Review Article

Ethnicity Differences in the Association of UCP1-3826A/G, UCP2-866G/A and Ala55Val, and UCP3-55C/T Polymorphisms with Type 2 Diabetes Mellitus Susceptibility: An Updated Meta-Analysis

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Background. The relationship between uncoupling protein (UCP) 1-3 polymorphisms and susceptibility to type 2 diabetes mellitus (T2DM) has been extensively studied, while conclusions remain contradictory. Thus, we performed this meta-analysis to elucidate whether the UCP1-3826A/G, UCP2-866G/A, Ala55Val, and UCP3-55C/T polymorphisms are associated with T2DM.

Methods. Eligible studies were searched from PubMed, Cochrane Library, and Web of Science database before 12 July 2020. Pooled odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated to evaluate the strength of the association. Heterogeneity analysis, subgroup analysis, sensitivity analysis, and publication bias were also performed.

Results. A total of 38 case-control studies were included in this meta-analysis. The overall results revealed significant association between T2DM and the UCP2 Ala55Val polymorphism (recessive model: OR = 1.25, 95% CI 1.12-1.40, \( P < 0.01 \); homozygous model: OR = 1.33, 95% CI 1.03-1.72, \( P = 0.029 \), respectively). In subgroup analysis stratified by ethnicity, T2DM risk was increased with the UCP2 Ala55Val polymorphism (allele model: OR = 1.17, 95% CI 1.02-1.34, \( P = 0.023 \); recessive model: OR = 1.28, 95% CI 1.13-1.45, \( P < 0.01 \); homozygous model: OR = 1.39, 95% CI 1.05-1.86, \( P = 0.023 \), respectively), while decreased with the UCP2-866G/A polymorphism in Asians (dominant model: OR = 0.86, 95% CI 0.74-1.00, \( P = 0.045 \)).

Conclusions. Our results demonstrate that the UCP2-866G/A polymorphism is protective against T2DM, while the UCP2 Ala55Val polymorphism is susceptible to T2DM in Asians.

1. Introduction

Diabetes is a serious public health problem characterized by chronic hyperglycemia. The International Diabetes Federation (IDF) estimates that there were approximately 463 million adults (aged 20–79 years) diagnosed with diabetes in 2019, and this number is expected to reach 700 million by 2045 across the world [1]. Among them, type 2 diabetes mellitus (T2DM) is the most prevalent which accounts for 90%-95%. Till now, the detailed etiology of T2DM have not been fully clarified, and genetic predisposition is believed to exert great effects together with environmental influences [2].

Uncoupling proteins (UCPs) are a family of mitochondrial anion transporters located in the mitochondrial inner membrane which plays crucial roles in regulating the flux of protons through the ATP synthase [3]. There are five members described in the mammal UCP family, including UCP1 to UCP5. UCP1 is specifically expressed in the brown adipose tissue (BAT); UCP2 is more broadly expressed, including pancreatic β cells and cells of the immune system,
skeletal muscle, spleen, liver, lung, and macrophages; UCP3 is primarily expressed in skeletal muscle, but it is also found in BAT and heart tissue; UCP4 and UCP5 are recently discovered mainly in the central nervous system [4, 5]. Previous studies have linked UCPs to energy expenditure both in animal models and in obese population, especially UCP1, UCP2, and UCP3 [6–9]. Moreover, the UCPs were also demonstrated to participate in reactive oxygen species production, oxidant stress, apoptosis, inflammation, and insulin resistance [10–14]. For those reasons, UCP1, UCP2, and UCP3 may be involved in the development of obesity, T2DM, and diabetic complications [15, 16].

Human UCP1 gene is located on chromosome 4q28-q31 and 8.9 kb in length, while both UCP2 and UCP3 genes map to chromosome 11q13 and spans 8.2 and 8.7 kb, respectively [17]. Over the past few decades, numerous studies have investigated the association between single-nucleotide polymorphisms (SNPs) of the UCP1-3 genes and T2DM susceptibility, and the most focused on the -3826A/G (rs1800592) polymorphism in the promoter region of the UCP1 gene, the -866G/A (rs659366) polymorphism in the promoter region and a missense variant in exon 4 (Ala55Val, C/T, rs660339) of the UCP2 gene, and the -55C/T (rs1800849) polymorphism in the promoter region of the UCP3 gene [18–21]. However, the results remain under debate. Consequently, this meta-analysis was carried out based on the latest publications in attempt to elucidate whether there is an association between the UCP polymorphisms and T2DM susceptibility.

2. Methods

This meta-analysis was performed in accordance to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines (File S1).

2.1. Literature Search. We systematically searched electronic databases of PubMed, Cochrane Library, and Web of Science for all relevant articles published before 12 July 2020. The search terms were applied as follows: (“diabetes” or “T2D” or “T2DM”) and (“uncoupling protein” or “UCP”) and (“polymorphism” or “mutation” or “variant”). To obtain more qualified studies, the references cited in the original research and review articles were also manually searched. The papers were restricted to humans and written in English.

