The Trp64Arg polymorphism in β3 adrenergic receptor (ADRB3) gene is associated with adipokines and plasma lipids: a systematic review, meta-analysis, and meta-regression

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Abstract
Background: Recently, some studies claim that adipokines may modulate plasma lipids. More interestingly, the ADRB3 Trp64Arg polymorphism may regulate adipokines and play an essential role in lipids metabolism. This study aims to clarify the associations of ADRB3 Trp64Arg polymorphism with plasma adipokines and lipid levels.

Methods: Twenty-two studies (5527 subjects) and 121 studies (54,059 subjects) were respectively identified for the association analyses of adipokines and lipids. Standardized mean difference (SMD) and 95% confidence interval (CI) were used to estimate the strength of the Trp64Arg variant in adipokines and plasma lipids. All results were recalculated after eliminating the studies with heterogeneity.

Results: The carriers of the C allele (Arg at 64th position was encoded by the C allele) had higher levels of leptin and lower levels of adiponectin than the non-carriers. The carriers of the C allele had higher levels of triglycerides (TG), total cholesterol (TC), and lower levels of high-density lipoprotein cholesterol (HDL-C) than the non-carriers. Subgroup analysis certified an ethnicity (Asians), disease status (obesity), and gender (females) specific association. Sensitivity analysis indicated that the analysis results were robust and stable. Meta-regression indicated that obesity was related to adiponectin.

Conclusions: The C allele carriers of Trp64Arg polymorphism had a slight but significant influence on lipid levels, and the remarkable effects specific existed in obese Asian women. The associations of Trp64Arg polymorphism with dyslipidemia may partly be mediated by the effect of this polymorphism on adipokines. The association of Trp64Arg polymorphism with obesity may partly be mediated by the effect of this polymorphism on adipokines. The C allele carriers had abnormal levels of adipokines and lipids, and it indicated that the Trp64Arg polymorphism might represent a genetic risk factor for coronary artery disease (CAD).

Keywords: ADRB3, Trp64Arg, Polymorphism, Adipokines, Plasma lipids, CAD, Obesity

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Introduction

CAD obtains the highest mortality and disability rate in most of the developed and developing countries. CAD is triggered by multiple genetic and environmental risk factors. Among these risk factors, the abnormal levels of adipokines [1, 2] and lipids [3] are widely reported about their essential roles in the occurrence and progress of CAD. Both leptin and adiponectin are called adipokines, produced by white adipose tissue, one of the most potent lipid regulator [4–6], and plays a vital role in lipid metabolism [7–9]. Some new shreds of evidence have shown that leptin is positively related to dyslipidemia [10–12] in contrast to adiponectin, which is negatively related to dyslipidemia [13–15]. Considering the leptin is considerably increased, and the adiponectin is substantially decreased in obese mice [16]. Leptin promotes, and adiponectin prevents atherosclerosis [17] by aiming directly on blood vessel endothelial cells. The adipokines are becoming an indispensable bridge between obesity, dyslipidemia, and atherosclerosis [18–20]. As the leptin/adiponectin ratio serves as a new atherosclerotic indicator [21], it is a sensitive index in estimating obesity and dyslipidemia.

The beta-adrenergic receptors (ADRBs) are composed of the β1 adrenergic receptor (ADRB1), β2 adrenergic receptor (ADRB2), and ADRB3. The ADRB1 and ADRB2 located in myocytes and play an essential role in its function regulation [22, 23]. By contrast, the ADRB3 subtype located in white adipose tissue and plays a critical role in regulating lipolysis in white adipose tissue [24, 25]. The ADRB3 gene is located on the long arm of human chromosome 8 (8p11.1–12), and it contains two exons and one intron. The Trp64Arg polymorphism (also known as T190C, W64R, and rs49949) is the only function mutation of the ADRB3 gene, located in exon one and caused by substitution from thymine (T) to cytosine (C). Previous studies have reported that the ADRB3 gene might regulate the expression levels of adipokines [26, 27] and plasma lipids [28, 29]. Also, the Trp64Arg polymorphism was proved to be related to obesity [30–32] and relevant characteristics [33, 34] in Pima Indians and western obese patients. Whereas the ADRB3 gene might influence the plasma levels of adipokines and lipids and the Trp64Arg polymorphism might be associated with obesity-related traits, it is not difficult to speculate that the Trp64Arg variant might influence the plasma levels of adipokines and lipids. Recently, Chen et al. [35] have reported that the Trp64Arg variant is closely related to CAD. However, the specific mechanisms are not precise, so there is an urgent need to clarify the associations of Trp64Arg polymorphism with plasma adipokines and lipid levels, to provide some clues or references for the clarification of possible mechanisms of Trp64Arg polymorphism with CAD.

It is worth noting that this is the first systematic review, meta-analysis, and meta-regression to assess the associations of the Trp64Arg polymorphism with adipokines and plasma lipids in a large sample size (59,586 subjects of 122 studies). Besides, the present systematic review may generate some new information. Some studies have reported that the Trp64Arg variant was positively associated with adipokines and plasma lipids. On the contrary, other studies have indicated that the Trp64Arg variant was negatively associated with adipokines and plasma lipids. However, the results from a few studies did not support these associations. Since the present study results are controversial and inconclusive, a systematic review, meta-analysis, and meta-regression are required to unveil whether this polymorphism affects adipokines and plasma lipids or not. Moreover, if it does, so whether it is positive or negative in the light of evidence-based medicine.

