Association of CD14 –159 (–260C/T) polymorphism and asthma risk: an updated genetic meta-analysis study

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Abstract

Background: It has been reported that the cluster of differentiation 14 (CD14) gene –159C/T variant may be associated with asthma risk. However, some studies yielded conflicting results. Therefore, a comprehensive meta-analysis was designed to assess the precise association.

Methods: A systematic search in PubMed, Embase (Ovid), China National Knowledge Internet (CNKI), and Wan fang databases was conducted up to August 15, 2015. Odds ratio (OR) and 95% confidence interval (CI) were used to pool the effect size. We used \textit{I²} to assess heterogeneity, and a funnel plot and Egger test to assess publication bias.

Results: In total, 34 studies involving 15,641 subjects were included in this meta-analysis. There was a statistically significant association between CD14 –159C/T polymorphism and asthma risk observed in dominant model (TT+TC vs CC: OR=0.86, 95% CI=0.77–0.97, \textit{P}=0.012) and codominant model (TC vs CC: OR=0.88, 95% CI=0.78–0.99, \textit{P}=0.035) in adults. However, there may be no significant association between CD14 159C/T and atopic and nonatopic asthma risk.

Conclusion: In summary, the overall results suggested that the CD14 –159C/T variant may decrease the risk of asthma susceptibility in adults. However, no significant association between CD14 159C/T and atopic and nonatopic asthma susceptibility was identified. More studies with larger sample size are needed to validate the findings from this study.

Abbreviations: 95% CIs = 95% confidence intervals, CD14 = cluster of differentiation 14, CNKI = China National Knowledge Internet, ESP1 = estrogen receptor 1, GWAS = genome-wide linkage studies, HWE = Hardy–Weinberg equilibrium, LPS = lipopolysaccharides, OR = Odds ratio, TGF-β1 = transforming growth factor beta 1.

Keywords: asthma, CD14, meta-analysis, polymorphism

1. Introduction

Characterized by airway hyperreactivity to some environmental stimuli, mucus hypersecretion, reversible airway obstruction, and bronchial epithelial desquamation, resulting in airway structural remodeling, asthma is a complex respiratory disease with a multifactorial etiology.\textsuperscript{[1,12]} Asthma is in high prevalence worldwide with an estimated 300 million affected people, leading to significant mortality and morbidity.\textsuperscript{[3,4]} Especially, atopic asthma accounted for 56% of all asthma population in the United States, which is triggered by Aeroallergens and endotoxin.\textsuperscript{[5]} Although the precise etiology of asthma remains unclear, a combination of genetic predisposition and environmental exposures is believed to contribute to pathogenesis of asthma.\textsuperscript{[1,4]} With numerous recent advances in genetic research, many genes that are related to asthma susceptibility have been identified in multiple populations, including transforming growth factor beta 1 (TGF-β1), prostaglandin-endoperoxide synthase 1 (PTGS1), and estrogen receptor 1 (ESR1), especially the CD14.\textsuperscript{[6–11]}

The CD14 gene, located on chromosome 5q31.3, is presented in 2 exons and linked to asthma in genome-wide association studies (GWAS).\textsuperscript{[12]} It encodes 2 glycoprotein isoforms expressed as a membrane-bound form on the surface of monocytes, macrophages, and neutrophils and a soluble form in the serum.\textsuperscript{[11,13]} CD14 acts as a multifunctional high-affinity receptor for the binding of endotoxins, lipopolysaccharides (LPS), and other bacterial wall components, involved in primary immune and inflammatory responses.\textsuperscript{[14,15]} Studies have demonstrated that –159C/T variant in CD14 may change CD14 protein structure and associated with CD14 and immunoglobulin E level.\textsuperscript{[16]} CD14 may activate innate immune system pathways that influence the balance of the Th1 versus Th2 cytokines, thereby affecting IgE responses, inducing lung inflammation, and triggering allergic conditions such as atopic asthma.\textsuperscript{[11,17]}

According to published data, the –159C/T variant in the CD14 gene was found to be involved in pathogenesis of asthma.\textsuperscript{[18–20]} Nevertheless, some other studies failed to replicate...
the association of CD14 –159CT variation with asthma risk. So far, 2 earlier meta-analyses based on different strategies have tried to detect the possible association of CD14 –159CT polymorphisms with asthma. Unfortunately, the former had several noteworthy errors pertaining to study inclusion, data abstraction. The latter had included 3 articles which deviated from Hardy–Weinberg equilibrium (HWE). Thereafter, some new studies have been reported about diverse ethnic populations and phenotypes of asthma. Therefore, the data needs to be updated and more reliable evaluates of CD14 –159CT variant with asthma risk are warranted. Due to the inconsistency of past studies and the critical role of CD14 –159CT variant in the pathogenesis of asthma, we conducted an updated meta-analysis to investigate the association between CD14 –159CT polymorphism and asthma risk by precise results.