2.2. Literature Inclusion. Studies were considered eligible when meeting the following inclusion criteria: (1) case-control study design; (2) evaluating the association between the UCP1-3826A/G, UCP2-866G/A and Ala55Val, and UCP3-55C/T polymorphisms and T2DM susceptibility; and (3) providing sufficient genotype data to calculate odds ratios (ORs) and 95% confidence intervals (CIs). The exclusion criteria were (1) editorials, case reports, letters, comments, reviews, or meta-analyses and (2) studies without detailed genotyping data. Furthermore, if there were duplicate publications based on the same data, only the latest or most complete study was included in our meta-analysis.

2.3. Data Extraction. Two reviewers (Huang R and Cai TT) independently extracted the following data from the enrolled studies: first author, publication year, ethnicity, genotyping method, total number of cases and controls, genotype and allele distributions of cases and controls, and controls with Hardy-Weinberg equilibrium (HWE) or not. All possible efforts were made to contact the corresponding authors if essential data were needed. Any discrepancy in data extraction was resolved by a third reviewer (Zhou YT).

2.4. Quality Assessment. Two investigators (Wang YM and Wang HY) separately performed the quality assessment of each included study using the Newcastle-Ottawa quality assessment scale (NOS). The NOS comprises the following three aspects: selection of study subjects (4 points), comparability of study subjects (2 points), and exposure or outcomes (3 points) [22]. The total score ranges from 0 to 9, and those with score ≥ 6 were considered as high-quality studies.

2.5. Statistical Analysis. HWE of the genotype distribution in the control subjects was assessed by $\chi^2$ test. Pooled ORs with corresponding 95% CIs were used to measure the strength of the association between UCP1-3826A/G, UCP2-866G/A and Ala55Val, and UCP3-55C/T polymorphisms and T2DM susceptibility under the following models: allele model, dominant model, recessive model, homozygous model, and heterozygous model. Subgroup analysis was performed according to the ethnicity of included populations. The heterogeneity across studies was estimated via $I^2$ test. $I^2 > 50 \%$ or $P_{Q} \leq 0.1$ was considered to indicate significant heterogeneity. If significant heterogeneity existed, random effects model (REM) was used; otherwise, fixed effects model (FEM) was applied. Galbraith plot was conducted to explore the outlier and main contributor to heterogeneity. To assess the stability of the results, sensitivity analysis was carried out by omitting each study in sequence. Additionally, potential publication bias was evaluated with Begg’s funnel plot and Egger’s test. All statistical analyses were performed using STATA Version 11.0 (College Station, TX, USA), and a two-sided $P$ value $< 0.05$ was considered statistically significant.

3. Results

3.1. Characteristics of Included Studies. As described in the flow chart, a total of 583 studies were retrieved through searching the electronic database (Figure 1). After excluding duplicated publications, 415 records were initially identified. Then, 240 articles were removed including editorials, case reports, letters, comments, reviews, and meta-analyses, and 175 articles were assessed in full. Finally, 38 relevant studies with sufficient data were included in our meta-analysis [17, 19, 20, 23–57]. Among the eligible studies, 9 analyzed the UCP1-3826A/G polymorphism, 23 analyzed the UCP2-866G/A polymorphism, 9 analyzed the UCP2 Ala55Val polymorphism, and 11 analyzed the UCP3-55C/T polymorphism. Table 1 detailly shows the main characteristics of the studies.
3.2. Synthesis Analysis. The results of meta-analysis and heterogeneity test for the association of UCP1-3826A/G, UCP2-866G/A and Ala55Val, and UCP3-55C/T polymorphisms with T2DM susceptibility under five inheritance models are summarized in details in Table 2. Figure 2 illustrates the pooled ORs (95% CI) of UCP1-3826A/G, UCP2-866G/A and Ala55Val, and UCP3-55C/T polymorphisms with T2DM risk stratified by ethnicity under an allele contrast inheritance model. Our results revealed significant association between T2DM and UCP2 Ala55Val polymorphism (recessive model: OR = 1.25, 95% CI 1.12-1.40, P < 0.01; homozygous model: OR = 1.33, 95% CI 1.03-1.72, P = 0.029, respectively), but no associations between T2DM and UCP1-3826A/G, UCP2-866G/A and Ala55Val, and UCP3-55C/T polymorphisms with T2DM risk stratified by ethnicity under an allele contrast inheritance model. Further in the subgroup analyses stratified by ethnicity, T2DM risk was increased with UCP2 Ala55Val polymorphism (allele model: OR = 1.17, 95% CI 1.02-1.34, P = 0.023; recessive model: OR = 1.28, 95% CI 1.13-1.45, P < 0.01; homozygous model: OR = 1.39, 95% CI 1.05-1.86, P = 0.023, respectively), while decreased with UCP2-866G/A polymorphism in Asians (dominant model: OR = 0.86, 95% CI 0.74-1.00, P = 0.045) (Table 2).