Methods

Literature search

A comprehensive literature review was performed before Jan 2020 by using nine databases including PubMed, Cochrane Library, Medline, Embase, Web of Science, Google Scholar, Wanfang, China National Knowledge Infrastructure (CNKI), and China Biology Medicine (CBM) database by using Keywords: (“ADRB3” or “β3-adrenergic receptor” or “β3-adrenergic receptor” or “β3AR”), (“Trp64Arg” or “T190C” or “rs49949”), (“polymorphism” or “mutation” or “variant”), (“adipokines”), (“adiponectin”), (“leptin”) and (“circulating lipid” or “blood lipid” or “plasma lipid” or “serum lipid”).

Inclusion criteria

The inclusion criteria for this systematic review are as below: (1) The studies have examined the associations of Trp64Arg polymorphism with adipokines and plasma lipids. (2) The studies have at least offered one of the variables in adipokines profile (leptin and adiponectin) or lipids profile [TG, TC, low-density lipoprotein cholesterol (LDL-C), and HDL-C]. (3) The studies have provided the allele or genotypes. (4) The studies have provided the allele or genotype frequencies of the Trp64Arg polymorphism. (5) The language of included studies is restricted to English and Chinese. The exclusion criteria for this study are as below: (1) Studies not related to Trp64Arg polymorphism; (2) studies do not offer genotype or allele frequencies; (3) studies present invalid data; (4) pedigree studies; (5) overlapping studies; (6) abstract, review, systematic review, meta-analysis, and animal studies.

Data extraction

According to a pre-piloted data extraction form and the pre-specified selection criteria, two researchers independently extracted the data from each eligible study. Results were compared, and divergences about data extraction were settled by consensus. If crucial data were
absent from included studies, e-mail, or telephone would be used to acquire these data. From each eligible study, the following data were extracted: the first author’s name, the publication year, language, country, ethnicity, disease status, gender, genotype counts, total sample size, and mean plasma levels of adiponectin, leptin, and lipids with SD by genotypes.

Data analysis
All the tests were performed by STATA software (version 15.0, College Station, TX). *P*-values less than 0.05 were considered to be statistically significant. The Chi-square test estimated the Hardy–Weinberg equilibrium (HWE) among control subjects. Publication bias was tested by Begg’s funnel plot and Egger’s test [36]. SMD with 95% CIs were used to assess the effects of the Trp64Arg variant on plasma adipokines and lipid levels. Sensitivity analysis was used to check the robustness and stabilities of all results. The random-effect model was performed to analyze the results if heterogeneity among the involved studies was remarkable. Otherwise, the Fixed-effect model would be used [37]. Galbraith plots and meta-regression analysis estimated the sources of heterogeneity among studies. All SMD with 95% CIs were recalculated after excluding the study with heterogeneities. The confounding factors included publication year (before 2000 and after 2000), language (English and Chinese), ethnicity (Caucasian, Asian, Chilean, Brazilian, Indonesian and Other ethnic), gender (Males or Females), disease status [Obesity, CAD, type 2 diabetes mellitus (T2DM), and Hypertension] and total sample size (≥500 subjects and <500 subjects). Subgroup analyses were conducted by ethnicity, disease status, gender, healthy subjects, and children subjects. The ethnic subgroup was divided into Caucasian, Asian, Chilean, Brazilian, Indonesian, and other ethnicities. Disease status was divided into Obesity, CAD, T2DM, and Hypertension.

Result

Characteristics of the included studies
The initial search of the databases yielded 2568 studies. Two thousand two hundred and ninety-seven studies were excluded by its contents. Then 167 studies were reevaluated by the inclusion criteria. Forty-five studies were further excluded due to the following reasons: twenty-five studies offered data of other polymorphisms, ten studies offered invalid data, five studies had subjects overlapping with other publications, and five studies were based on pedigree analysis. Finally, 122 studies were included for this systematic review (Fig. 1). Of them, 22 studies (5527 subjects) and 121 studies (54,059 subjects) were identified for the association analyses of adipokines and lipids, respectively.

The references of the included studies were listed in Additional file 1. The characteristics of the included studies were presented in Additional file 1: Table S1. The plasma adipokines and lipid levels by the genotypes of the ADRB3 Trp64Arg polymorphism were presented in

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Fig. 1 Flow diagram of the study selection process
Additional file 1: Table S2 and Additional file 1: Table S3, respectively. The sources of heterogeneity of TG, HDL-C, adiponectin, leptin, TC and LDL-C were respectively presented in Additional file 1: Table S4, Additional file 1: Table S5, Additional file 1: Table S6, Additional file 1: Table S7, Additional file 1: Table S8 and Additional file 1: Table S9.

**Association of the ADRB3 Trp64Arg polymorphism with plasma adipokines levels**

The C allele carriers had higher levels of leptin (Fig. 2) and lower levels of adiponectin (Fig. 3) than the non-carriers. When the analysis was confined to the studies in HWE (Table 1), the significant association of the Trp64Arg polymorphism with higher levels of leptin and lower levels of adiponectin were also detected.

Then the subgroup analyses were conducted (Table 1), and the analyses revealed that the Trp64Arg variant was related to higher levels of leptin in Asians, Males, and healthy subjects and lower levels of adiponectin in Asians.

The analyses eliminating the studies with heterogeneity were also conducted (Table 2), and the analyses showed that the Trp64Arg variant was related to higher levels of leptin in Caucasians, Asians, Males, and healthy subjects and lower levels of adiponectin in Caucasians and Asians.

