazra (2007)             |                      | 1.03 (0.92, 1.16) | 5.44   |
| Hirose (2005)            |                      | 0.97 (0.88, 1.07) | 7.33   |
| Kurn (2006)              |                      | 1.39 (0.97, 1.90) | 0.09   |
| Levine (2000)            |                      | 0.98 (0.85, 1.12) | 4.29   |
| Lightfoot (2008)         |                      | 1.07 (0.91, 1.25) | 2.97   |
| Maruigame (2000)         |                      | 1.04 (0.87, 1.24) | 2.29   |
| Mitrou (2006)            |                      | 0.97 (0.88, 1.07) | 8.69   |
| Pufulete (2003)          |                      | 0.90 (0.85, 1.06) | 0.39   |
| Ulrich (1999)            |                      | 0.84 (0.83, 1.06) | 5.64   |
| van den (2005)           |                      | 1.00 (0.81, 1.11) | 7.27   |
| Williams (2013)          |                      | 1.13 (0.94, 1.50) | 0.88   |
| Yamaji (2009)            |                      | 0.95 (0.87, 1.03) | 8.82   |
| **Subtotal**             | (I-squared = 0.0%, p = 0.569) | 0.98 (0.95, 1.01) | 96.89 |
| **hyperplastic polyps**  |                      |                   |        |
| Al-Ghanniemi (2007)      |                      | 0.98 (0.63, 1.62) | 0.23   |
| Ulrich (2000)            |                      | 0.99 (0.94, 1.17) | 2.88   |
| **Subtotal**             | (I-squared = 0.0%, p = 0.978) | 0.99 (0.84, 1.16) | 3.11   |
| **Overall**              | (I-squared = 0.0%, p = 0.692) | 0.98 (0.95, 1.01) | 100.00 |

**Figure 2**

Subgroup analysis by disease type of association between *MTHFR* rs1801133 polymorphism and colorectal polyp risk under the allele T vs. allele C model.
Pooled analysis for MTHFR rs1801131

Next, ten studies containing 2951 cases and 3527 controls were included in the meta-analysis of MTHFR rs1801131. Pooled analysis in the overall population (Table 3) indicated a null association under all genetic models (all \( P > 0.05 \)). The results of the subgroup analysis for the UK, containing five studies of 1257 cases/1407 controls, suggested an increased risk in cases of colorectal polyps compared with controls under the genetic models of CC vs. AA (\( P = 0.032 \), RR = 1.27, 95% CIs = 1.02, 1.57) and CC vs. AA+AC (\( P = 0.036 \), RR = 1.27, 95% CIs = 1.02, 1.60). We showed the related forest plots in Figs. 3 and 4. Nevertheless, no difference between cases and controls was observed in other subgroup meta-analyses (all \( P > 0.05 \), Table 3). For example, no increased or decreased risk of adenomatous polyps in cases was detected, compared with controls, under the allele C vs. allele A (Table 3, \( P = 0.138 \)); CC vs. AA (\( P = 0.114 \)); AC vs. AA (\( P = 0.576 \)); AC+CC vs. AA (\( P = 0.303 \)); CC vs. AA+AC (\( P = 0.122 \)); or carrier C vs. carrier C (\( P = 0.376 \)). Thus, the C/C genotype of the MTHFR rs1801131 polymorphism may be related to an enhanced colorectal polyp risk in the UK population.

Heterogeneity, publication bias and sensitivity analysis

In addition, we evaluated the between-study heterogeneity and did not detect remarkable heterogeneity in any of the above comparisons (Table 4, all \( I^2 < 50.0\% \), \( P \) value of heterogeneity > 0.1). Thus, a fixed-effects model was applied. We also conducted both Begg’s test and Egger’s test to assess the presence of publication bias. As shown in Table 4, the \( P \) values of Begg’s test and Egger’s test were larger than 0.05 in all genetic models, indicating the absence of large publication bias. We showed Begg’s funnel plot and the association between the MTHFR rs1801131 polymorphism and colorectal polyp risk under the CC vs. AA model in Fig. 5a. Additionally, similar pooled RRs were detected in our sensitivity analysis under other genetic models (Fig. 5b for CC vs. AA model of