3.3. Heterogeneity Analysis. As shown in Table 2, significant heterogeneity was found among studies in almost all genetic models of the overall population except the heterozygous model of the UCP2-866G/A polymorphism, the recessive model of the UCP2 Ala55Val polymorphism, and the dominant and heterozygous models of the UCP3-55C/T polymorphism, but no heterogeneity was found in all genetic models for the UCP1-55C/T polymorphism. After stratification by ethnicity, the heterogeneity was only eliminated between the studies of the UCP3-55C/T polymorphism in populations of European descent in the recessive and homozygous genetic models, but not in Asian descent. The heterogeneity was also existed in studies of the UCP2-866G/A and Ala55Val polymorphisms both in Asian descent and European descent. Therefore, Galbraith plot analysis was performed to detect the outlier and main contributor to heterogeneity, and the results indicated that Bulotta et al. 2005 and Hou et al. 2020, Vimaleswaran et al. 2011, and Wang LL et al. 2012 were the outliers and main contributor to heterogeneity of the UCP2-866G/A, Ala55Val, and UCP3-55C/T polymorphisms, respectively (Figure S1-S3).

3.4. Sensitivity Analysis. To evaluate the influence of a single study on the pooled results, sensitivity analysis was performed by sequentially omitting one study at a time in the overall population. The results showed that the pooled ORs lay within the overall range of 95% CIs after omitting any single study in all compared inheritance models, except for excluding the study of the Bulotta et al. 2005 in the
| First author | Year | Ethnicity | Genotyping method | Case w | Case m | Control w | Control m | HWE Score |
|--------------|------|-----------|-------------------|--------|--------|-----------|-----------|-----------|
| Boullu-Sanchis | 1999 | Asian | PCR-RFLP | 89 | 30 | 13 | 46 | 73 | 105 | 100 | 38 | 14 | 48 | 90 | 110 | No | 7 |
| Heilbronn | 2000 | Caucasian | PCR-RFLP | 45 | 22 | 19 | 4 | 63 | 27 | 99 | 59 | 36 | 4 | 154 | 44 | Yes | 6 |
| Sivenius | 2000 | Caucasian | PCR-RFLP | 70 | 38 | 20 | 12 | 96 | 44 | 123 | 65 | 32 | 26 | 162 | 84 | Yes | 9 |
| Mori | 2001 | Asian | PCR-RFLP | 320 | 83 | 156 | 81 | 322 | 138 | 250 | 58 | 116 | 76 | 232 | 268 | Yes | 7 |
| Lindholm | 2004 | Caucasian | PCR-RFLP | 434 | 253 | 181 | ND | ND | ND | 106 | 68 | 38 | ND | ND | Yes | 7 |
| Sramkova | 2007 | Caucasian | PCR-RFLP | 295 | 157 | 124 | 14 | 438 | 152 | 120 | 61 | 49 | 10 | 171 | 69 | Yes | 7 |
| Lin-1 | 2009 | Asian | TaqMan | 178 | 42 | 79 | 57 | 163 | 193 | 108 | 24 | 54 | 30 | 102 | 114 | Yes | 9 |
| Lin-2 | 2009 | Asian | TaqMan | 184 | 44 | 91 | 49 | 179 | 189 | 37 | 12 | 15 | 10 | 39 | 35 | Yes | 9 |
| Vimaleswaran | 2010 | Asian | PCR-RFLP | 810 | 292 | 372 | 146 | 956 | 664 | 990 | 396 | 446 | 148 | 1238 | 742 | Yes | 8 |
| de Souza | 2013 | Caucasian | TaqMan | 981 | 489 | 370 | 122 | 1348 | 664 | 990 | 396 | 446 | 148 | 1238 | 742 | Yes | 8 |
| Leprebre | 1998 | Caucasian | PCR-RFLP | 49 | 4 | 25 | 20 | 33 | 35 | 46 | 50 | 65 | 50 | 7 | 8 | Yes | 8 |
| Krempier | 2002 | Caucasian | PCR-RFLP | 201 | 65 | 106 | 30 | 236 | 166 | 391 | 186 | 156 | 49 | 528 | 254 | Yes | 9 |
| D’Adamo | 2004 | Caucasian | PCR-RFLP | 483 | 222 | 197 | 64 | 641 | 325 | 559 | 247 | 260 | 52 | 754 | 364 | Yes | 8 |
| Ji-1 | 2004 | Asian | PCR-RFLP | 184 | 53 | 94 | 37 | 200 | 168 | 134 | 37 | 69 | 28 | 143 | 125 | Yes | 7 |
| Ji-2 | 2004 | Asian | PCR-RFLP | 158 | 35 | 79 | 44 | 149 | 167 | 156 | 39 | 76 | 41 | 154 | 158 | Yes | 7 |
| Sasahara | 2004 | Asian | PCR-RFLP | 413 | 116 | 205 | 92 | 437 | 389 | 172 | 50 | 90 | 32 | 190 | 154 | Yes | 7 |
| Wang | 2004 | Caucasian | Pyrosequencing | 131 | ND | ND | ND | 176 | 86 | 118 | ND | ND | ND | 137 | 99 | Yes | 9 |
| Bulotta | 2005 | Caucasian | PCR-RFLP | 746 | 374 | 317 | 55 | 1065 | 427 | 327 | 142 | 44 | 41 | 428 | 148 | Yes | 9 |
| Pindhi | 2006 | Caucasian | ASA | 342 | 167 | 145 | 30 | 479 | 205 | 305 | 147 | 124 | 34 | 418 | 192 | Yes | 8 |
| Rai | 2007 | Asian | PCR-RFLP | 762 | 320 | 351 | 91 | 991 | 533 | 924 | 286 | 518 | 120 | 1090 | 758 | No | 6 |
| Lee | 2008 | Asian | TaqMan | 753 | 529 | 224 | ND | ND | ND | 630 | 488 | 142 | ND | ND | Yes | 8 |
| Lin-1 | 2009 | Asian | TaqMan | 178 | 59 | 90 | 29 | 208 | 148 | 107 | 33 | 56 | 18 | 122 | 92 | Yes | 9 |
| Lin-2 | 2009 | Asian | TaqMan | 184 | 73 | 88 | 23 | 234 | 134 | 38 | 19 | 13 | 6 | 51 | 25 | Yes | 9 |