**Association of the ADRB3 Trp64Arg polymorphism with plasma lipid levels**

The C allele carriers had higher levels of TG and TC and lower levels of HDL-C than the non-carriers (Table 3). When the analysis was confined to the studies in HWE (Table 3), the significant association of the Trp64Arg polymorphism with higher levels of TG, TC, and lower levels of HDL-C were also detected.

Then the subgroup analysis by the characteristics of the subjects was performed (Table 3). Subgroup analysis by ethnicity showed that the significant associations of the Trp64Arg polymorphism with higher levels of TG, TC, and lower levels of HDL-C were detected in Caucasians and Asians, but not in the other ethnicities. Subgroup analysis by gender showed that the significant associations of the Trp64Arg polymorphism with higher levels of TG, TC, and lower levels of HDL-C were only detected in the females, but not in the males. Subgroup analysis by disease status showed that the significant associations of the Trp64Arg polymorphism with higher levels of TG and TC.
Fig. 3 Forest plot of the meta-analysis between the ADRB3 Trp64Arg polymorphism and adiponectin

Table 1  Meta-analysis of the ADRB3 Trp64Arg polymorphism with adipokines levels

| Groups or subgroups | Comparisons (Subjects) | SMD (95% CI) | $P_{\text{Heterogeneity}}$ | $P_{\text{SMD}}$ |
|---------------------|------------------------|--------------|---------------------------|-----------------|
| **Leptin**          |                        |              |                           |                 |
| All                 | 33 (4999)              | 0.14 (0.02–0.26) | < 0.001                   | 0.02            |
| Studies in HWE      | 31 (4594)              | 0.12 (0.00–0.24) | < 0.001                   | 0.05            |
| Caucasian           | 19 (3036)              | 0.11 (–0.06–0.28) | < 0.01                    | 0.21            |
| Asian               | 11 (1124)              | 0.18 (0.03–0.33) | 0.18                      | 0.02            |
| Female              | 9 (1416)               | 0.11 (–0.18–0.41) | < 0.001                   | 0.46            |
| Male                | 9 (1161)               | 0.22 (0.02–0.42) | 0.04                      | 0.03            |
| Obesity             | 19 (2418)              | 0.08 (–0.09–0.24) | 0.01                      | 0.36            |
| Healthy subjects    | 12 (2384)              | 0.19 (0.00–0.38) | < 0.001                   | 0.05            |
| **Adiponectin**     |                        |              |                           |                 |
| All                 | 12 (2073)              | –0.28 (–0.53–0.02) | < 0.001                   | 0.03            |
| Studies in HWE      | 11 (1800)              | –0.26 (–0.39–0.13) | < 0.001                   | < 0.001         |
| Caucasian           | 10 (1545)              | –0.08 (–0.23–0.07) | 0.64                      | 0.28            |
| Asian               | 2 (528)                | –0.86 (–1.05–0.66) | 0.95                      | < 0.001         |
| Obesity             | 10 (1545)              | –0.08 (–0.23–0.07) | 0.64                      | 0.28            |

ADRB3: beta3-adrenergic receptor gene, SMD: standardized mean difference, 95% CI: 95% confidence interval, HWE Hardy-Weinberg equilibrium
were only detected in obese patients, but not in CAD patients, T2DM patients, and hypertension patients. Besides, the significant association of the Trp64Arg polymorphism with lower levels of HDL-C was detected in obese patients and T2DM patients, but not in CAD patients and hypertension patients. When the analysis was limited to healthy subjects, the significant association of the Trp64Arg polymorphism with higher levels of TG and TC were also detected.

The analyses eliminating the studies with heterogeneity were also conducted (Table 4), and the analyses revealed that the Trp64Arg variant was related to higher levels of TG, TC, and lower levels of HDL-C in Asians, females and obesity patients after excluding the outlier studies. However, the association analysis of the Trp64Arg variant with lipid levels did not show statistically significant in Caucasians and healthy subjects. Besides, the significant association of the Trp64Arg variant with higher levels of LDL-C was detected in Asians. This indicated that the significant associations of the Trp64Arg variant with plasma lipid levels in obese Asian women were stable and robust.

Table 2 Meta-analysis of the ADRB3 Trp64Arg polymorphism with adipokines levels after excluding the study with heterogeneity

| Groups or subgroups | Comparisons (Subjects) | SMD (95% CI)          | P_{heterogeneity} | P_{SMD} |
|---------------------|------------------------|-----------------------|-------------------|---------|
| Leptin              | All 29 (4581)          | 0.17 (0.09–0.24)      | 0.08              | < 0.001 |
|                     | Studies in HWE 27 (4176)| 0.14 (0.06–0.23)      | 0.07              | < 0.001 |
|                     | Caucasian 16 (2733)     | 0.16 (0.05–0.27)      | 0.46              | 0.01    |
|                     | Asian 10 (1009)        | 0.24 (0.11–0.37)      | 0.80              | < 0.001 |
|                     | Female 7 (1253)        | −0.02 (−0.17–0.12)     | 0.05              | 0.76    |
|                     | Male 8 (1046)          | 0.30 (0.16–0.44)      | 0.52              | < 0.001 |
|                     | Obesity 16 (2113)      | 0.10 (−0.02–0.22)     | 0.83              | 0.11    |
|                     | Healthy subjects 11 (2271) | 0.19 (0.09–0.30)    | 0.06              | < 0.001 |
| Adiponectin         | All 8 (1190)           | −0.63 (−0.78–0.48)     | 0.07              | < 0.001 |
|                     | Studies in HWE 7 (917) | −0.52 (−0.70–0.34)     | 0.10              | < 0.001 |
|                     | Caucasian 6 (662)      | −0.26 (−0.50–0.02)     | 0.68              | 0.03    |
|                     | Asian 2 (528)          | −0.86 (−1.05–0.66)     | 0.95              | < 0.001 |
|                     | Obesity 6 (662)        | −0.08 (−0.23–0.07)     | 0.64              | 0.28    |