2. Materials and methods

The PRISMA protocol was prospectively performed. Ethical approval was unnecessary in this study because it was a meta-analysis analyzing existing articles and did not involve handling of individual patient data.

2.1. Study selection

Two independent reviewers exhaustively searched PubMed, Embase (Ovid), China National Knowledge Internet (CNKI), and Wan fang database to identify studies, which had detected the association of CD14 polymorphisms and asthma susceptibility. The latest electronic search was carried out on August 15, 2015. The search terms were used as follows: “asthma” or “asthmatic” and “CD14” or “cluster of differentiation 14” and “polymorphism” or “variant” or “mutation” or “polymorphisms” or “variants” or “mutations.” No language restrictions were imposed. Studies eligible for this meta-analysis fulfilled the following inclusion criteria: using a case-control design, investigating the association between –159CT polymorphism in CD14 gene and asthma risk, genotype distributions should be available for estimating the odds ratio (OR) with 95% confidence interval (CI), and genotype distribution of control groups should be consistent with HWE. Exclusion criteria were as follows: conference, review, and overlapping publications; study with no available genotype distributions; genotype distribution in the control population is not consistent with HWE. We also inspected the reference list of review or past meta-analysis for potentially relevant publications. Two investigators independently screened all abstracts and citations to extract potentially eligible studies.

2.2. Data extraction

Two independent investigators collected the information of each eligible study based on the inclusion criteria. First author, publication year, country, ethnicity, genotype and allele distributions, case and control size, and type of diseases were extracted. In case of dispute, 2 investigators would check the collected data and reach a consensus through discussion. The information is presented in Tables 1 and 2.

2.3. Statistical method

In this meta-analysis, all data were presented as OR with 95% CI to assess the association between –159CT polymorphism in the CD14 gene and asthma risk. Heterogeneity was evaluated using χ²-based Q-test and I² statistics. If no or low heterogeneity existed (I² < 50% and P < 0.10), the random-effects model was applied to estimate pooled OR. Otherwise, the fixed-effects model was used. The genetic models were evaluated for the pooled OR of the CD14 –159CT polymorphism in allele, dominant, recessive, codominant model. To explore the source of the heterogeneity and evaluate the ethnicity-specific and age-specific effects, subgroup analyses were conducted based on ethnicity and age. In addition, subjects were divided into different classifications according to asthma phenotype definition: atopic asthma, nonatopic asthma, and mixed asthma (atopic asthma not mentioned). Moreover, we also performed a subgroup analysis to further assess the ethnicity-specific, age-specific effects for atopic, nonatopic, and mixed asthma.

In order to assess the stability of the results, we performed a sensitivity analysis by sequentially excluding each study. Potential publication bias was tested by several methods. Visual inspection of asymmetry in funnel plots was carried out. Furthermore, Egger regression and Begg test were also utilized to detect publication bias, and a P-value < 0.05 was considered statistically significant. Moreover, to obtain further evidence, HWE was recalculated in control groups by Pearson χ² test before this meta-analysis was conducted. All data analysis was performed with STATA 11.0 software (Data Corp LP, College Station, TX).

3. Results

3.1. Included study characteristics

In total, 437 articles (393 articles in English and 44 papers in Chinese) based on the inclusion criteria were identified after we systematically searched PubMed, Embase (Ovid), CNKI, and Wan fang databases. After reading titles and abstracts, 62 articles were screened in full-text review (Fig. 1). Three articles were excluded because they did not evaluate the association of CD14 –159CT variant and asthma susceptibility, but other gene polymorphisms. Three articles were excluded because the genotype frequencies for the controls deviated from HWE. Seventeen articles were excluded because of insufficient data, and 5 studies were overlapped for 4 data sets. We retained the studies with the largest number of subjects. Therefore, in total, 34 studies from 34 articles (31 articles in English, 2 papers in Chinese, and 1 article in Polish) were identified, which contained 15,641 subjects (7535 cases and 8106 controls) to investigate the relationship between CD14 –159CT variant and the risk of asthma. The characteristics of included studies are shown in Tables 1 and 2.