| Yang | 2009 | Asian | PCR-RFLP | 199 | 56 | 124 | 19 | 236 | 162 | 155 | 41 | 99 | 15 | 181 | 129 | No | 6 |
| Betelshees | 2010 | Caucasian | Pyrosequencing or TaqMan | 107 | 37 | 56 | 14 | 130 | 84 | 341 | 132 | 151 | 58 | 415 | 267 | No | 6 |
| Heidari | 2010 | Asian | PCR-RFLP | 75 | 29 | 38 | 8 | 96 | 54 | 75 | 27 | 41 | 7 | 95 | 55 | Yes | 8 |
| Vimaleswaran | 2011 | Asian | PCR-RFLP | 487 | 185 | 239 | 63 | 609 | 365 | 919 | 358 | 432 | 129 | 1148 | 690 | Yes | 8 |
| Xiao | 2011 | Asian | PCR-RFLP | 930 | ND | ND | ND | 986 | 874 | 867 | ND | ND | ND | 850 | 884 | Yes | 7 |
| Wang S | 2012 | Asian | PCR-RFLP | 370 | 113 | 169 | 88 | 395 | 345 | 166 | 55 | 71 | 40 | 181 | 151 | Yes | 8 |
| de Souza | 2013 | Caucasian | TaqMan | 778 | 272 | 372 | 134 | 916 | 640 | 435 | 152 | 211 | 72 | 515 | 355 | Yes | 8 |
| Qin | 2013 | Asian | PCR-RFLP | 354 | 88 | 184 | 82 | 360 | 348 | 363 | 102 | 187 | 74 | 391 | 335 | Yes | 6 |
| Shen | 2014 | Asian | DNA sequencing | 454 | 140 | 217 | 97 | 497 | 411 | 448 | 153 | 205 | 90 | 511 | 385 | Yes | 8 |
| Gozel | 2017 | Caucasian | PCR-RFLP | 50 | 26 | 23 | 1 | 75 | 25 | 50 | 19 | 28 | 3 | 66 | 34 | Yes | 8 |
| First author | Year | Ethnicity | Genotyping method | Case | Control | Controls with HWE Score |
|--------------|------|-----------|-------------------|------|---------|------------------------|
|              |      |           |                   | Total |         |                        |
|              |      |           |                   | ww   | mw      | mm                     |
|              |      |           |                   | w    | m       | Total                  |
|              |      |           |                   |       |         |                        |
|              |      |           |                   |       |         |                        |
| Gomathi      | 2019 | Asian     | PCR-RFLP          | 318  | 128     | 147 43 403 233 312 164 |
|              |      |           |                   |      |         |                        |
| Hou          | 2020 | Asian     | PCR-RFLP          | 470  | 174     | 225 71 573 367 536 284 |
|              |      |           |                   |      |         |                        |
| Kubota       | 1998 | Asian     | PCR-RFLP          | 210  | 60      | 107 43 227 193 218 64 97 57 225 211 |
| Shinoki      | 1999 | Asian     | PCR-RFLP          | 100  | 30      | 53 17 113 87 120 28 71 21 127 113 |
| Cho          | 2004 | Asian     | PCR-RFLP          | 500  | 158     | 227 115 543 457 133 30 76 27 136 130 |
| Wang         | 2004 | Caucasian | Pyrosequencing    | 131  | ND      | ND ND 97 165 118 458 412 99 1228 610 |
| Vimaleswaran | 2011 | Asian     | PCR-RFLP          | 487  | 264     | 198 25 726 248 919 408 |
| de Souza     | 2013 | Caucasian | TaqMan            | 784  | 265     | 371 148 901 667 453 142 229 82 513 393 |
| Qin          | 2013 | Asian     | PCR-RFLP          | 292  | 55      | 147 90 257 327 369 59 203 107 321 417 |
| Shen         | 2014 | Asian     | DNA sequencing    | 472  | 166     | 219 87 551 393 441 121 204 116 446 436 |
| Su           | 2018 | Asian     | MALDI-TOF-MS      | 387  | 132     | 191 64 455 319 398 142 194 62 478 318 |
| Meirhaeghe-1 | 2000 | Caucasian | NA                | 49   | 36      | 13 0 85 13 894 542 312 40 1396 392 |
| Meirhaeghe-2 | 2000 | Caucasian | NA                | 171  | 116     | 49 6 281 61 124 70 46 8 186 62 |
| Dalgaard     | 2001 | Caucasian | NA                | 455  | 253     | 169 33 675 235 521 280 192 49 752 290 |
| Cho          | 2004 | Asian     | PCR-RFLP          | 499  | 251     | 204 44 706 292 132 62 59 11 183 81 |
| Lindholm     | 2004 | Caucasian | PCR-RFLP          | 434  | 220     | 214 ND ND 106 51 55 ND ND |
| Pinelli      | 2006 | Caucasian | ASA               | 342  | 240     | 94 8 574 110 305 224 78 3 526 84 |
| Lee          | 2008 | Asian     | TaqMan            | 753  | 381     | 372 ND ND 630 296 334 ND ND |
| Vimaleswaran | 2011 | Asian     | PCR-RFLP          | 487  | 278     | 180 29 736 238 919 460 377 82 1297 541 |
| Wang LL      | 2012 | Asian     | PCR-RFLP          | 100  | 41      | 25 34 107 93 113 67 21 25 155 71 |
| de Souza     | 2013 | Caucasian | TaqMan            | 822  | 559     | 231 32 1349 295 351 239 99 13 577 125 |
| Su           | 2018 | Asian     | MALDI-TOF-MS      | 394  | 180     | 182 32 542 246 398 192 175 31 559 237 |
| Sharma       | 2020 | Caucasian | TaqMan            | 425  | ND      | ND ND 748 102 342 ND ND ND |