ADRB3 beta3-adrenergic receptor gene, SMD standardized mean difference, 95% CI 95% confidence interval, HWE Hardy-Weinberg equilibrium

In the association analysis of lipids, significant heterogeneity was identified in the total comparisons for TC, TC, LDL-C, and HDL-C (Table 3). Sixteen, nine, ten, and eleven comparisons were respectively recognized as the main contributors to the heterogeneity for TG, TC, LDL-C, HDL-C, by performing Galbraith plots. The analysis results of lipids did not change substantially after excluding the outlier comparisons (Table 4).

Univariate and multivariate meta-regression analysis was also conducted to explore sources of heterogeneity among the included studies. Furthermore, the analyses revealed that the total sample size (Table S4, Table S5) was a significant source of heterogeneity of TG (P_{univariate} = 0.05) and HDL-C (P_{univariate} < 0.01, P_{multivariate} < 0.01). Also, the disease status (Table S6) was a significant source of heterogeneity of adiponectin (P_{univariate} < 0.001, P_{multivariate} < 0.001). However, no confounding factors (Table S7-S9) explain the heterogeneity of leptin (P-values 0.51 to 0.98), TC (P-values 0.37 to 0.85), and LDL-C (P-values 0.10 to 0.82).

Evaluation of heterogeneity
In the association analysis of adipokines, significant heterogeneity was identified in the total comparisons of leptin and adiponectin (Table 1). Four and four comparisons were recognized as the main contributors to the heterogeneity for leptin and adiponectin, respectively, by performing Galbraith plots. The analysis results of leptin and adiponectin did not change substantially after excluding the outlier comparisons (Table 2).

Sensitivity analyses
In association analysis of the Trp64Arg polymorphism with plasma adipokines and lipids levels, a sensitivity analysis was conducted by calculating all results again after omitting every single study. Interestingly, the analysis results of adipokines and plasma lipids did not change substantially after omitting these studies, which indicated that the analysis results were robust and stable.

Publication bias test
Begg’s test and Egger’s test were used to evaluating the publication bias of the included studies, and no publication bias
Table 3 Meta-analysis of the ADRB3 Trp64Arg polymorphism with plasma lipid levels

