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# Effect of *KCNQ1* rs2237892 polymorphism on the predisposition to type 2 diabetes mellitus: An updated meta-analysis

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## Abstract

**Objectives:** Previous studies have analyzed the potential effect of *KCNQ1* rs2237892 polymorphism on the predisposition to type 2 diabetes mellitus, but the findings are inconclusive and the subject of debate. The purpose of our study was to provide further insight into the potential association between *KCNQ1* rs2237892 polymorphism and the risk of type 2 diabetes mellitus.

**Methods:** In total, 50 articles (60 studies) with 77,276 cases and 76,054 controls were utilized in our analysis. The pooled odds ratio (OR), 95% confidence interval (95% CI), and *p* value were used to evaluate the significance of our findings. Funnel plots and Beggar's regression tests were utilized to determine the presence of publication bias.

**Results:** Our meta-analysis results indicated that *KCNQ1* rs2237892 polymorphism could be correlated with the risk of type 2 diabetes mellitus under the C allelic, recessive, and dominant genetic models (OR = 1.25, 95% 1.19–1.32, $p < 0.001$; OR = 1.50, 95% CI 1.34–1.68, $p < 0.001$; OR = 1.26, 95% CI 1.14–1.40, $p < 0.001$, respectively). Additionally, ethnicity analysis revealed that the source of control, case size, and Hardy–Weinberg Equilibrium status were correlated to the polymorphism in the three genetic models.

**Conclusions:** Our meta-analysis demonstrated significant evidence to support the association between *KCNQ1* rs2237892 polymorphism and predisposition to type 2 diabetes mellitus.

**Keywords:** *KCNQ1* rs2237892, Polymorphism, T2DM, Meta-analysis

## Background

The worldwide prevalence of type 2 diabetes mellitus (T2DM) is increasing, along with associated comorbidities such as cardiovascular disease [1]. The International Diabetes Federation (IDF) reports that there were 9.3% (463 million) adults with diabetes in 2019, and 700 million people will have diabetes by 2045 [2]. Researchers consider T2DM to be a polygenic metabolic disorder with genetic heterogeneity that is affected by nongenetic (environmental), genetic, and lifestyle factors. However, the pathogenesis of T2DM still remains unclear [3].

Previous studies have reported that the potassium voltage-gated channel KQT-like sub-family, member 1 gene (*KCNQ1*) is associated with T2DM in Japanese, Korean, Chinese, Indian, and European populations [4–7]. Case–control studies investigating the role of *KCNQ1* polymorphisms in T2DM, have indicated that rs2237892, a single nucleotide polymorphism (SNP) located on intron 15, has a strong association with T2DM. Therefore, rs2237892 has been widely investigated in subsequent studies. However, there are disagreements between the different studies, and their validity has been limited by insufficient sample size and lack of ethnic diversity in the study populations [8–11].

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Although a previous meta-analysis in 2012 investigated the association between *KCNQ1* rs2237892 polymorphism and T2DM risk, the authors only utilized 25 articles [12]. Therefore, our objective in the present meta-analysis, was to further examine and elucidate the connection between *KCNQ1* rs2237892 polymorphism and an increased risk of T2DM.

## Methods

### Publication search

We systematically searched for relevant publications published through March 11, 2021 using Cochrane Library, PubMed, EMBASE, Web of Science, and China National Knowledge Infrastructure. We used the following search terms: ("*KCNQ1*", OR "potassium voltage-gated channel", OR "KQT-like subfamily, member 1", OR "rs2237892") AND ("variant", OR "polymorphism", OR "mutation") AND ("T2DM", OR "type 2 diabetes mellitus", OR "type 2 diabetes", OR "T2D"). Two investigators independently checked the references of retrieved articles to select the publications they would include in the analysis.

## Selection criteria

Studies were selected according to the following inclusion criteria: full text could be found; the case–control studies focused on the relevance of *KCNQ1* rs2237892 polymorphism and T2DM risk; the *KCNQ1* rs2237892 genotype was obtained, and association between the *KCNQ1* rs2237892 SNP and T2DM prevalence was assessed. Studies were excluded if they met the following exclusion criteria: they were repetitions of other articles; they were not case–control studies; they were unpublished studies, conference articles, meta-analyses, systematic evaluations, and they were pedigree studies. We consulted the Preferred Reporting Project (PRISMA) Guide for Systematic Evaluation and Meta-Analysis to comply with standards for conducting and presenting results from meta-analyses [13].

## Data extraction

Referring to the inclusion/exclusion criteria, two investigators independently extracted data that included: first author, country, publication year, amount of cases and controls, Hardy–Weinberg equilibrium (HWE), control group source, and the availability of *KCNQ1* rs2237892 genotype. Only articles with maximum sample size were selected when similar data appeared in multiple publications. A third investigator reviewed the final results to ensure data accuracy, and discussions were held to resolve any conflicts.

## Study quality assessment

Two investigators performed independent quality assessments for each eligible article according to the 9-point Newcastle–Ottawa Scale [14]. The third investigator resolved any conflicting results produced by the two investigators. The assessment score included these criteria: case and control selection (4 points); confounding factor quality corrected in cases and controls (2 points), exposure ascertainment (3 points). The total scores ranged from 0 to 9, and scores > 6 were indicative of high-quality articles.

## Statistical analysis

We estimated the significance of the data describing *KCNQ1* rs2237892 SNP and T2DM risk using the OR and 95% CI. The Chi-Square-Based Q-test and I-Squared test were utilized to analyze the heterogeneity with $p < 0.1$ suggesting heterogeneity [15, 16]. We estimated the pooled OR by fixed effect model (Mantel–Haenszel) when no heterogeneity existed, or by the DerSimonian and Laird random effects model [17, 18]. We performed the Chi-squared test in controls, to examine HWE. To estimate the influence of the pooled ORs caused by an individual data set, we performed sensitivity analysis for each of the comparison models. The publication bias was tested by Funnel plot and Begg linear regression (19, 20), and Stata 12.0 was used to perform all analyses.

## Results

### Study characteristics

Figure 1 shows flowcharts of the selection of publications for the present study. There were 535 publications located in several electronic databases. After examining the research title, content, and abstract of the publications, the two investigators excluded 169 duplicate documents, 298 irrelevant papers, and examined the remaining 68 articles in full. Finally, our meta-analysis included 50 (60 case–control) publications. Among the 60 case–control studies, 51 included Asian populations, 4 included Caucasian, and 5 involved other populations. Of the studies in our meta-analysis, 24 were based on population (PB), 19 were based on hospital (HB), and 17 studies were based on no report (NR). The sample group of 21 studies was less than 500 patients, 10 studies included between 500 and 1000 patients, 4 studies included between 1001 and 2000 patients, and the remaining 6 studies had a sample group of greater than 2000. HWE balance ($p < 0.05$) was not met in 5 of the control groups. Due to lack of control group descriptions, 19 studies did not meet HWE assessment.