UCP: uncoupling protein; T2DM: type 2 diabetes mellitus; HWE: Hardy-Weinberg equilibrium; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; ASA: allele specific amplification; MALDI-TOF-MS: matrix-assisted laser desorption/ionization time of flight mass spectrometry; ND: no data. For each SNPs, w: wild allele; m: mutation allele; ww: wild homozygote; mw: mutation heterozygote; mm: mutation homozygote.
| Inheritance model | Overall | Caucasian | Asian |
|-------------------|---------|-----------|-------|
|                   | n | P^2 (%) | PQ | OR (95% CI) | P | n | P^2 (%) | PQ | OR (95% CI) | P |
| **UCP1-3826A/G**  |   |         |    |             |   |   |         |    |             |   |
| Allele            | 9 | 13.0    | 0.326 | 0.95 (0.88-1.03) | 0.242 | 4 | 3.4    | 0.376 | 1.00 (0.88-1.15) | 0.966 | 5 | 22.6 | 0.271 | 0.92 (0.83-1.02) | 0.130 |
| Dominant          | 9 | 12.4    | 0.332 | 0.93 (0.80-1.08) | 0.367 | 4 | 28.5   | 0.241 | 0.98 (0.75-1.30) | 0.909 | 5 | 15.3 | 0.317 | 0.91 (0.76-1.09) | 0.318 |
| Recessive         | 10 | 0.0    | 0.679 | 0.93 (0.83-1.04) | 0.230 | 5 | 0.0    | 0.585 | 0.98 (0.83-1.15) | 0.769 | 5 | 0.0    | 0.527 | 0.90 (0.77-1.05) | 0.167 |
| Homozygous        | 9 | 17.0   | 0.291 | 0.91 (0.77-1.07) | 0.251 | 4 | 29.3   | 0.236 | 1.00 (0.75-1.33) | 0.980 | 5 | 16.1   | 0.312 | 0.87 (0.71-1.06) | 0.165 |
| Heterozygous      | 9 | 0.0    | 0.517 | 0.95 (0.81-1.12) | 0.559 | 4 | 15.6   | 0.314 | 0.97 (0.72-1.31) | 0.831 | 5 | 0.0    | 0.461 | 0.95 (0.78-1.15) | 0.576 |