3.2. Quantitative data synthesis

All 34 studies involving 15,641 subjects (7535 cases and 8106 controls) were pooled to investigate association between CD14 –159CT variant and asthma risk. For presence of a moderate heterogeneity, random-effects model was used in allele, codominant model and fixed-effects model in other genetic models. The overall results suggested that no significant association of CD14 –159CT polymorphism and asthma susceptibility was observed in any genetic model (Table 3). Then, we found no statistically significant relationship between CD14 –159CT and asthma risk in any model when studies were subset by ethnicity (Caucasian and Asian) (Table 3). In the subgroup analysis done on the basis of age, however, a significant
association of CD14 -159C/T and asthma risk was found in dominant model (TT+TC vs CC: OR=0.86, 95% CI=0.77–0.97, \( P=0.012 \)) (Fig. 2) and codominant model (TC vs CC: OR=0.88, 95% CI=0.78–0.99, \( P=0.035 \)) in adults (Table 3). Other genetic models are also summarized in Table 3.

### 3.3. Subgroup analysis

#### 3.3.1. Atopic asthma

All 18 studies\(^{[11,17–19,22,23,33,35–38,42,44,47,48,50,51]}\) containing 7029 subjects reported the association between CD14 -159C/T polymorphism and atopic asthma risk.

No statistically significant association of CD14 -159C/T polymorphism and atopic asthma risk was identified in dominant model (TT+TC vs CC: OR=0.95, 95% CI=0.84–1.06, \( P=0.351 \)) (Fig. 3) and any other genetic models (Table 3).

Subgroup analyses were performed to investigate the potential effect of ethnicity and age. We found no statistically significant relationship of CD14 -159C/T polymorphism and atopic asthma risk in either Asian or Caucasian subjects. Additionally, in the subgroup analysis of age, CD14 -159C/T variant was also found with no significant association with the risk of atopic asthma in all genetic models (Table 3).

#### 3.3.2. Mixed asthma

A total of 3420 cases and 4808 controls from 17 studies\(^{[20–22,26–28,30–32,34,39–41,43,45,46,49]}\) were included in our meta-analysis. Random-effects model was used to calculate the pooled OR and 95% CI because of the presence of moderate heterogeneity in dominant and codominant model (TC vs CC) (\( I^2=57.2\% \), \( P=0.05 \)), fixed-effects model in other models (Table 4). By total analysis, the overall gene effect showed no significant association of CD14 -159C/T polymorphism and mixed asthma susceptibility in any model (Table 3).

Subgroup analyses were also performed according to ethnicity and age. We found no statistically significant association of CD14 -159C/T polymorphism and mixed asthma risk in any genetic model in either Asian or Caucasian subjects (Table 3). Moreover, in subgroup analysis based on age, we found a strong association between the heterozygote (TC) and mixed asthma susceptibility in adults (TC vs CC: OR=0.84, 95% CI=0.71–1.00, \( P=0.047 \), \( I^2=3.3\% \)). Other genetic models are also shown in Table 3.

#### 3.3.3. Nonatopic asthma

A total of 7 case–control studies\(^{[11,17–19,22,23,33,36,47]}\) conducted among nonatopic asthma were included in this meta-analysis. Overall, the pooled results indicated that there was no significant relationship of CD14 -159C/T and nonatopic asthma risk in dominant model (TT+TC vs CC: OR=1.05, 95% CI=0.82–1.33, \( P=0.700 \)) (Fig. 3) and any other genetic comparisons (Table 3). Further subgroup analysis of
Table 2

Distributions of CD14 – 159C/T allele and genotypes in different groups.