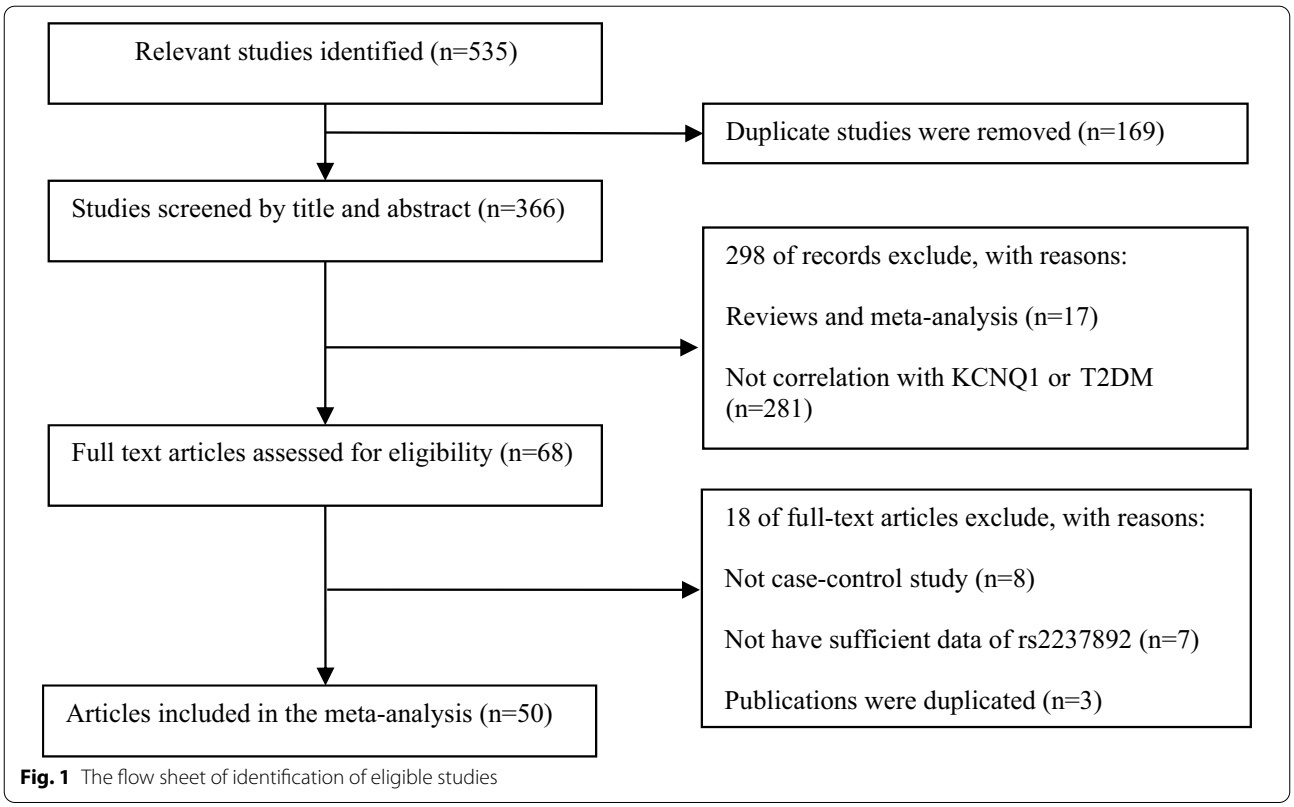


**Fig. 1** The flow sheet of identification of eligible studies

Table 1 shows the main features of the study and the genotype distribution results of the HWE test.

## Meta-analysis results

The meta-analysis included 153,330 participants (77,276 cases and 76,054 controls). *KCNQ1* rs2237892 polymorphism was significantly associated with T2DM risk under the C allelic, recessive, and dominant genetic models (OR:1.25, 1.50 and 1.26; 95% CI 1.19–1.32, 1.34–1.68, and 1.14–1.40; $p < 0.001$, respectively). In ethnic subgroup analysis shown in Table 2, *KCNQ1* rs2237892 polymorphism was correlated with increased risk of T2DM in the dominant genetic model of East Asians, in the C allelic genetic model of East Asians, and in the C allelic genetic model of West Asian populations (OR = 1.39, 1.32 and 1.25; 95% CI 1.31–1.49, 1.27–1.37 and 1.19–1.32; $p < 0.001$, respectively). In the stratified analysis by source of control, marked correlation was found in the C allelic genetic model (HB, PB, and NR: OR = 1.24, 1.25 and 1.16; 95% CI 1.14–1.37, 1.19–1.32 and 1.02–1.32; $p < 0.001$, respectively) and the dominant genetic model (HB and PB: OR = 1.25 and 1.48; 95% CI 1.08–1.46 and 1.38–1.59, $p < 0.05$, respectively). In the case size stratification, the C allelic genetic model (OR = 1.23, 1.14, 1.25 and 1.33; 95% CI 1.09–1.38, 0.88–1.48, 1.19–1.32 and 1.27–1.39; $p < 0.001$, respectively), the dominant genetic model (OR = 1.24, 1.13, 1.41 and 1.43; 95% CI 1.05–1.46, 0.81–1.58 and 1.33–1.53; $p < 0.001$, respectively) and the recessive genetic model (500–1000: OR = 1.32, 95% CI 0.91–1.91, $p < 0.001$) found notable association between *KCNQ1* rs2237892 polymorphism and increased T2DM risk. Finally, we stratified by sample size—significant correlation was found in the C allelic genetic model (< 500, 1001–2000 and > 2000: OR = 1.23, 1.25 and 1.33; 95% CI 1.09–1.38, 1.19–1.32 and 1.27–1.39; $p < 0.001$, respectively) and the dominant genetic model (< 500, 1001–2000 and > 2000: OR = 1.24, 1.41 and 1.43; 95% CI 1.05–1.46, 1.14–1.75 and 1.33–1.53; $p < 0.001$, respectively).

## Discussion

The association of *KCNQ1* rs2237892 polymorphism with T2DM has been reported in many previous studies [21–62]. In 2008, two independently conducted genome-wide association studies (GWAS) in Japanese populations identified *KCNQ1* as a novel T2DM susceptibility gene [5, 6, 8]. Subsequently, the SNP locus rs2237892 of this gene was found to be correlated with the incidence of T2DM in Korean population [15]. In our present meta-analysis, there were 60 studies, 77,276 cases and 76,057 controls, that we evaluated for the possible association between *KCNQ1*