| **UCP2-866G/A**   |   |         |    |             |   |   |         |    |             |   |         |    |             |   |
| Allele            | 24 | 74.2   | <0.001 | 0.97 (0.88-1.07) | 0.595 | 9 | 66.0   | 0.003 | 1.04 (0.89-1.21) | 0.630 | 15 | 78.4   | <0.001 | 0.94 (0.83-1.07) | 0.337 |
| Dominant          | 23 | 47.4   | 0.006 | 0.92 (0.80-1.05) | 0.208 | 8 | 53.1   | 0.037 | 1.06 (0.81-1.40) | 0.651 | 15 | 40.6   | 0.052 | 0.86 (0.74-1.00) | 0.045 |
| Recessive         | 22 | 74.0   | <0.001 | 0.93 (0.80-1.07) | 0.307 | 8 | 65.5   | 0.005 | 0.97 (0.78-1.21) | 0.782 | 14 | 78.2   | <0.001 | 0.90 (0.80-1.07) | 0.327 |
| Homozygous        | 22 | 63.3   | <0.001 | 0.90 (0.75-1.09) | 0.298 | 8 | 62.0   | 0.010 | 1.02 (0.73-1.43) | 0.909 | 14 | 65.1   | <0.001 | 0.85 (0.67-1.08) | 0.179 |
| Heterozygous      | 22 | 13.5   | 0.280 | 0.96 (0.87-1.06) | 0.410 | 8 | 47.1   | 0.067 | 1.05 (0.88-1.26) | 0.587 | 14 | 0.0    | 0.727 | 0.92 (0.81-1.04) | 0.169 |

| **UCP2 Ala55Val** |   |         |    |             |   |   |         |    |             |   |         |    |             |   |
| Allele            | 9 | 65.4   | 0.003 | 1.11 (0.97-1.28) | 0.126 | 2 | 68.9   | 0.073 | 0.90 (0.63-1.27) | 0.534 | 7 | 58.7   | 0.024 | 1.17 (1.02-1.34) | 0.023 |
| Dominant          | 8 | 62.9   | 0.009 | 1.17 (0.92-1.47) | 0.196 | 1 | —     | 0.095 | 0.70 (0.50-1.00) | 0.735 | 7 | 64.4   | 0.010 | 1.21 (0.93-1.58) | 0.161 |
| Recessive         | 8 | 33.7   | 0.159 | 1.25 (1.12-1.40) | <0.01 | 1 | —     | 1.12 (0.87-1.43) | 0.376 | 7 | 37.5   | 0.143 | 1.28 (1.13-1.45) | <0.01 |
| Homozygous        | 8 | 58.2   | 0.019 | 1.33 (1.03-1.72) | 0.029 | 1 | —     | 1.03 (0.74-1.45) | 0.846 | 7 | 57.6   | 0.028 | 1.39 (1.05-1.86) | 0.023 |
| Heterozygous      | 8 | 56.7   | 0.024 | 1.09 (0.86-1.36) | 0.481 | 1 | —     | 0.90 (0.65-1.23) | 0.503 | 7 | 58.9   | 0.024 | 1.12 (0.87-1.46) | 0.380 |

| **UCP3-55C/T**    |   |         |    |             |   |   |         |    |             |   |         |    |             |   |
| Allele            | 10 | 67.3   | 0.001 | 1.04 (0.90-1.22) | 0.582 | 6 | 46.8   | 0.094 | 1.10 (0.93-1.30) | 0.274 | 4 | 83.4   | <0.001 | 0.94 (0.69-1.26) | 0.693 |
| Dominant          | 9 | 36.8   | 0.124 | 1.10 (0.89-1.35) | 0.381 | 5 | 14.8   | 0.320 | 1.20 (0.86-1.67) | 0.281 | 4 | 60.2   | 0.057 | 1.04 (0.80-1.35) | 0.790 |
| Recessive         | 11 | 53.1   | 0.019 | 1.07 (0.93-1.24) | 0.329 | 6 | 32.5   | 0.192 | 1.10 (0.92-1.32) | 0.290 | 5 | 71.2   | 0.008 | 1.02 (0.79-1.30) | 0.905 |
| Homozygous        | 9 | 54.1   | 0.026 | 1.05 (0.74-1.49) | 0.792 | 5 | 28.1   | 0.234 | 1.19 (0.74-1.91) | 0.469 | 4 | 73.7   | 0.010 | 0.94 (0.54-1.65) | 0.834 |
| Heterozygous      | 9 | 0.0    | 0.782 | 1.11 (0.89-1.39) | 0.360 | 5 | 0.0    | 0.541 | 1.14 (0.81-1.63) | 0.451 | 4 | 0.0    | 0.655 | 1.09 (0.82-1.45) | 0.571 |

UCP: uncoupling protein; T2DM: type 2 diabetes mellitus; PQ: P value for Q test; OR: odds ratio; CI: confidence interval.
### Caucasian

| Study ID       | OR (95% CI)       | % Weight |
|----------------|-------------------|----------|
| Sivenius (2000)| 1.13 (0.73, 1.76) | 3.17     |
| Heilbronn (2000)| 0.67 (0.38, 1.17) | 2.48     |
| Sramkova (2007)| 1.16 (0.83, 1.63) | 5.37     |
| de Souza (2013)| 0.99 (0.84, 1.16) | 25.63    |
| Subtotal (I-squared = 3.4%, p = 0.376) | 1.00 (0.88, 1.15) | 36.65    |