### Table 3 Pooled analysis for the MTHFR rs1801131 polymorphism

| Comparison                  | Subgroup                      | Sample size | Test of association |   |
|-----------------------------|-------------------------------|-------------|---------------------|---|
|                             |                               |             | cases/control       | RRs (95% CIs) | z  | \( P \) |
| allele C vs. allele A       | overall                       | 10          | 2951/3527           | 1.05 (0.99, 1.11) | 1.60 | 0.109 |
|                             | UK                            | 5           | 1257/1407           | 1.08 (0.99, 1.17) | 1.79 | 0.073 |
|                             | Caucasian                     | 8           | 2225/2858           | 1.04 (0.98, 1.10) | 1.22 | 0.222 |
|                             | adenomatous polyps            | 9           | 2934/3451           | 1.04 (0.99, 1.10) | 1.48 | 0.138 |
| CC vs. AA                   | overall                       | 10          | 2951/3527           | 1.15 (0.98, 1.35) | 1.69 | 0.091 |
|                             | UK                            | 5           | 1257/1407           | 1.27 (1.02, 1.57) | 2.14 | 0.032 |
|                             | Caucasian                     | 8           | 2225/2858           | 1.14 (0.96, 1.35) | 1.50 | 0.133 |
|                             | adenomatous polyps            | 9           | 2934/3451           | 1.14 (0.97, 1.34) | 1.58 | 0.114 |
| AC vs. AA                   | overall                       | 10          | 2951/3527           | 1.02 (0.96, 1.08) | 0.63 | 0.528 |
|                             | UK                            | 5           | 1257/1407           | 1.02 (0.93, 1.11) | 0.39 | 0.698 |
|                             | Caucasian                     | 8           | 2225/2858           | 1.01 (0.95, 1.07) | 0.25 | 0.805 |
|                             | adenomatous polyps            | 9           | 2934/3451           | 1.02 (0.96, 1.08) | 0.56 | 0.576 |
| AC + CC vs. AA              | overall                       | 10          | 2951/3527           | 1.03 (0.98, 1.08) | 1.13 | 0.258 |
|                             | UK                            | 5           | 1257/1407           | 1.04 (0.97, 1.12) | 1.08 | 0.279 |
|                             | Caucasian                     | 8           | 2225/2858           | 1.02 (0.97, 1.08) | 0.72 | 0.471 |
|                             | adenomatous polyps            | 9           | 2934/3451           | 1.03 (0.98, 1.08) | 1.03 | 0.303 |
| CC vs. AA + AC              | overall                       | 10          | 2951/3527           | 1.15 (0.97, 1.36) | 1.64 | 0.100 |
|                             | UK                            | 5           | 1257/1407           | 1.27 (1.02, 1.60) | 2.10 | 0.036 |
|                             | Caucasian                     | 8           | 2225/2858           | 1.14 (0.96, 1.36) | 1.49 | 0.135 |
|                             | adenomatous polyps            | 9           | 2934/3451           | 1.14 (0.97, 1.35) | 1.55 | 0.122 |
| carrier C vs. carrier A     | overall                       | 10          | 2951/3527           | 1.03 (0.97, 1.09) | 0.96 | 0.336 |
|                             | UK                            | 5           | 1257/1407           | 1.04 (0.96, 1.14) | 1.00 | 0.318 |
|                             | Caucasian                     | 8           | 2225/2858           | 1.02 (0.96, 1.09) | 0.68 | 0.499 |
|                             | adenomatous polyps            | 9           | 2934/3451           | 1.03 (0.97, 1.09) | 0.88 | 0.376 |

PB Population-based control, HB Hospital-based control, RRs Risk ratios, CIs Confidence intervals

Bold entries are significant
MTHFR rs1801131; other data not shown), suggesting the reliability of pooling outcomes.

Discussion
Several meta-analyses have reported the role of MTHFR polymorphisms in the susceptibility to colorectal cancer (CRC) and adenoma. For example, in 2005, Kono, S. and colleague included a total of 16 case-control studies for a meta-analysis on the genetic relationship between MTHFR rs1801133 polymorphism and the risk of colorectal cancer and reported the potential role of the TT genotype in reduced CRC susceptibility [11]. In 2007, Huang, Y. et al. performed another meta-analysis to report that MTHFR rs1801133 and rs1801131 polymorphisms may confer no increasing or decreasing effect on the risk of colorectal adenoma patients [6]. In addition, Edwards, T. L. and colleagues included 2551 colorectal adenoma cases and 3285 controls in the Caucasian population and performed genome-wide association studies (GWASs) to identify potential susceptibility factors, but MTHFR polymorphisms did not reach a genome-wide significant P value [35]. However, Kono, S. and colleagues reported that the TT genotype of the MTHFR rs1801133 polymorphism may be associated with high susceptibility to colorectal adenoma patients with poor folate status [11]. In 2016, Montazeri, Z. and colleague conducted a systematic review and meta-analyses to assess the association between 37 polymorphisms within 26 genes and colorectal rs1801133 polymorphism was related to a reduced risk of CRC, particularly in the Asian population [34]. These data supported the protective effect of MTHFR polymorphism, especially rs1801133, on CRC risk. However, inconsistent results regarding the role of the MTHFR polymorphism in the risk of colorectal adenoma were observed in the quantitative synthesis.

Meta-analysis of Huang, Y. et al. revealed that MTHFR rs1801133 and rs1801131 polymorphisms may have no increasing or decreasing effect on the risk of colorectal adenoma patients [6]. In addition, Edwards, T. L. and colleagues included 2551 colorectal adenoma cases and 3285 controls in the Caucasian population and performed genome-wide association studies (GWASs) to identify potential susceptibility factors, but MTHFR polymorphisms did not reach a genome-wide significant P value [35]. However, Kono, S. and colleagues reported that the TT genotype of the MTHFR rs1801133 polymorphism may be associated with high susceptibility to colorectal adenoma patients with poor folate status [11]. In 2016, Montazeri, Z. and colleague conducted a systematic review and meta-analyses to assess the association between 37 polymorphisms within 26 genes and colorectal
adenoma risk and observed the potential genetic role of the MTHFR rs1801133 polymorphism, but with a relatively lower statistical power [12].