| Author       | Year | Case          | Control         |       |
|--------------|------|---------------|-----------------|-------|
|              |      | TT | TC | CC | T (%) | C (%) | TT | TC | CC | T (%) | C (%) | HWE |
| Hakonarson   | 2001 | 17 | 46 | 31 | 80 (42.55) | 108 (57.45) | 19 | 46 | 29 | 84 (44.68) | 104 (55.32) | 0.92 |
| Koppelman    | 2001 | 32 | 76 | 51 | 140 (44.03) | 178 (55.97) | 42 | 85 | 31 | 169 (44.68) | 174 (55.32) | 0.31 |
| Lis          | 2001 | 6  | 24 | 20 | 36 (60.00)  | 24 (40.00)  | 11 | 34 | 28 | 56 (38.36)  | 80 (61.64)  | 0.9  |
| Heinzmann    | 2003 | 42 | 89 | 51 | 173 (47.53) | 191 (52.47) | 58 | 124 | 79 | 240 (45.98) | 282 (54.02) | 0.48 |
| Woo          | 2003 | 35 | 94 | 46 | 164 (46.86) | 186 (53.14) | 6  | 35 | 20 | 47 (38.52)  | 75 (61.48)  | 0.1  |
| Sharma       | 2004 | 52 | 92 | 43 | 196 (52.41) | 178 (47.59) | 85 | 112 | 30 | 282 (46.50) | 172 (53.50) | 0.47 |
| Keedda       | 2005 | 136| 284| 148| 556 (48.94) | 580 (51.06) | 93 | 226 | 124| 412 (46.50) | 474 (53.50) | 0.59 |
| Bernstein    | 2006 | 12 | 33 | 17 | 57 (45.97)  | 67 (54.03)  | 15 | 45 | 15 | 75 (50.00)  | 75 (50.00)  | 0.08 |
| Barnes       | 2006 | 15 | 147| 160| 177 (27.48) | 467 (72.52) | 47 | 204 | 200| 298 (33.04) | 604 (66.96) | 0.64 |
| Park         | 2006 | 30 | 39 | 16 | 99 (58.24)  | 71 (41.76)  | 193| 267 | 90 | 653 (59.36) | 447 (40.64) | 0.88 |
| Smit         | 2007 | 19 | 47 | 34 | 85 (42.50)  | 115 (57.50) | 15 | 47 | 26 | 77 (43.75)  | 90 (56.25)  | 0.32 |
| Hong         | 2007 | 229| 284| 113| 542 (48.94) | 580 (51.06) | 103| 267 | 90| 653 (59.36) | 447 (40.64) | 0.88 |
| Chen         | 2008 | 80 | 134| 55 | 294 (54.65) | 244 (45.35) | 38 | 77 | 26 | 153 (53.48) | 147 (46.52) | 0.23 |
| Kovar        | 2008 | 79 | 152| 141| 310 (41.67) | 434 (58.33) | 45 | 73 | 42 | 163 (50.94) | 157 (49.06) | 0.27 |
| Wang         | 2009 | 160| 230| 57 | 550 (42.50) | 580 (57.50) | 177| 236 | 96| 590 (57.96) | 428 (42.04) | 0.27 |
| Smit         | 2009 | 67 | 107| 49 | 241 (50.40) | 205 (49.60) | 133| 276 | 145| 542 (48.92) | 566 (51.08) | 0.94 |
| Chen         | 2009 | 25 | 62 | 63 | 112 (37.33) | 188 (62.67) | 42 | 68 | 40 | 152 (50.67) | 48 (49.33)  | 0.25 |
| Bjornvold    | 2009 | 19 | 47 | 34 | 85 (42.50)  | 115 (57.50) | 15 | 47 | 26 | 77 (43.75)  | 90 (56.25)  | 0.32 |
| Wu           | 2010 | 81 | 117| 54 | 241 (46.36) | 294 (53.64) | 85 | 233 | 161| 403 (42.07) | 555 (57.93) | 0.96 |
| Kuo Chou     | 2010 | 35 | 64 | 17 | 134 (57.76) | 98 (42.24)  | 69 | 118 | 45 | 256 (55.17) | 208 (44.83) | 0.67 |
| Munk         | 2011 | 11 | 55 | 31 | 177 (39.67) | 244 (60.33) | 45 | 73 | 42 | 163 (50.94) | 157 (49.06) | 0.27 |
| Wu           | 2011 | 75 | 90 | 23 | 240 (63.83) | 136 (36.17) | 25 | 30 | 5  | 80 (66.67)  | 40 (33.33)  | 0.33 |
| Perin        | 2011 | 64 | 101| 82 | 229 (46.36) | 265 (53.64) | 39 | 70 | 49 | 148 (46.84) | 168 (53.16) | 0.17 |
| Micheal      | 2011 | 32 | 53 | 25 | 117 (53.18) | 103 (46.82) | 13 | 29 | 8  | 98 (80.77)  | 23 (19.23)  | 0.33 |
| Rennie       | 2013 | 16 | 53 | 30 | 85 (42.93)  | 113 (57.07) | 79 | 229 | 126| 387 (44.59) | 481 (55.41) | 0.16 |
| Hussein      | 2013 | 75 | 215| 210| 365 (36.50) | 635 (63.50) | 12 | 70 | 68 | 94 (31.33)  | 206 (68.67) | 0.3  |
| Bose         | 2013 | 5  | 12 | 3  | 22 (50.00)  | 22 (50.00)  | 10 | 70 | 30 | 97 (32.76)  | 193 (67.24) | 0.22 |
| Kljic-Bukvic | 2014 | 121| 201| 75 | 443 (55.79) | 391 (44.21) | 97 | 197 | 78 | 391 (52.59) | 353 (47.41) | 0.23 |
| Feng         | 2015 | 56 | 76 | 20 | 188 (61.84) | 116 (38.16) | 42 | 60 | 14 | 144 (62.07) | 88 (37.93)  | 0.29 |
| Martinez-Aguilar | 2015 | 97 | 206| 118| 400 (47.51) | 442 (52.49) | 116| 198 | 116| 430 (50.00) | 430 (50.00) | 0.1  |