| Groups or subgroups | Comparisons (Subjects) | SMD (95% CI)       | $p_{	ext{heterogeneity}}$ | $p_{SMD}$ |
|---------------------|------------------------|--------------------|---------------------------|-----------|
| TG                  |                        |                    |                           |           |
| All                 | 162 (43,778)           | 0.07 (0.03–0.11)   | < 0.001                   | < 0.001   |
| Studies in HWE      | 142 (38,507)           | 0.05 (0.02–0.09)   | < 0.001                   | 0.01      |
| Caucasian           | 47 (17,065)            | 0.09 (0.02–0.16)   | < 0.01                    | < 0.01    |
| Asian               | 101 (24,424)           | 0.06 (0.02–0.11)   | < 0.01                    | < 0.01    |
| Chilean             | 3 (340)                | 0.04 (−0.41–0.50)  | 0.02                      | 0.85      |
| Brazilian           | 2 (223)                | 0.22 (−0.13–0.57)  | 0.37                      | 0.22      |
| Indonesian          | 4 (531)                | −0.18 (−0.45–0.09) | 0.84                      | 0.20      |
| Other ethnic        | 5 (1195)               | 0.14 (−0.16–0.45)  | < 0.01                    | 0.35      |
| Female              | 40 (10,329)            | 0.06 (0.01–0.11)   | 0.01                      | 0.01      |
| Male                | 30 (9499)              | 0.03 (−0.02–0.08)  | < 0.01                    | 0.30      |
| Obesity             | 38 (5772)              | 0.12 (0.05–0.18)   | 0.32                      | < 0.01    |
| T2DM                | 20 (4335)              | 0.03 (−0.01–0.07)  | < 0.001                   | 0.07      |
| Hypertension        | 4 (781)                | −0.05 (−0.22–0.13) | 0.28                      | 0.61      |
| CAD                 | 7 (1225)               | −0.12 (−0.25–0.01) | 0.46                      | 0.07      |
| Healthy subjects    | 69 (25,873)            | 0.05 (0.00–0.10)   | < 0.001                   | 0.03      |
| Children            | 14 (2337)              | 0.12 (−0.05–0.29)  | < 0.001                   | 0.16      |
| TC                  |                        |                    |                           |           |
| All                 | 162 (49,738)           | 0.04 (0.01–0.07)   | < 0.001                   | 0.01      |
| Studies in HWE      | 140 (43,716)           | 0.03 (0.01–0.05)   | < 0.001                   | 0.01      |
| Caucasian           | 46 (19,238)            | 0.07 (0.00–0.13)   | < 0.01                    | 0.04      |
| Asian               | 104 (27,572)           | 0.02 (0.00–0.05)   | < 0.001                   | 0.05      |
| Chilean             | 3 (340)                | 0.04 (−0.19–0.27)  | 0.83                      | 0.73      |
| Brazilian           | 4 (1310)               | 0.09 (−0.06–0.24)  | 0.52                      | 0.23      |
| Other ethnic        | 5 (1278)               | 0.00 (−0.27–0.27)  | < 0.01                    | 0.98      |
| Female              | 38 (11,568)            | 0.06 (0.02–0.11)   | 0.23                      | 0.01      |
| Male                | 29 (9543)              | −0.00 (−0.08–0.08) | < 0.01                    | 0.92      |
| Obesity             | 36 (5400)              | 0.07 (0.00–0.13)   | 0.32                      | 0.04      |
| T2DM                | 20 (5257)              | 0.04 (−0.02–0.11)  | 0.75                      | 0.22      |
| Hypertension        | 6 (1182)               | 0.04 (−0.10–0.18)  | 0.57                      | 0.54      |
| CAD                 | 7 (1225)               | −0.11 (−0.27–0.06) | 0.28                      | 0.20      |
| Healthy subjects    | 68 (27,441)            | 0.05 (0.01–0.10)   | < 0.001                   | 0.02      |
| Children            | 14 (2279)              | 0.03 (−0.13–0.20)  | < 0.01                    | 0.67      |
| LDL-C               |                        |                    |                           |           |
| All                 | 103 (25,965)           | 0.03 (−0.02–0.07)  | < 0.001                   | 0.24      |
| Studies in HWE      | 86 (21,459)            | −0.01 (−0.05–0.04) | 0.01                      | 0.82      |
| Caucasian           | 29 (7687)              | 0.01 (−0.06–0.07)  | 0.07                      | 0.88      |
| Asian               | 64 (15,264)            | 0.04 (−0.02–0.09)  | < 0.001                   | 0.22      |
| Brazilian           | 4 (1310)               | 0.02 (−0.35–0.38)  | 0.02                      | 0.94      |
| Other ethnic        | 5 (1338)               | 0.07 (−0.17–0.30)  | 0.01                      | 0.59      |
| Female              | 24 (5800)              | 0.05 (−0.02–0.11)  | 0.30                      | 0.17      |
| Male                | 19 (3140)              | −0.04 (−0.17–0.08) | 0.01                      | 0.51      |
| Obesity             | 30 (4930)              | 0.01 (−0.06–0.08)  | 0.36                      | 0.81      |
| T2DM                | 10 (2345)              | 0.17 (−0.06–0.40)  | < 0.001                   | 0.14      |
was detected ($P = 0.90$ for leptin, $0.68$ for adiponectin, $0.89$ for TG, $0.28$ for TC, $0.39$ for LDL-C, $0.37$ for HDL-C, respectively).

**Discussion**

The present study showed that the ADRA3 Trp64Arg polymorphism is robustly associated with abnormal levels of adipokines and lipids. This indicates that the ADRA3 Trp64Arg polymorphism may represent a genetic risk factor for CAD.

The specific mechanisms in which the ADRA3 Trp64Arg polymorphism with abnormal adipokines have not been clarified yet. One possible mechanism can be proposed to explain the relationship between the Trp64Arg variant and abnormal adipokines levels. The mutation C allele of ADRA3 results in low mRNA expression levels [38] and low protein activity [39] of hormone-sensitive lipase (HSL), the reduce lipase concentration and protein activity will no doubt initiate or accelerate obesity [30–32]. Interestingly, this hypothesis is verified in this meta-analysis, since the data shows that the mutation C allele of ADRA3 is robustly associated with obesity (Table 3, Table 4), as described above, the obesity is related to abnormal levels of adipokines [16]. This may explain the present findings.

Several possible mechanisms can be proposed to explain the relationship between the ADRA3 Trp64Arg variant and dyslipidemia. At first, HSL can promote the free fatty acid and glycerol release from white adipose tissue [40, 41] into the plasma, and the changed lipase concentration and protein activity caused by C allele [38, 39] will no doubt influence the plasma concentration of free fatty acid and glycerol, thereby induced dyslipidemia. Secondly, Li et al. [42] have conducted an animal study in 40 apolipoprotein E (APOE) gene knock-out mice. Their data suggest that the ADRA3 gene may trigger dyslipidemia by regulating the expression of proprotein convertase subtilisin/kexin type 9 (PCSK9) gene and LDL receptor (LDLR) gene. It is widely known that both PCSK9 and LDLR are lipid metabolism-regulated genes, thereby the Trp64Arg polymorphism may indirectly affect plasma lipids levels by regulating lipid metabolism-regulated genes expression. Thirdly, whereas both leptin [10–12] and adiponectin [13–15] are related to dyslipidemia, the Trp64Arg variant may indirectly affect lipid levels through the mediation of adipokines. Interestingly, this hypothesis may also verify in this meta-analysis. The data in the present study shows that the mutation C allele of Trp64Arg polymorphism only has a slight effect on plasma levels of lipids (Table 3, Table 4), but a strong effect on plasma levels of adipokines (Table 1, Table 2). Whose SMD values are much larger than those calculated in plasma lipids. As mentioned above, adipokines as a lipid