In this study, we intended to reassess the role of the MTHFR rs1801133 polymorphism in the susceptibility to colorectal adenomas in terms of colorectal polyps by means of a meta-analysis containing twenty-three case-control studies with 8339 cases and 17,731 controls. Our findings did not show any association between the MTHFR rs1801133 polymorphism and the risk of colorectal adenomatous polyps or hyperplastic polyps.

Moreover, we performed another meta-analysis of ten case-control studies with 2969 cases and 3527 controls and found that the C/C genotype of the MTHFR rs1801131 polymorphism and the risk of colorectal polyp patients of other regions.

The case-control studies in our analysis were screened by fulfilling our strict selection criteria. All the studies exhibit high quality. In addition, we observed no heterogeneity in any of the Mantel-Haenszel statistics and excluded the large publication bias. Moreover, the stability of the statistical outcomes was detected by the sensitivity analysis. Nevertheless, we are also aware of several limitations. The main problem is the small sample size in the included case-control studies. Therefore, the subgroup analysis data for Australia, the USA, Korea, and Japan, with one or two case-control studies, exhibits very limited statistical power. We still cannot exclude the potential effect of the MTHFR rs1801131 polymorphism in colorectal polyp patients of other regions.

FIG. 4 Subgroup analysis by country of association between MTHFR rs1801131 polymorphism and colorectal polyp risk under the CC vs. AA+AC model
### Table 4 The assessment of heterogeneity and publication bias

| Polymorphism | Comparison | $I^2$ | $P$ value | Model  | Begg's test | Egger's test |
|--------------|------------|-------|-----------|--------|-------------|--------------|
| rs1801133    | allele T vs. allele C | 0.0%  | 0.736     | Fixed  | 0.69 | 0.492 | 0.46 | 0.651 |
|              | TT vs. CC  | 0.0%  | 0.799     | Fixed  | 0.90 | 0.367 | 0.75 | 0.463 |
|              | CT vs. CC  | 0.0%  | 0.705     | Fixed  | 0.79 | 0.428 | -0.41 | 0.685 |
|              | TT + CT vs. CC | 0.0%  | 0.725     | Fixed  | 0.11 | 0.916 | -0.02 | 0.984 |
|              | CT vs. CC + CT | 0.0%  | 0.790     | Fixed  | 0.73 | 0.463 | 0.70 | 0.492 |
|              | carrier T vs. carrier C | 0.0%  | 0.999     | Fixed  | 0.32 | 0.751 | 0.27 | 0.787 |
| rs1801131    | allele C vs. allele A | 9.6%  | 0.354     | Fixed  | 1.16 | 0.245 | 1.41 | 0.195 |
|              | CC vs. AA  | 14.3% | 0.311     | Fixed  | 1.52 | 0.128 | 1.96 | 0.085 |
|              | AC vs. AA  | 0.0%  | 0.800     | Fixed  | 0.45 | 0.655 | -0.25 | 0.807 |
|              | AC + CC vs. AA | 0.0%  | 0.623     | Fixed  | 1.34 | 0.180 | 0.64 | 0.541 |
|              | CC vs. AA+AC | 8.3%  | 0.366     | Fixed  | 1.52 | 0.128 | 2.17 | 0.061 |
|              | carrier C vs. carrier A | 0.0%  | 0.918     | Fixed  | 0.98 | 0.325 | 1.04 | 0.327 |

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**FIG. 5** Begg's funnel plot and sensitivity analysis for MTHFR rs1801131 polymorphism and colorectal polyp risk under the CC vs. AA model.

- **a** Begg's funnel plot
- **b** Sensitivity analysis
**Conclusion**

Taken together, our findings conclude that *MTHFR* rs1801131, rather than rs1801133, is more likely to be associated with an increased susceptibility to colorectal polyps in the UK population. Additionally, the C/C genotype of *MTHFR* rs1801131 may confer an increased susceptibility to patients with colorectal polyps in the UK region. However, this conclusion merits further confirmation with a larger sample size.

**Additional file**

**Additional file 1**: Table S1. The search terms used with the PubMed, WOS and EMBASE databases. (DOCX 30 kb)

**Abbreviations**

CI: Confidence interval; CRC: Colorectal cancer; FAP: Familial adenomatous polyposis; GWAS: Genome-wide association studies; HWE: Hardy-Weinberg Equilibrium; *MTHFR*: Methylenetetrahydrofolate reductase; NOS: Newcastle-Ottawa Scale; RRs: Risk ratios

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**Authors’ contributions**

MS and JZ conceived and designed the study. MS and JZ performed the database searching and study screening. MS, JZ, LZ and SS extracted, analyzed, and interpreted the data. MS and JZ drafted the manuscript. All authors have read and approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

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