HWE = Hardy–Weinberg equilibrium.

Figure 1. Flow diagram of included and excluded studies.
studies comparing nonatopic asthmatics and nonasthmatics by ethnicity and age did not meaningfully change the results.

3.4. Sensitivity analysis

In order to examine the influence of the individual data set on the pooled ORs and evaluate the stability of the results, in this current meta-analysis, we carried out a sensitivity analysis by sequentially excluding individual studies to assess the stability of the results. The corresponding pooled ORs were similar in all genetic models, indicating that the results were stable (data not shown).

3.5. Publication bias

Publication bias was assessed through the Begg funnel plot and Egger regression intercept tests. The shape of the Begg funnel plot did not reveal basically asymmetric distribution in all comparisons of the overall population. Moreover, the result of Egger test ($P = 0.203$) further provided no evidence of significant publication bias. Our observation of symmetric funnel plots and nonsignificant statistical tests confirmed no publication bias (Fig. 4).

4. Discussion

Asthma is a complex disease caused by many genetic and environmental risk factors, leading to heterogeneous clinical features.$^{[1,52]}$ Although the exact etiology of asthma remains incompletely clear, there is accumulating evidence showing that the initiation and progression of asthma are affected by $CD14 - 159C/T$ polymorphism.$^{[23,29,53]}$ Recently, many new case–control studies on this subject have been published. However, the data have yielded conflicting results.$^{[11,21,30–36]}$ Therefore, we performed this updated meta-analysis to investigate the more precise association between the $CD14 - 159C/T$ variant and asthma risk.

In this meta-analysis, we investigated the $CD14 - 159C/T$ polymorphism with 34 separate case–control studies (7535 cases and 8106 controls) regarding the association of this gene to the risk of asthma. No significant overall association was detected between $CD14 - 159C/T$ and asthma. Nevertheless, a moderate heterogeneity was detected in this meta-analysis, which may be attributed to different characteristics of the cohort, intrinsic complexity of asthma architecture, and different asthma definitions. Therefore, we carried out subgroup analysis to investigate heterogeneity by ethnicity, age, and asthma subtypes. Strongly and significantly decreased risk of asthma was observed when the analysis was restricted to adults in dominant
CD14 is an essential membrane receptor for LPS and plays a role in innate immunity and inflammatory response. One variant on the CD14 gene in the pathway of pathogenesis, 159C/T (rs2569190), may alter the structure and function of protein and influence the CD14–LPS interactions and sCD14 levels. But CD14–159C/T variant plays no clear role in developing asthma, atopic and nonatopic asthma, based on this review. The results were consistent with some recent studies. However, this may be due to the mediating environmental conditions and the unclear relationship between −159C/T variant and sCD14 levels. It was demonstrated that the association of the −159C/T polymorphism and asthma is dependent on different degrees of endotoxin exposure: individuals with TT genotypes were protective for asthma at low levels of endotoxin, but were at risk at high levels of endotoxin exposure. Conversely, carriers of C allele upon exposure to high levels of endotoxin showed a reversed protective effect.