| Groups or subgroups | Comparisons (Subjects) | SMD (95% CI) | $p_{	ext{heterogeneity}}$ | $p_{	ext{SMD}}$ |
|---------------------|------------------------|--------------|---------------------------|----------------|
| CAD                 | 6 (1040)               | −0.05 (−0.18–0.09) | 0.87                      | 0.51           |
| Healthy subjects    | 39 (12,149)            | 0.05 (−0.02–0.12)  | < 0.001                   | 0.20           |
| Children            | 11 (2080)              | 0.10 (−0.09–0.03)  | < 0.001                   | 0.30           |
| HDL-C               |                        |               |                           |                |
| All                 | 164 (49,069)           | −0.05 (−0.08–0.02) | < 0.001                   | < 0.01         |
| Studies in HWE      | 144 (43,919)           | −0.04 (−0.07–0.01) | < 0.001                   | 0.03           |
| Caucasian           | 45 (17,720)            | −0.06 (−0.08–0.04) | 0.60                      | 0.05           |
| Asian               | 102 (27,648)           | −0.05 (−0.09–0.01) | < 0.001                   | 0.02           |
| Chilean             | 3 (340)                | −0.10 (−0.33–0.13) | 0.37                      | 0.38           |
| Brazilian           | 4 (1310)               | −0.14 (−0.33–0.04) | 0.62                      | 0.22           |
| Indonesian          | 4 (531)                | −0.07 (−0.34–0.20) | 0.52                      | 0.59           |
| Other ethnic        | 4 (613)                | −0.32 (−0.58–0.07) | 0.13                      | 0.01           |
| Female              | 40 (12,250)            | −0.04 (−0.08–0.00) | 0.22                      | 0.05           |
| Male                | 31 (9407)              | −0.01 (−0.08–0.07) | 0.01                      | 0.91           |
| Obesity             | 36 (5310)              | −0.06 (−0.10–0.02) | < 0.01                    | 0.04           |
| T2DM                | 19 (3575)              | −0.17 (−0.30–0.04) | < 0.01                    | 0.01           |
| Hypertension        | 4 (957)                | 0.01 (−0.15–0.16)  | 0.10                      | 0.91           |
| CAD                 | 8 (1532)               | −0.14 (−0.37–0.09) | 0.01                      | 0.23           |
| Healthy subjects    | 72 (27,600)            | −0.00 (−0.03–0.03) | 0.16                      | 0.93           |
| Children            | 15 (2409)              | −0.09 (−0.18–0.00) | 0.06                      | 0.06           |

ADRA3 beta3-adrenergic receptor gene, SMD standardized mean difference, 95% CI 95% confidence interval, HWE Hardy-Weinberg equilibrium, TG triglycerides, TC total cholesterol, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, CAD coronary artery disease, T2DM type 2 diabetes mellitus.
Table 4 Meta-analysis of the ADRB3 Trp64Arg polymorphism with plasma lipid levels after excluding the study with heterogeneity

| Groups or subgroups | Comparisons (Subjects) | SMD (95% CI) | P_{heterogeneity} | P_{SMD} |
|---------------------|------------------------|--------------|-------------------|---------|
| **TG**              |                        |              |                   |         |
| All                 | 146 (38,535)           | 0.04 (0.01–0.06) | 0.07              | < 0.01  |
| Studies in HWE      | 130 (34,679)           | 0.02 (0.00–0.05) | 0.24              | 0.05    |
| Caucasian           | 42 (14,786)            | 0.04 (−0.01–0.09) | 0.37              | 0.08    |
| Asian               | 92 (21,766)            | 0.04 (0.01–0.07) | 0.05              | 0.01    |
| Chilean             | 2 (234)                | −0.18 (−0.47–0.10) | 0.79              | 0.21    |
| Brazilian           | 2 (223)                | 0.22 (−0.13–0.57) | 0.37              | 0.22    |
| Indonesian          | 4 (531)                | −0.18 (−0.45–0.09) | 0.84              | 0.20    |
| Other ethnic        | 4 (995)                | −0.05 (−0.19–0.09) | 0.28              | 0.51    |
| Female              | 38 (10,163)            | 0.05 (0.00–0.10) | 0.05              | 0.05    |
| Male                | 26 (7602)              | 0.01 (−0.05–0.06) | 0.30              | 0.83    |
| Obesity             | 37 (5290)              | 0.09 (0.02–0.16) | 0.49              | 0.01    |
| T2DM                | 17 (3592)              | 0.13 (0.05–0.21) | 0.42              | < 0.01  |
| Hypertension        | 4 (781)                | −0.05 (−0.22–0.13) | 0.28              | 0.61    |
| CAD                 | 7 (1225)               | −0.12 (−0.25–0.01) | 0.46              | 0.07    |
| Healthy             | 62 (22,922)            | 0.02 (−0.02–0.05) | 0.08              | 0.35    |
| Children            | 11 (2025)              | 0.06 (−0.01–0.18) | 0.68              | 0.08    |
| **TC**              |                        |              |                   |         |
| All                 | 153 (46,775)           | 0.03 (0.01–0.05) | 0.11              | < 0.01  |
| Studies in HWE      | 133 (41,641)           | 0.03 (0.01–0.06) | 0.17              | 0.01    |
| Caucasian           | 42 (17,507)            | 0.04 (−0.01–0.08) | 0.43              | 0.11    |
| Asian               | 99 (26,340)            | 0.03 (0.01–0.06) | 0.20              | 0.01    |
| Chilean             | 3 (340)                | 0.04 (−0.19–0.27) | 0.83              | 0.73    |
| Brazilian           | 4 (1310)               | 0.09 (0.06–0.24) | 0.52              | 0.23    |
| Other ethnic        | 5 (1278)               | 0.00 (−0.27–0.27) | < 0.01            | 0.98    |
| Female              | 36 (11,377)            | 0.05 (0.00–0.10) | 0.76              | 0.04    |
| Male                | 25 (7681)              | −0.01 (−0.06–0.05) | 0.34              | 0.81    |
| Obesity             | 35 (5269)              | 0.08 (0.00–0.15) | 0.70              | 0.04    |
| T2DM                | 20 (5257)              | 0.04 (−0.02–0.11) | 0.75              | 0.22    |
| Hypertension        | 6 (1182)               | 0.04 (−0.10–0.18) | 0.57              | 0.54    |
| CAD                 | 7 (1225)               | −0.13 (−0.26–0.00) | 0.28              | 0.06    |
| Healthy             | 62 (25,355)            | 0.03 (0.00–0.06) | 0.13              | 0.07    |
| Children            | 12 (2039)              | 0.04 (−0.05–0.14) | 0.39              | 0.36    |
| **LDL-C**           |                        |              |                   |         |
| All                 | 93 (22,397)            | 0.02 (−0.01–0.05) | 0.54              | 0.16    |
| Studies in HWE      | 81 (19,151)            | 0.02 (−0.02–0.05) | 0.49              | 0.38    |
| Caucasian           | 27 (7116)              | −0.01 (−0.08–0.06) | 0.49              | 0.84    |
| Asian               | 58 (12,539)            | 0.04 (0.00–0.08) | 0.52              | 0.04    |
| Brazilian           | 3 (1238)               | −0.03 (−0.19–0.12) | 0.20              | 0.67    |
| Other ethnic        | 4 (1138)               | −0.07 (−0.20–0.06) | 0.85              | 0.31    |
| Female              | 23 (5740)              | 0.04 (−0.03–0.10) | 0.66              | 0.29    |
| Male                | 17 (2512)              | 0.01 (−0.08–0.10) | 0.12              | 0.84    |
| Obesity             | 29 (4688)              | 0.02 (−0.05–0.09) | 0.57              | 0.55    |
| T2DM                | 8 (1890)               | 0.03 (−0.08–0.14) | 0.44              | 0.62    |
regulator [4–6] play a critical role in lipid metabolism [7–9]. This may also explain the present findings.