**Table 1** Studies and data included in this meta- analysis

| Authors | Year | Country | Source of control | Sample size | | Cse | | | | | Control | | | | | NOS score | HWE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Case | Control | CC | CT | TT | C | T | CC | CT | TT | C | T | | |
| Yasuda K et al | 2008 | Japanese | NR | 2954 | 2988 | | | | 5954 | 2802 | | | | 5206 | 3618 | 7 | NK |
| Yasuda K et al | 2008 | China/ Korea | NR | 6552 | 6621 | | | | 9042 | 4062 | | | | 8078 | 5164 | 7 | NK |
| Yasuda K et al | 2008 | European | NR | 63 | 752 | | | | 120 | 6 | | | | 1399 | 105 | 7 | NK |
| Lee YH et al | 2008 | Korea | HB | 865 | 496 | 389 | 377 | 99 | 1155 | 575 | 182 | 239 | 75 | 603 | 389 | 7 | 0.811 |
| Chen Z et al | 2009 | China | HB | 57 | 341 | 27 | 24 | 6 | 78 | 36 | 162 | 144 | 35 | 468 | 214 | 6 | 0.720 |
| Takeuchi F et al | 2009 | Japan | NR | 519 | 503 | 228 | 236 | 55 | 692 | 346 | 183 | 244 | 76 | 610 | 396 | 7 | 0.717 |
| Takeuchi F et al | 2009 | Japan | NR | 1110 | 1014 | 492 | 488 | 130 | 1472 | 748 | 398 | 452 | 164 | 1248 | 780 | 7 | 0.063 |
| Takeuchi F et al | 2009 | Japan | NR | 3990 | 4878 | 1740 | 1785 | 465 | 5265 | 2715 | 1695 | 2345 | 838 | 5735 | 4021 | 7 | 0.580 |
| Qi Q et al | 2009 | China | PB | 424 | 1908 | | | | 617 | 231 | | | | 2576 | 1240 | 8 | NK |
| Qi Q et al | 2009 | China | PB | 152 | 1183 | | | | 235 | 69 | | | | 1614 | 752 | 8 | NK |
| Hu C et al | 2009 | China | PB | 1719 | 1720 | 947 | 643 | 129 | 2537 | 901 | 706 | 816 | 198 | 2228 | 1212 | 8 | 0.101 |
| Liu Y et al | 2009 | China | NR | 1880 | 1996 | 902 | 813 | 165 | 2617 | 1143 | 853 | 919 | 224 | 2625 | 1367 | 7 | 0.318 |
| Tan JT et al | 2009 | Chinese | PB | 1541 | 2196 | | | | 2127 | 955 | | | | 2943 | 1449 | 7 | NK |
| Tan JT et al | 2009 | Malay | PB | 1076 | 2257 | | | | 1549 | 603 | | | | 3070 | 1444 | 7 | NK |
| Tan JT et al | 2009 | Indian | PB | 246 | 364 | | | | 482 | 10 | | | | 684 | 44 | 7 | NK |
| Zhang S et al | 2009 | China | HB | 104 | 98 | 52 | 44 | 8 | 148 | 60 | 42 | 46 | 10 | 130 | 66 | 7 | 0.615 |
| Yamauchi T et al | 2010 | Japanese | PB | 4878 | 3345 | | | | 6439 | 3317 | | | | 4108 | 2582 | 7 | NK |
| Yamauchi T et al | 2010 | Japanese | PB | 2886 | 3087 | | | | 3861 | 1911 | | | | 3772 | 2402 | 7 | NK |
| Han X et al | 2010 | China | PB | 990 | 959 | 525 | 396 | 69 | 1446 | 534 | 415 | 437 | 107 | 1267 | 651 | 8 | 0.616 |
| Xu M et al | 2010 | China | PB | 1825 | 2200 | | | | 2548 | 1102 | | | | 2820 | 1580 | 8 | NK |
| Zhou JB et al | 2010 | China | PB | 537 | 510 | | | | 773 | 301 | | | | 663 | 357 | 8 | NK |
| Been LF et al | 2011 | India | PB | 1290 | 1019 | 1259 | 30 | 1 | 2548 | 32 | 982 | 36 | 1 | 2000 | 38 | 8 | 0.269 |
| Been LF et al | 2011 | US-India | PB | 139 | 557 | 133 | 6 | 0 | 272 | 6 | 523 | 32 | 2 | 1078 | 36 | 8 | 0.055 |
| Saif-Ali R et al | 2011 | Malaysia | HB | 234 | 177 | 135 | 79 | 20 | 349 | 119 | 81 | 75 | 21 | 237 | 117 | 7 | 0.572 |
| Tabara Y et al | 2011 | Japan | NR | 493 | 394 | 243 | 206 | 44 | 692 | 294 | 136 | 193 | 65 | 465 | 323 | 8 | 0.803 |
| Saif-Ali R et al | 2011 | Malaysia | HB | 300 | 230 | 183 | 99 | 18 | 465 | 135 | 113 | 90 | 27 | 316 | 144 | 7 | 0.171 |
| Da W et al | 2011 | China | PB | 223 | 201 | 115 | 92 | 16 | 322 | 124 | 79 | 88 | 34 | 246 | 156 | 8 | 0.268 |
| Dai XP et al | 2012 | China | NR | 367 | 212 | 233 | 112 | 22 | 578 | 156 | 110 | 82 | 20 | 302 | 122 | 7 | 0.412 |
| Yu W et al | 2012 | China | PB | 5409 | 614 | 2773 | 2245 | 391 | 7791 | 3027 | 235 | 313 | 66 | 783 | 445 | 8 | 0.011 |
| Yu W et al | 2012 | China | PB | 2994 | 3256 | 1608 | 1162 | 224 | 4378 | 1610 | 1391 | 1490 | 375 | 4272 | 2240 | 8 | 0.426 |
| Gamboa-Melendez MA et al | 2012 | Mexico | HB | 1027 | 990 | | | | 1479 | 575 | | | | 1313 | 667 | 7 | NK |
| Turki A et al | 2012 | Tunisia | NR | 883 | 591 | 763 | 106 | 14 | 1632 | 134 | 528 | 57 | 6 | 1113 | 69 | 7 | 0.003 |
| Iwata M et al | 2012 | Japan | HB | 724 | 763 | 342 | 300 | 82 | 984 | 464 | 283 | 329 | 151 | 895 | 631 | 8 | 0.002 |
| Van Vliet-Ostaptchouk JV et al | 2012 | Netherlands | NR | 4511 | 5152 | 4149 | 348 | 14 | 8646 | 376 | 4638 | 507 | 7 | 9783 | 521 | 7 | 0.073 |

**Table 1** (continued)

| Authors | Year | Country | Source of control | Sample size | | Cse | | | | | Control | | | | | NOS score | HWE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Case | Control | CC | CT | TT | C | T | CC | CT | TT | C | T | | |
| Odgerel Z et al | 2012 | China | PB | 177 | 216 | | | | 223 | 131 | | | | 315 | 117 | 8 | NK |
| Gao X et al | 2012 | China | HB | 200 | 200 | 95 | 88 | 17 | 278 | 122 | 72 | 102 | 26 | 246 | 154 | 8 | 0.276 |
| Yamakawa-Kobayashi K et al | 2012 | Japan | PB | 333 | 417 | | | | 426 | 240 | | | | 484 | 350 | 8 | NK |
| Tam CH et al | 2013 | China | PB | 5882 | 2569 | | | | 8458 | 3306 | | | | 3371 | 1767 | 7 | NK |
| Almawi WY et al | 2013 | Lebanon | NR | 994 | 1077 | 499 | 371 | 124 | 1369 | 619 | 801 | 225 | 51 | 1827 | 327 | 7 | 0.000 |
| Long J et al | 2013 | America | PB | 1551 | 2725 | | | | 2823 | 279 | | | | 4851 | 600 | 8 | NK |
| Lin YD et al | 2013 | China | PB | 2899 | 3261 | 1491 | 1174 | 234 | 4156 | 1642 | 1433 | 1431 | 397 | 4297 | 2225 | 7 | 0.174 |
| Yang HL et al | 2013 | China | HB | 222 | 140 | 123 | 87 | 12 | 333 | 111 | 60 | 59 | 21 | 179 | 101 | 8 | 0.308 |
| Wang T et al | 2013 | China | HB | 300 | 200 | 150 | 132 | 18 | 432 | 168 | 72 | 102 | 26 | 246 | 154 | 8 | 0.276 |
| Bazzi MD et al | 2014 | Saudi | HB | 78 | 96 | 71 | 7 | 0 | 149 | 7 | 89 | 7 | 0 | 185 | 7 | 7 | 0.711 |
| The STDC | 2014 | Mexico/USA | NR | 4366 | 3848 | | | | 6435 | 2297 | | | | 5487 | 2209 | 6 | NK |
| Zhu AN et al | 2014 | China | HB | 238 | 240 | 106 | 118 | 14 | 330 | 146 | 109 | 98 | 33 | 316 | 164 | 6 | 0.153 |
| Zhang WL et al | 2015 | China | NR | 530 | 452 | 274 | 217 | 39 | 765 | 295 | 194 | 192 | 66 | 580 | 324 | 8 | 0.104 |
| Qian Y et al | 2015 | China | PB | 2925 | 3281 | 1504 | 1185 | 236 | 4193 | 1657 | 1442 | 1440 | 399 | 4324 | 2238 | 8 | 0.177 |
| Cui LJ et al | 2016 | China | HB | 100 | 100 | 39 | 46 | 15 | 124 | 76 | 53 | 35 | 12 | 141 | 59 | 7 | 0.113 |
| Zhou XY et al | 2016 | China | HB | 305 | 200 | 148 | 136 | 21 | 432 | 178 | 72 | 102 | 26 | 246 | 154 | 7 | 0.276 |
| Riobello C et al | 2016 | Spain | HB | 180 | 501 | 155 | 25 | 0 | 335 | 25 | 450 | 51 | 0 | 951 | 51 | 6 | 0.230 |
| Al-Shammari MS et al | 2017 | Saudi | NR | 330 | 516 | 319 | 9 | 2 | 647 | 13 | 496 | 15 | 5 | 1007 | 25 | 7 | 0.000 |
| Plengvidhya N et al | 2018 | Thailand | HB | 500 | 500 | 285 | 192 | 23 | 762 | 238 | 254 | 205 | 41 | 713 | 287 | 8 | 0.968 |
| Chen JF et a | 2018 | China | HB | 84 | 104 | 34 | 42 | 8 | 110 | 58 | 57 | 36 | 11 | 150 | 58 | 7 | 0.155 |
| Huang Q et al | 2018 | China | PB | 506 | 497 | 250 | 220 | 36 | 720 | 292 | 215 | 231 | 51 | 661 | 333 | 8 | 0.336 |
| Yang KL et al | 2018 | China | PB | 522 | 522 | 270 | 215 | 37 | 755 | 289 | 237 | 232 | 53 | 706 | 338 | 8 | 0.732 |
| Li YH et al | 2018 | China | NR | 284 | 99 | 210 | 68 | 6 | 488 | 80 | 84 | 15 | 0 | 183 | 15 | 8 | 0.415 |
| Li YH et al | 2018 | China | NR | 293 | 208 | 144 | 128 | 21 | 416 | 170 | 88 | 97 | 23 | 273 | 143 | 8 | 0.628 |
| Xu T et al | 2018 | China | HB | 100 | 100 | 31 | 45 | 24 | 107 | 93 | 32 | 41 | 27 | 105 | 95 | 8 | 0.075 |
| Totomoch-Serra A et al | 2018 | Mexico | HB | 415 | 416 | | | | 523 | 307 | | | | 541 | 291 | 8 | NK |