### Asian

| Study ID       | OR (95% CI)       | % Weight |
|----------------|-------------------|----------|
| Mori (2001)    | 1.17 (0.93, 1.48) | 11.11    |
| Vimaleswaran (2010)| 0.86 (0.75, 0.99) | 39.19    |
| Boullu-Sanchis (1999)| 0.85 (0.56, 1.28) | 4.29     |
| Lin-1 (2009)   | 0.94 (0.67, 1.32) | 5.91     |
| Lin-2 (2009)   | 0.85 (0.52, 1.40) | 2.86     |
| Subtotal (I-squared = 22.6%, p = 0.271) | 0.92 (0.83, 1.02) | 63.35    |
| Overall (I-squared = 13.0%, p = 0.326) | 0.95 (0.88, 1.03) | 100.00   |

### Overall

- Caucasian: I-squared = 3.4%, p = 0.376
- Asian: I-squared = 22.6%, p = 0.271
- Overall: I-squared = 13.0%, p = 0.326

**Figure 2:** Continued.
| Study ID | OR (95% CI)  | % Weight |
|----------|--------------|----------|
| Asian    |              |          |
| Kūbota (1998) | 1.10 (0.84, 1.44) | 10.15   |
| Cho (2004) | 1.14 (0.87, 1.49) | 10.08   |
| Vimalaśwaran (2011) | 1.45 (1.22, 1.73) | 13.58   |
| de Souza (2013) | 1.02 (0.82, 1.27) | 11.89   |
| Qin (1999) | 1.16 (0.79, 1.69) | 7.14    |
| Shen (2014) | 1.37 (1.14, 1.65) | 13.16   |
| Su (2018) | 0.95 (0.78, 1.16) | 12.53   |
| Subtotal (I-squared = 58.7%, \( p = 0.024 \)) | 1.17 (1.02, 1.34) | 78.52   |

| Caucasian |              |          |
| Wang (2004) | 0.72 (0.50, 1.03) | 7.57    |
| de Souza (2013) | 1.03 (0.88, 1.22) | 13.90   |
| Subtotal (I-squared = 68.9%, \( p = 0.073 \)) | 0.90 (0.63, 1.27) | 21.48   |
| Overall (I-squared = 65.4%, \( p = 0.003 \)) | 1.11 (0.97, 1.26) | 100.00  |

Note: Weights are from random effects analysis

Figure 2: Meta-analysis for the association between the UCP polymorphisms and T2DM susceptibility stratified by ethnicity (allele model). (a) UCP1-3826A/G polymorphism; (b) UCP2-866G/A polymorphism; (c) UCP2 Ala55Val polymorphism; (d) UCP3-55C/T polymorphism. The area of the squares reflects the study-specific weight, and the diamond illustrates the summary random effects OR (95% CI).
dominant model of the UCP2-866G/A polymorphism, the Wang et al. 2004 in the allele model, and the Vimaleswaran et al. 2011 and the Shen et al. 2014 in the homozygous model of the UCP2 Ala55Val polymorphism (OR = 0.88, 95% CI 0.78-0.99, \( P = 0.039 \); OR = 1.15, 95% CI 1.02-1.29, \( P = 0.024 \); OR = 1.21, 95% CI 0.99-1.47, \( P = 0.064 \); OR = 1.25, 95% CI 0.96-1.64, \( P = 0.102 \), respectively) (Figure 3).

![Figure 3: Sensitivity analysis for the association between the UCP polymorphisms and T2DM susceptibility. (a) Dominant model of the UCP2-866G/A polymorphism; (b) allele model of the UCP2 Ala55Val polymorphism; (c) homozygous model of the UCP2 Ala55Val polymorphism.](image-url)

3.5. Publication Bias. Begg’s funnel plot and Egger’s test were conducted to assess the publication bias of the literature. As expected, the funnel plots were visually symmetrical, and all \( P \) values obtained from Egger’s test were >0.05, which interpreted that there is no publication bias for any of the UCP polymorphisms analyzed (for example, in the allele model, Figure 4).

4. Discussion

T2DM is one of the most common noncommunicable diseases which is thought to be the result of interactions between complex gene-gene and gene-environment. A number of studies have examined the associations of the UCP1-3826A/G, the UCP2-866G/A, Ala55Val, and UCP3-55C/T polymorphisms with T2DM, but the results are still inconsistent. As a single study might lack sufficient power, especially when the sample size is not adequate, we designed this meta-analysis of 38 published studies from different populations to obtain a more precise conclusion. Our results showed that only the UCP2 Ala55Val polymorphism is associated with T2DM in the overall population. In a stratified analysis according to ethnicity, we found that the UCP2 Ala55Val polymorphism is significantly associated with increased risk of T2DM, while the UCP2-866G/A polymorphism is associated with decreased risk of T2DM in Asian population. However, the correlation of UCP1-3826A/G and UCP3-55C/T polymorphisms with T2DM lacked corresponding evidence in either subjects of Asian or of Caucasian descent.