In the present meta-analysis, the significant effects of the Trp64Arg variant on lipid levels were only in Asians (Table 4), it indicates that there is an interaction between the Trp64Arg variant and ethnicity in modulating the plasma lipids. Gender might modulate the association of the Trp64Arg variant with plasma lipids since the significant effects of the Trp64Arg variant on lipid levels were only in Females (Table 4). Disease status might also modulate the association of the Trp64Arg variant with plasma lipids since the significant effects of the Trp64Arg variant on lipid levels were mainly from patients with obesity (Table 3, Table 4). Besides, whose SMD values were much smaller than those calculated in adipokines (Table 1, Table 2). When combined with the previous findings [43], it indicated that the association of the Trp64Arg variant with obesity might partly be mediated by the effect of this variant on adipokines.

**Strengths and limitations**

Several strengths of the present meta-analysis should be put forward. Firstly, the present meta-analysis had the sufficiently high statistical power to examine the associations of the Trp64Arg polymorphism with adipokines and plasma lipids in a large sample size, which would increase the reliability of the calculated results. Secondly, the calculated results were obtained after excluding the studies with heterogeneity, which would undoubtedly contribute to drawing some scientific and precise conclusions in the present meta-analysis. Thirdly, the multi-level analyses were performed by ethnicity, disease status, gender, healthy subjects, and children subjects, which would undoubtedly be beneficial to generate some comprehensive and diversified results in this present study. The main limitation of the present meta-analysis was that multiple genetic and environmental factors triggered dyslipidemia. However, the interactions between Trp64Arg polymorphism and other genetic or environmental factors on plasma lipids have not been investigated in this work due to the lack of original data.

**Conclusions**

The C allele carriers of Trp64Arg polymorphism had a slight but significant influence on lipid levels, and the remarkable effects specific existed in obese Asian women. The associations of Trp64Arg polymorphism with dyslipidemia may partly be mediated by the effect of this polymorphism on adipokines. The association of Trp64Arg polymorphism with obesity may partly be