**Table 2** Pooled ORs and 95% CIs of the association between *KCNQ1* rs2237892 polymorphism and T2DM

| Total and subgroups | Studies | CC vs CT + TT | | | | CC + CT vs TT | | | | C VS T | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | OR | 95%CI | $I^2$ | P | OR | 95%CI | $I^2$ | P | OR | 95%CI | $I^2$ | P |
| Total | 41/60 | 1.26 | 1.14–1.40 | 87.2% | < 0.001 | 1.50 | 1.34–1.68 | 66.6% | < 0.001 | 1.25 | 1.19–1.32 | 86.6% | < 0.001 |
| Ethnicity | | | | | | | | | | | | | |
| East Asian | 30/42 | 1.39 | 1.31–1.49 | 61.4% | < 0.001 | 1.59 | 1.50–1.68 | 0.0% | 0.575 | 1.32 | 1.27–1.37 | 69.4% | < 0.001 |
| Southeast Asian | 3/4 | 1.43 | 1.20–1.72 | 0.00% | 0.453 | 1.79 | 1.27–2.52 | 0.0% | 0.712 | 1.30 | 1.17–1.45 | 20.0% | 0.290 |
| South Asian | 1/2 | 1,53 | 0.94–2.48 | — | — | 1.26 | 0.08–20.27 | – | – | 2.07 | 1.03–4.17 | 64.6% | 0.093 |
| West Asian | 3/3 | 0.64 | 0.26–1.57 | 82.3% | 0.003 | 1.50 | 1.39–1.68 | 68.5% | 0.075 | 1.25 | 1.19–1.32 | 83.0% | 0.003 |
| Caucasian | 2/4 | 1.00 | 0.56–1.76 | 79.0% | 0.029 | 0.44 | 0.18–1.08 | – | – | 1.19 | 1.02–1.38 | 36.7% | 0.192 |
| Other | 2/5 | 0.91 | 0.52–1.61 | 43.5% | 0.184 | 0.68 | 0.27–1.70 | 0.0% | 0.677 | 1.06 | 0.90–1.25 | 75.1% | 0.003 |
| Source of control | | | | | | | | | | | | | |
| HB | 17/19 | 1.25 | 1.08–1.46 | 59.2% | 0.001 | 1.68 | 1.44–1.97 | 10.6% | 0.335 | 1.24 | 1.14–1.37 | 63.4% | < 0.001 |
| PB | 11/24 | 1.48 | 1.38–1.59 | 47.4% | 0.040 | 1.50 | 1.34–1.68 | 0.0% | 0.984 | 1.25 | 1.19–1.32 | 67.6% | < 0.001 |
| NR | 13/17 | 1.13 | 0.87–1.42 | 94.6% | < 0.001 | 1.21 | 0.91–1.62 | 86.2% | < 0.001 | 1.16 | 1.02–1.32 | 95.0% | < 0.001 |
| Case size | | | | | | | | | | | | | |
| < 500 | 21 | 1.24 | 1.05–1.46 | 63.6% | < 0.001 | 1.77 | 1.50–2.08 | 0.0% | 0.483 | 1.23 | 1.09–1.38 | 71.5% | < 0.001 |
| 500–1000 | 10 | 1.13 | 0.81–1.58 | 95.3% | < 0.001 | 1.32 | 0.91–1.91 | 88.5% | < 0.001 | 1.14 | 0.88–1.48 | 95.7% | < 0.001 |
| 1001–2000 | 4 | 1.41 | 1.14–1.75 | 82.4% | 0.001 | 1.44 | 1.26–1.65 | 0.0% | 0.670 | 1.25 | 1.19–1.32 | 67.3% | < 0.001 |
| > 2000 | 6 | 1.43 | 1.33–1.53 | 58.0% | 0.036 | 1.56 | 1.41–1.72 | 35.2% | 0.173 | 1.33 | 1.27–1.39 | 80.1% | < 0.001 |
| HWE status | | | | | | | | | | | | | |
| Yes | 36/36 | 1.36 | 1.28–1.45 | 57.3% | < 0.001 | 1.57 | 1.48–1.67 | 2.9% | 0.420 | 1.32 | 1.26–1.38 | 53.2% | < 0.001 |
| No | 5/5 | 0.95 | 0.46–1.96 | 97.8% | < 0.001 | 0.99 | 0.45–2.18 | 94.0% | < 0.001 | 1.25 | 1.19–1.32 | 98.1% | < 0.001 |
| NK | 0/19 | – | – | – | – | – | – | – | – | 1.25 | 1.18–1.34 | 82.8% | < 0.001 |

rs2237892 polymorphism and T2DM risk. Our results showed that *KCNQ1* rs2237892 polymorphism could be associated with T2DM in the dominant (CC vs CT + TT), recessive (CC + CT vs TT) and allele models (C vs T). In a stratified analysis based on ethnicity, source of control, and case size, we found that *KCNQ1* rs2237892 polymorphism was significantly associated with T2DM in the dominant model, the allele model of East Asians, and in the allele model of West Asian populations. In Southeast Asian, South Asian, Caucasian, and other populations, *KCNQ1* rs2237892 polymorphism was not significantly related to T2DM. In the stratified analysis according to the source of control, we found that *KCNQ1* rs2237892 polymorphism was significantly correlated with T2DM in the dominant model and the allele model of HB and PB group, and in the allele model of NR group. But the correlation between *KCNQ1* rs2237892 polymorphism and T2DM in children lacked corresponding evidence. The stratified analysis of the sample size showed that the correlation between populations occurred when the number of samples in the case group was less than 500, within 1001–2000, and > 2000. The above analysis shows that the ethnicity, the source of the control group, and the sample size of the case group may be the factors in the association occurred (Fig. 2).