Furthermore, some studies have reported that −159C/T variant was correlated with sCD14 levels and the potential effect on asthma was described but the effect may be affected by several polymorphisms and many additional regulatory elements influencing the gene expression. Consequently, only increasing the number of populations, without taking gene-environment and gene-gene interaction into account, will not guarantee the validity of the results. In addition, some GWAS have reported some loci were correlated with total IgE, such as HLA-DQB1, but no CD14–159C/T variant. This may be due to the slight effect of this polymorphism on asthma risk. When subgroup analysis was stratified based on adults, the genotype-specific ORs showed a protective effect. This result was in line with the

### Table 3

| Subgroup | TT+TC vs CC | TT vs TC+CC | TT vs CC | TC vs CC | T vs C |
|----------|-------------|-------------|----------|----------|--------|
| Overall  | 6.04 (0.72–1.00) | 0.97 (0.84–1.13) | 1.06 (0.89–1.25) | 0.86 (0.71–1.04) | 0.93 (0.80–1.07) |
| Caucasian | 3.65 (0.84–1.50) | 0.98 (0.72–1.34) | 1.07 (0.81–1.41) | 0.86 (0.62–1.18) | 0.93 (0.70–1.24) |
| Asian    | 1.15 (0.76–1.75) | 0.99 (0.72–1.40) | 1.06 (0.79–1.41) | 0.85 (0.59–1.22) | 0.92 (0.67–1.26) |

**Notes:**
- CI = confidence interval.
- OR = odds ratio.
- TT vs CC = heterozygote.
- TT vs CC = homozygote.
- TT vs TC+CC = recessive model.
- TT+TC vs CC = dominant model.

**Table 3**

Summary of overall results and subgroup for the association between CD14 − 159C/T and asthma.

| Subgroup | TT+TC vs CC | TT vs TC+CC | TT vs CC | TC vs CC | T vs C |
|----------|-------------|-------------|----------|----------|--------|
| Overall  | 6.04 (0.72–1.00) | 0.97 (0.84–1.13) | 1.06 (0.89–1.25) | 0.86 (0.71–1.04) | 0.93 (0.80–1.07) |
| Caucasian | 3.65 (0.84–1.50) | 0.98 (0.72–1.34) | 1.07 (0.81–1.41) | 0.86 (0.62–1.18) | 0.93 (0.70–1.24) |
| Asian    | 1.15 (0.76–1.75) | 0.99 (0.72–1.40) | 1.06 (0.79–1.41) | 0.85 (0.59–1.22) | 0.92 (0.67–1.26) |

**Notes:**
- CI = confidence interval.
- OR = odds ratio.
- TT vs CC = heterozygote.
- TT vs CC = homozygote.
- TT vs TC+CC = recessive model.
- TT+TC vs CC = dominant model.

The P-values of Z test for odds ratios test.

† Significant difference.
hypothesis at low endotoxin exposure levels by Martinez.\textsuperscript{55}

Some studies reported that serum sCD14 might be increased at specific time points, suggesting a time window at which adults may be more vulnerable for exposure.

There were several potential limitations in this meta-analysis. First, several risk factors, such as environment–gene/gene interaction, different characteristics of the cohort, and life style, may affect the susceptibility to asthma. However, no further analysis could be conducted due to lack of original information. Second, a majority of studies were conducted regarding Asian and Caucasian populations and the pooled results may be only applicable to the 2 ethnic populations. Therefore, we need to verify the association in other ethnicities. Despite these limitations, a strict protocol, data identification, and statistical analysis were performed to reduce potential bias through the whole process. Thus, the objectivity and reliability of the results are guaranteed.

5. Conclusion

The meta-analysis results suggested $\text{CD14} - 159C/T$ polymorphism may be significantly associated with decreased risk of asthma in adults. However, there may be no significant association between $\text{CD14} - 159C/T$ and atopic and nonatopic asthma risk. In the future, there is a need for larger sample size and more ethnic groups to further validate the results of the current meta-analysis.

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