The -3826A/G polymorphism in the promoter region of the UCP1 gene was found to be linked to reduced mRNA expression, which indicated that the polymorphism may be of functional importance [58]. Thus, numerous studies have been carried out to evaluate the association between this polymorphism and obesity or obesity-related disorders.
Results concluded from previous meta-analyses showed that the UCP1-3826A/G polymorphism is not associated with any change in BMI or obesity regardless of the inheritance model or stratification analysis by ethnicity [59, 60]. In our study, we confirmed no relationship between the UCP1-3826A/G polymorphism and susceptibility to T2DM either in Asian population or in Caucasian population, which was also supported by a previous meta-analysis by de Souza et al. 2013 [19].

The -866G/A polymorphism in the core promoter of the UCP2 gene seems to be connected with putative binding sites for specific transcription factors [61]. Previous study revealed that the A allele of the UCP2-866G/A polymorphism contributes to insulin resistance and obesity when compared with G allele [34]. Thus, it is reasonable to draw the conclusion that the UCP2 rs659366 is significantly associated with increased risk of T2DM by Xu et al. 2021, especially in Asian population or in Caucasian population, which was also supported by a previous meta-analysis by de Souza et al. 2013 [19]. Nevertheless, there were no association found in the meta-analyses performed by Xu et al. 2011, Qin et al. 2013, and de Souza et al. 2013 [18–20].

Figure 4: Funnel plot for the association between the UCP polymorphisms and T2DM susceptibility (allele model). (a) UCP1-3826A/G polymorphism (\( P = 0.822 \)); (b) UCP2-866G/A polymorphism (\( P = 0.534 \)); (c) UCP2 Ala55Val polymorphism (\( P = 0.267 \)); (d) UCP3-55C/T polymorphism (\( P = 0.757 \)).
example, different nutrient intakes were found to influence the roles of genetic polymorphisms in obesity and obesity-related diseases [64, 65]. Thus, it is reasonable that there exists ethnicity difference in the association of UCP2 Ala55-Val polymorphism with T2DM susceptibility owing to different diet patterns.

The UCP3 -55C/T promoter variant is of interest because of its position at 4 bp downstream of a peroxisome proliferator-activated receptor (PPAR) responsive region, which could modify PPAR-dependent responsiveness [66]. Thus, many studies have linked this polymorphism to the regulation of lipid metabolism and insulin sensitivity [67, 68]. Previous meta-analyses also showed that the UCP3-55C/T polymorphism is related to prominent increase in BMI, as well as risk for T2DM in Asians [18, 19, 59]. In contrast, our results failed to find any association of UCP3-55C/T polymorphism with T2DM. We could not fully exclude the possibility that the latest publications included in our meta-analysis might vary the final results.

Although some previous meta-analyses reported the role of UCP polymorphisms in the risk for T2DM, our meta-analysis included the most recent publications and conducted a series of analyses, including subgroup analysis, heterogeneity analysis, sensitivity analysis, and publication bias, to achieve more accurate results. Certainly, some limitations should be acknowledged in the present study for better interpreting the results [69]. Firstly, there was substantial heterogeneity among included studies, despite the use of random effects model, which may affect the precision of the results. Secondly, sensitivity analysis of this meta-analysis indicated that the overall results were somewhat unstable. Thirdly, the small number and sample size of studies may confound the pooled results to a certain degree, especially for Caucasian origin included in the UCP2 Ala55Val polymorphism. Fourthly, due to lack of original information for each included subjects, the overall results of our study were based on individual unadjusted OR. Additionally, we only considered the role of individual polymorphism and did not take into account their interaction with other polymorphisms and environmental factors.

In conclusion, our results demonstrated that the -866G/A polymorphism is protective against T2DM, while the Ala55-Val polymorphism of UCP2 gene is susceptible to T2DM in Asians. Nevertheless, given the presence of between-study heterogeneity and confounding factors in this meta-analysis, further well-designed and large-scale studies, particularly, studies that take the effects of gene-gene and gene-environment interactions into consideration, should be conducted to verify the current findings.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors’ Contributions

Ma JH and Huang R designed the study; Huang R, Cai TT, and Zhou YT collected the data; Wang YM and Wang HY assessed the quality of each study; Huang R, Shen ZY, Xia WQ, and Liu XM performed the analyses; Huang R, Ding B, Luo Y, and Yan RN wrote the first draft; and Li HQ, Wu JD, and Ma JH checked the manuscript and revised it. All authors approved the final submission.

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Supplementary Materials

File S1: PRISMA 2009 Checklist. Figure S1: Galbraith plot of UCP2-866G/A polymorphism and T2DM risk. (a) Allele model; (b) dominant model; (c) recessive model; (d) homozygous model. Figure S2: Galbraith plot of UCP2 Ala55Val polymorphism and T2DM risk. (a) Allele model; (b) dominant model; (c) recessive model; (d) homozygous model. Figure S3: Galbraith plot of UCP3-55C/T polymorphism and T2DM risk. (a) Allele model; (b) recessive model; (c) homozygous model. (Supplementary Materials)

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