Previously, a meta-analysis was performed in 2012 to investigate the association between *KCNQ1* rs2237892 polymorphism and T2DM risk; however, only 25 articles were included in the analysis. Recently, a meta-analysis was performed to investigate the relationship between several *KCNQ1* SNPs and T2DM risk, and a significant relationship between *KCNQ1* polymorphism rs2237892 and T2DM risk was found [63]. However, the analysis was limited to 38 articles and incomplete sample size as well as selective bias are potential limitations of that study [63] (Fig. 3).

Compared to previous studies, our results demonstrate robust evidence to support a correlation between *KCNQ1* rs2237892 polymorphism and T2DM risk. Scientists do not currently understand the biological mechanisms that cause an association between *KCNQ1* and T2DM. There is biological evidence supporting the hypothesis that *KCNQ1* might play a role in the predisposition to T2DM. *KCNQ1*, encoding the alpha subunit of the IKsK + channel, is expressed in the tissues or cells of the heart [64], as well as in pancreas islets, which play an important role in the regulation of insulin secretion [23] (Fig. 4).

This meta-analysis has several limitations. Firstly, most of the articles included in the meta-analysis involved the Asian population, while there were few articles involving Caucasian and other populations. Therefore, we could not perform the analysis grouped by different populations, and the ability to apply our results to a more general population is subsequently limited. Secondly, T2DM is caused by complex interactions between genetic, lifestyle, and environmental factors. Our study focused exclusively on the impact of genetic factors on T2DM risk. In the future, further studies should be conducted to determine interconnection between *KCNQ1* rs2237892, lifestyle factors, and environmental factors on T2DM.

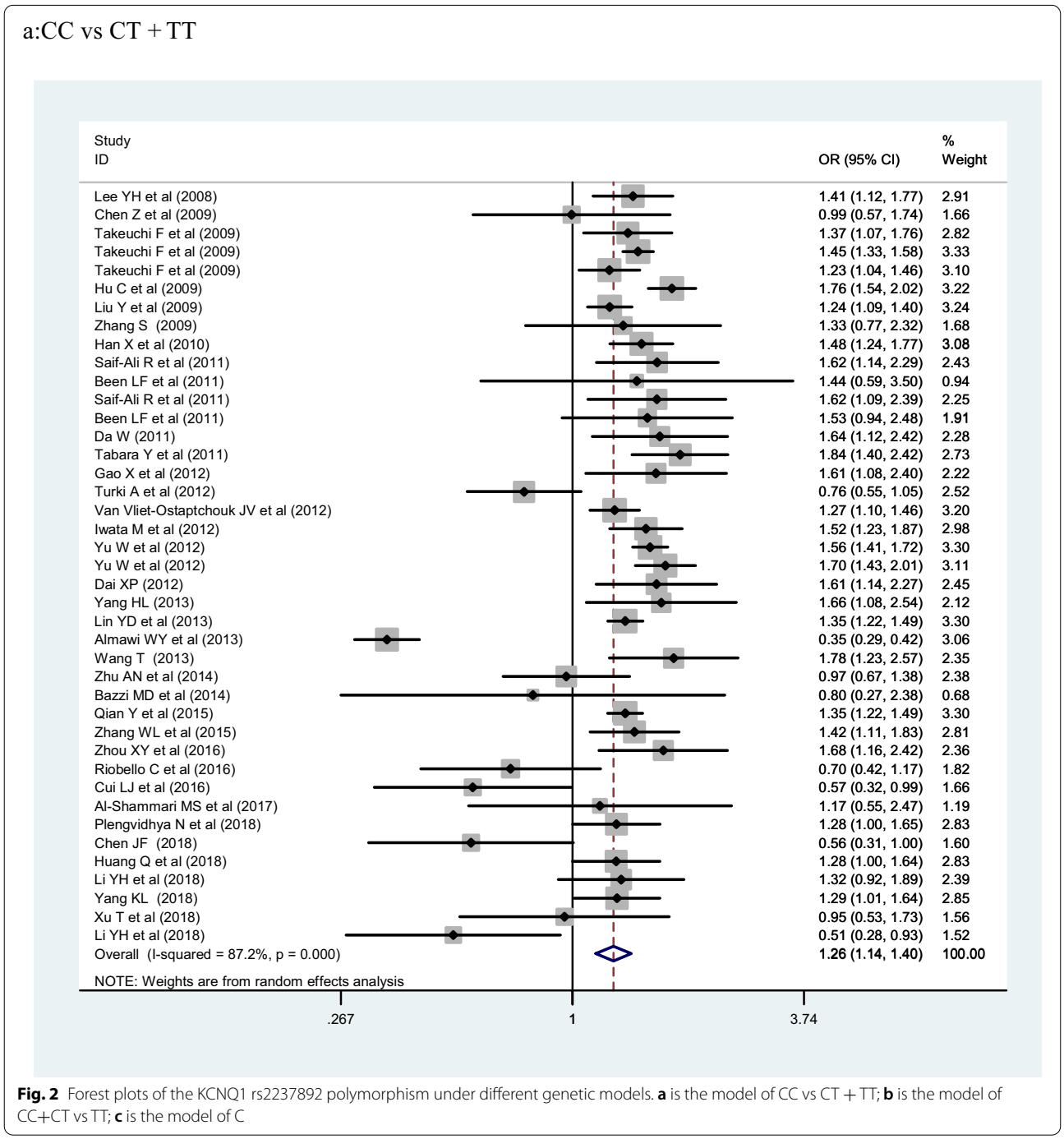


**Fig. 2** Forest plots of the KCNQ1 rs2237892 polymorphism under different genetic models. **a** is the model of CC vs CT + TT; **b** is the model of CC+CT vs TT; **c** is the model of C