| Groups or subgroups | Comparisons (Subjects) | SMD (95% CI) | P_{heterogeneity} | P_{soo} |
|---------------------|------------------------|--------------|-------------------|--------|
| CAD                 | 6 (1040)               | −0.05 (−0.18–0.09) | 0.87 | 0.51 |
| Healthy             | 34 (9862)              | 0.05 (−0.00–0.09)  | 0.22 | 0.07 |
| Children            | 8 (1768)               | 0.10 (−0.00–0.20)  | 0.42 | 0.06 |
| HDL-C               |                        |              |                   |        |
| All                 | 150 (43,951)           | −0.04 (−0.06–0.02) | 0.55 | 0.01 |
| Studies in HWE      | 134 (39,781)           | −0.03 (−0.06–0.01) | 0.22 | 0.01 |
| Caucasian           | 45 (17,720)            | −0.04 (−0.09–0.00) | 0.60 | 0.06 |
| Asian               | 90 (23,675)            | −0.03 (−0.06–0.01) | 0.05 | 0.02 |
| Chilean             | 3 (340)                | −0.10 (−0.33–0.13) | 0.37 | 0.38 |
| Brazilian           | 3 (295)                | 0.21 (−0.09–0.50)  | 0.42 | 0.17 |
| Indonesian          | 4 (531)                | −0.07 (−0.34–0.20) | 0.52 | 0.59 |
| Other ethnic        | 3 (483)                | −0.23 (−0.42–0.04) | 0.55 | 0.02 |
| Female              | 38 (11,946)            | −0.05 (−0.10–0.00) | 0.73 | 0.03 |
| Male                | 27 (8774)              | −0.02 (−0.07–0.03) | 0.13 | 0.50 |
| Obesity             | 33 (5017)              | −0.05 (−0.10–0.00) | 0.17 | 0.05 |
| T2DM                | 15 (1923)              | −0.15 (−0.25–0.05) | 0.68 | <0.01 |
| Hypertension        | 4 (957)                | 0.01 (−0.15–0.16)  | 0.10 | 0.91 |
| CAD                 | 7 (1403)               | −0.07 (−0.19–0.06) | 0.09 | 0.31 |
| Healthy             | 67 (24,960)            | −0.02 (−0.05–0.01) | 0.49 | 0.21 |
| Children            | 14 (2279)              | −0.07 (−0.15–0.02) | 0.33 | 0.15 |

ADRB3 beta3-adrenergic receptor gene, SMD standardized mean difference, 95% CI 95% confidence interval, HWE Hardy-Weinberg equilibrium, TG triglycerides, TC total cholesterol, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, CAD coronary artery disease, T2DM type 2 diabetes mellitus
mediated by the effect of this polymorphism on adipokines. The C allele carriers had abnormal levels of adipokines and lipids, and it indicated that the Trp64Arg polymorphism might represent a genetic risk factor for CAD.

**Supplementary information**

**Supplementary information** accompanies this paper at https://doi.org/10.1186/s12944-020-01290-y.

### Additional file 1 Table S1. Characteristics of the included studies in this systematic review of plasma adipokines and lipids levels for the ADR83 Trp64Arg polymorphism.

| Study | Region | Participants | Number of Participants | Trp64Arg Polymorphism | Adipokines | Lipids |
|-------|--------|--------------|------------------------|-----------------------|------------|--------|
| Study 1 | Country 1 | Gender | Age | Obesity | Gene | Adipokines | Lipids |
| Study 2 | Country 2 | Gender | Age | Obesity | Gene | Adipokines | Lipids |

**Table S2.** Plasma adipokines levels by the genotypes of the ADR83 Trp64Arg polymorphism.

| Genotype | Adipokines | Lipids |
|----------|------------|--------|
| Trp64C   | A          | B       |
| Trp64R   | C          | D       |

**Table S3.** Plasma lipids levels by the genotypes of the ADR83 Trp64Arg polymorphism.

| Genotype | Cholesterol | Triglycerides |
|----------|--------------|---------------|
| Trp64C   | E            | F              |
| Trp64R   | G            | H              |

**Meta-regression analysis explores the sources of heterogeneity of plasma triglycerides (TG) levels.**

**Table S4.** Meta-regression analysis explores the sources of heterogeneity of plasma high-density lipoprotein cholesterol (HDL-C) levels.

| Source | Coefficient | Standard Error |
|--------|-------------|----------------|
| Factor 1 | A           | B              |
| Factor 2 | C           | D              |

**Table S5.** Meta-regression analysis explores the sources of heterogeneity of plasma low-density lipoprotein cholesterol (LDL-C) levels.

| Source | Coefficient | Standard Error |
|--------|-------------|----------------|
| Factor 1 | A           | B              |
| Factor 2 | C           | D              |

**Table S6.** Meta-regression analysis explores the sources of heterogeneity of plasma adiponectin levels.

| Source | Coefficient | Standard Error |
|--------|-------------|----------------|
| Factor 1 | A           | B              |
| Factor 2 | C           | D              |

**Table S7.** Meta-regression analysis explores the sources of heterogeneity of plasma total cholesterol (TC) levels.

| Source | Coefficient | Standard Error |
|--------|-------------|----------------|
| Factor 1 | A           | B              |
| Factor 2 | C           | D              |

**Table S8.** Meta-regression analysis explores the sources of heterogeneity for circulating low-density lipoprotein cholesterol (LDL-C) levels.

| Source | Coefficient | Standard Error |
|--------|-------------|----------------|
| Factor 1 | A           | B              |
| Factor 2 | C           | D              |

**Additional references:** The reference list of the included studies in this systematic review.

### Abbreviations

- ADR83: B3 adrenergic receptor; CAD: Coronary artery disease; T2DM: Type 2 diabetes mellitus; TG: Triglycerides; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; HSL: Hormone-sensitive lipase; SMD: Standardized mean difference; CI: 95% confidence interval; SD: Standard deviation; APDE: Apolipoprotein E; PCSK9: Proprotein convertase subtilisin/kexin type 9; LDLR: LDL receptor; CNKI: China National Knowledge Infrastructure; CBM: China Biology Medicine; HWE: Hardy-Weinberg equilibrium.

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No.

### Availability of data and materials

All extracted data in this study have been used in previously published articles.

### Authors’ contributions

Luo Z designed and carried out this study and drafted the manuscript. Luo Z, Cao WZ, Zhang T, Wang SP, He YX, and Ye QT conducted the literature selection process and extracted the data. Luo Z, Cao WZ, and Zhang T performed the statistical analyses. All authors approved the final manuscript.

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### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no conflict of interest.

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