b:CC+CT vs TT

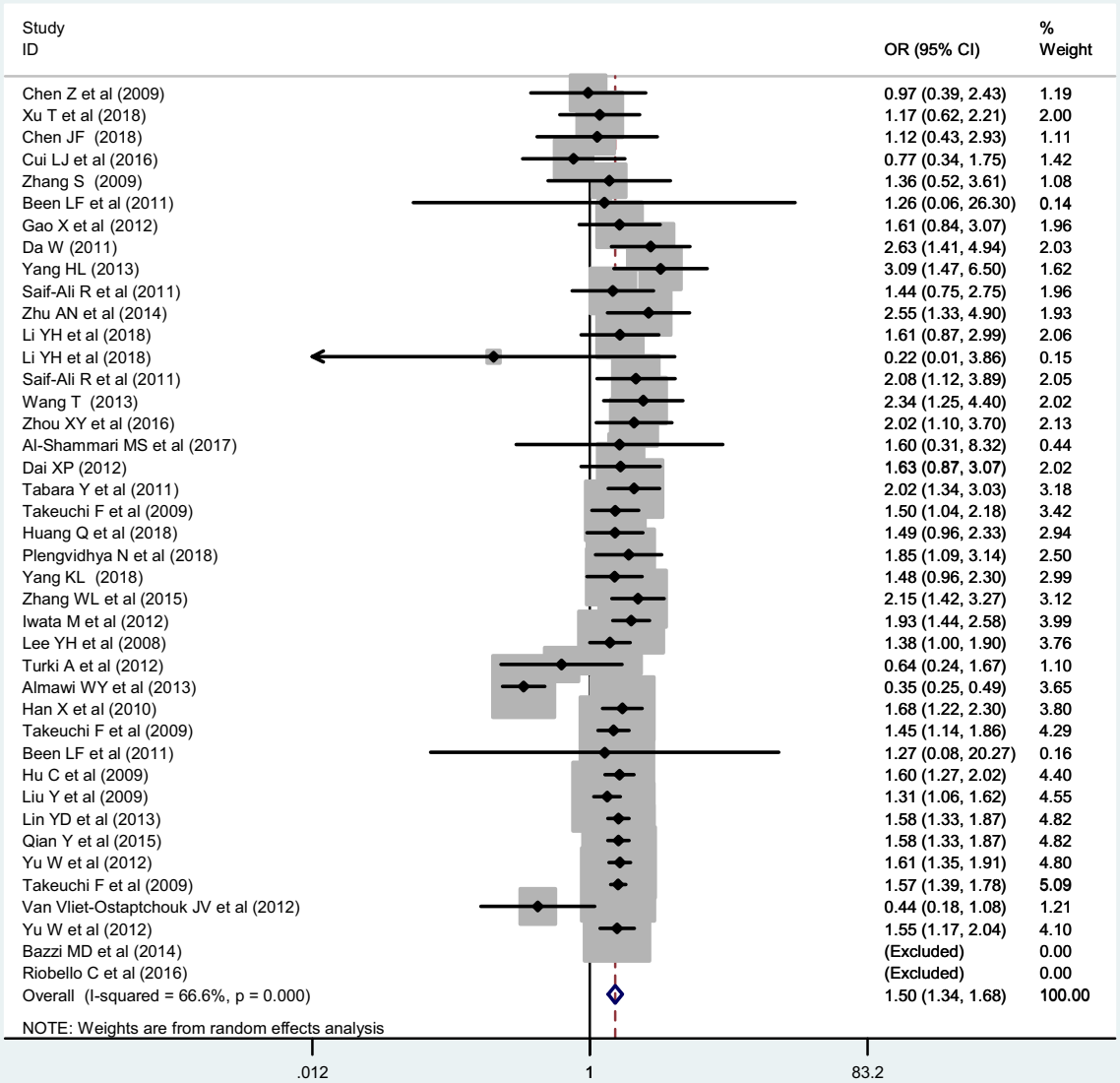


**Fig. 2** continued

c:C vs T

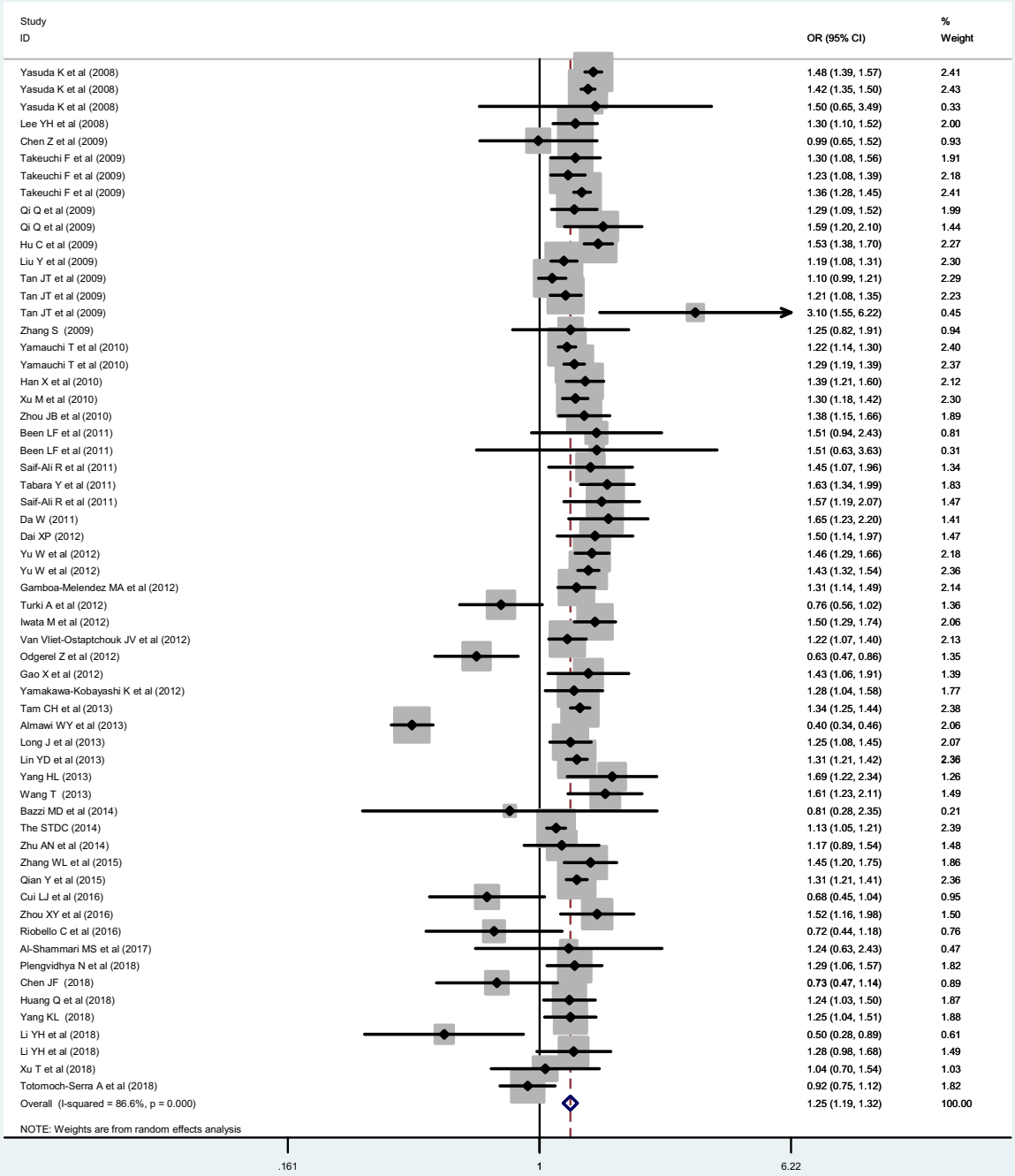


**Fig. 2** continued

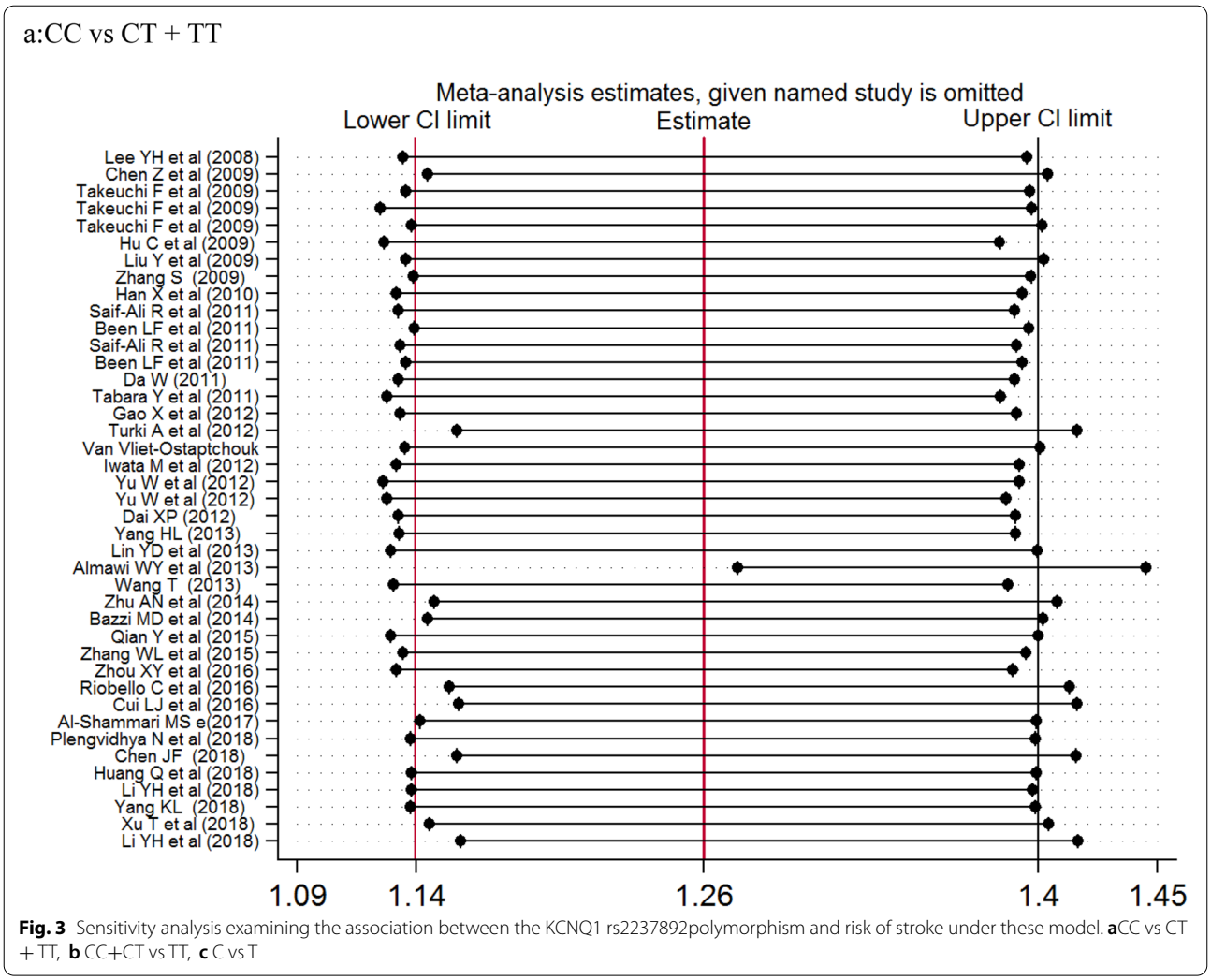


**Fig. 3** Sensitivity analysis examining the association between the KCNQ1 rs2237892polymorphism and risk of stroke under these model. **a**CC vs CT + TT, **b** CC+CT vs TT, **c** C vs T

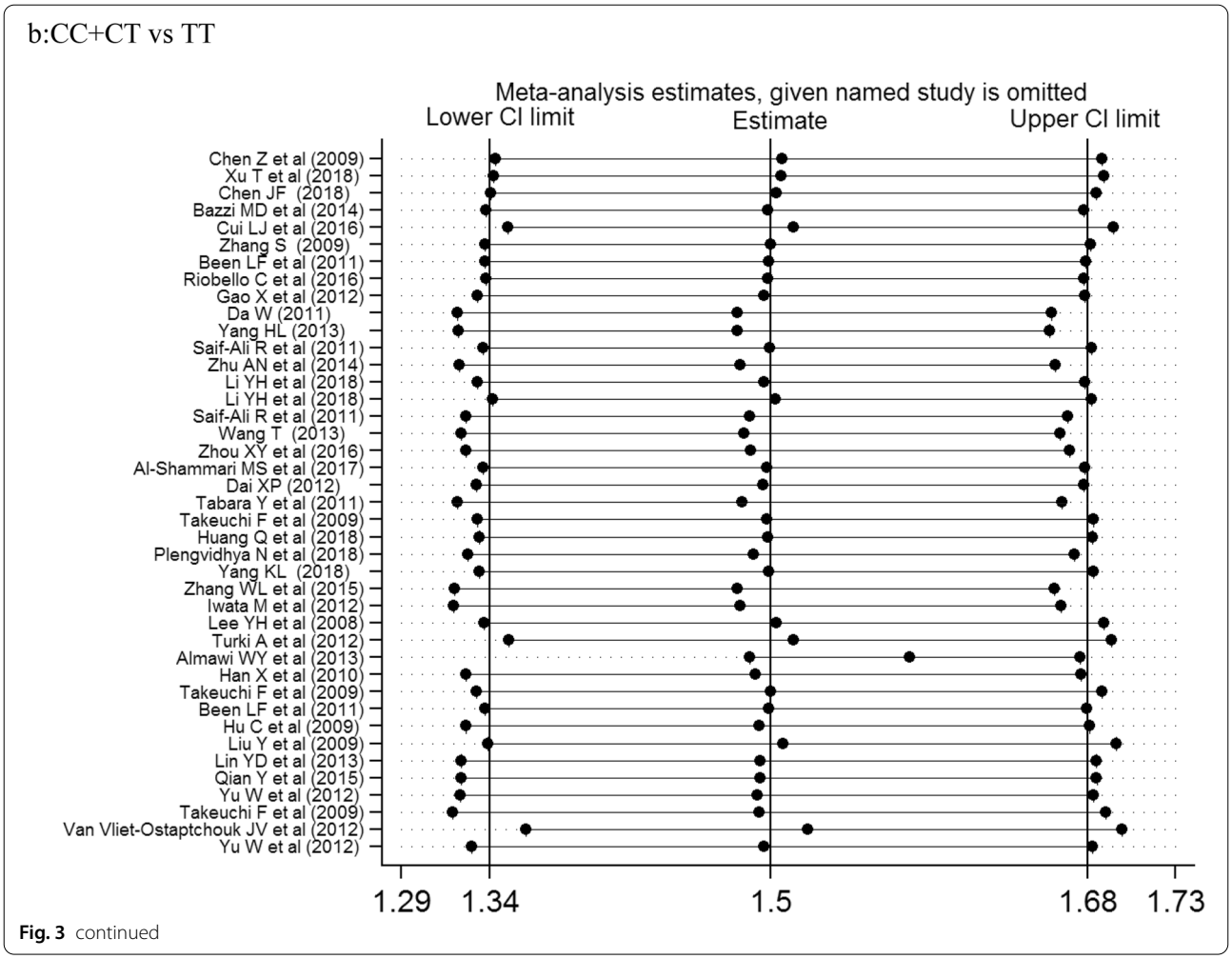


**Fig. 3** continued

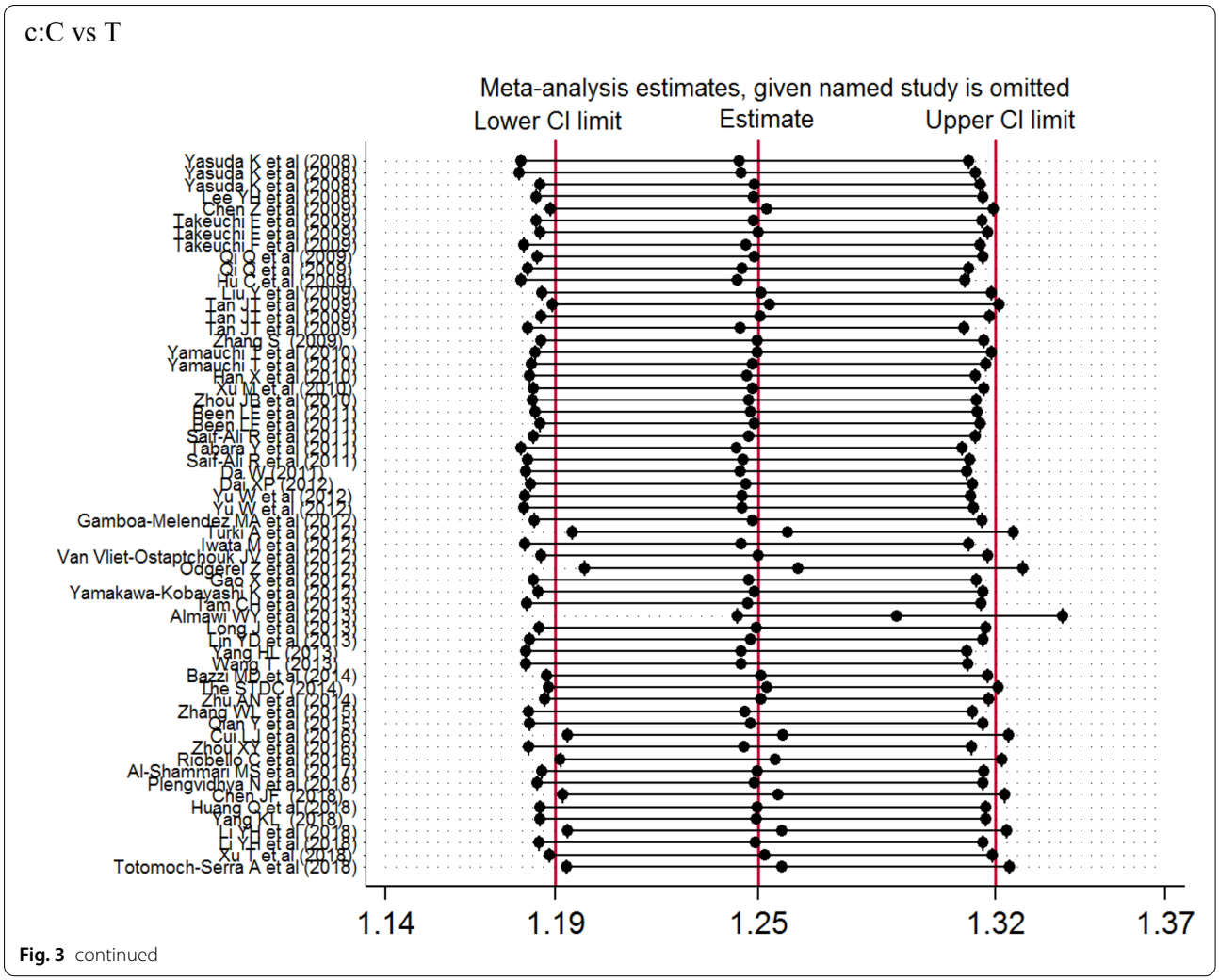


**Fig. 3** continued

## Conclusion

Our meta-analysis demonstrated an association between *KCNQ1* rs2237892 polymorphism and the predisposition to T2DM. There was notable correlation between *KCNQ1* rs2237892 and T2DM in East Asian populations and West Asian populations. However, for the Southeast Asian, South Asian, Caucasian, and other populations, the relevance of the KCNQ1 rs2237892 SNP was not confirmed because of the relatively limited sample size and the sparse amount of research into this subject. In addition, the source of the control group and the sample size of the case would also have an impact on the study results in the stratified analysis of this study. Therefore, in future research, we suggest exploring the relationship between *KCNQ1* rs2237892 polymorphism and T2DM in a wide variety of populations. Although two meta-analyses were performed previously, the number of articles included in these was less than that in our study. Therefore, we believe that our study is superior than the two previous meta- studies.

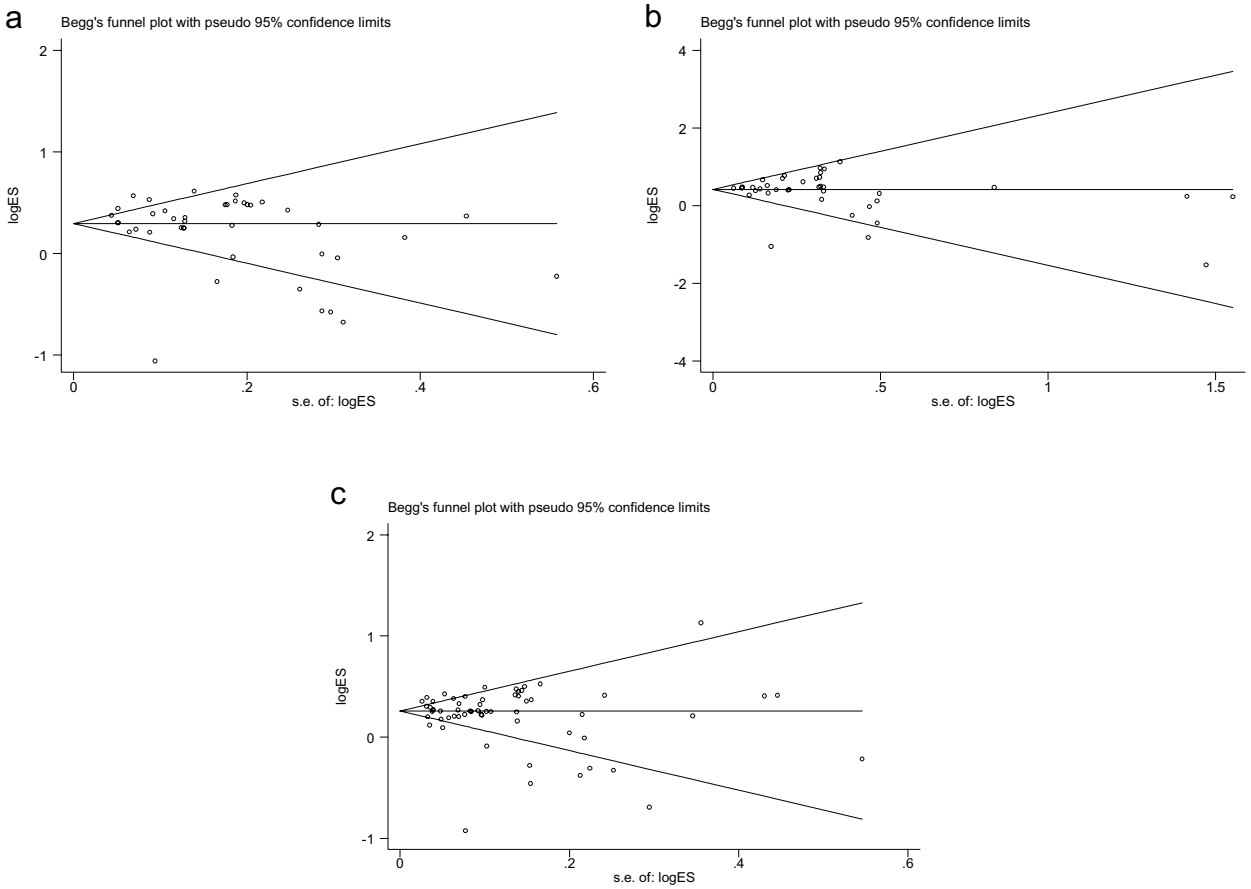


**Fig. 4** Begg's funnel plot for publication bias analysis. **a** is the model of CC vs CT + TT; **b** is the model of CC+CT vs TT; **c** is the model of C vs T

**Abbreviations**
T2DM: Type 2 diabetes mellitus; IDF: International Diabetes Federation; PRISMA: Preferred Reporting Project; HWE: Hardy–Weinberg equilibrium; SNP: Single nucleotide polymorphism.

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**Authors' contributions**
Manuscript writing, editing and review were conducted by HLJ; YJD and XL participated in the articles search; HLJ and HD performed data analysis and evaluation the quality of the selected studies. All authors read and approved the final manuscript.

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**Availability of data and materials**
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

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