Association Between ABCA1 (R219K) Polymorphism and Lipid Profiles: A Meta-Analysis

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Research

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Abstract

Background

Conflicting evidence was found about the relationship between lipid profiles and R219K in adenosine triphosphate-binding cassette exporter A1 (*ABCA*1) gene. A meta-analysis was conducted to assess the effect of R219K on lipid level.

Methods

Multi-database literature search was performed in accordance with PRISMA guidelines. The effect of each study was expressed by standard mean difference (SMD) and 95% confidence interval and pooled by meta-analysis in a random-effects model. Sub-group and meta-regression analyses were also conducted to explore potential heterogeneity sources.

Results

Overall pooled effect showed that individuals with RR genotype had significantly lower HDLC level (*SMD* = -0.17 mmol/L, 95% CI: -0.22 ~ -0.12, z = -6.39, P < 0.001) than those with K allele. However, this effect mainly presented in Asians (*SMD* = -0.24 mmol/L, 95% CI: -0.32 ~ -0.17, z = 6.60, P < 0.001) rather than Caucasian populations, and the difference was significant (Q = 5.20, df = 1, P = 0.02). The relationship between R219K polymorphism and LDLC, TC, and TG levels was not determined.

Conclusions

R219K polymorphism in the *ABCA*1 gene was associated with HDLC level in Asian populations in the present meta-analysis. This correlation was not substantially affected by the age, gender or health condition of individuals.

Background

An optimal blood lipid level is important for every human population regardless of age, ethnicity or gender. The lipid profile serves as an initial screening tool for lipid abnormalities, a routine clinical test and an important predictor for noncommunicable diseases, such as blood lipid disorders, cardiovascular diseases (CVD), diabetes, obesity, and stroke.

High heritability is observed in human standard lipid profiles measuring traditional lipids (referred to as high-density lipoprotein cholesterol, HDLC; low-density lipoprotein cholesterol, LDLC; total cholesterol, TC; and triglycerides, TG). Approximately 10–15% of the variances among individual blood lipid levels can be explained by genetic effects [1]. Understanding the genetic architecture and regulation of lipid profiles

could help in predicting, monitoring and treating human diseases (e.g., CVD, diabetes, etc) [2]. To date, many genes which involved in lipid metabolism have been identified associated with lipid levels [3, 4].

ABCA1, an ATP-binding cassette (ABC) subfamily A exporter, mediates the transfer of cellular phospholipids and cholesterol into the extracellular medium to control circulating lipoprotein levels [5]. Genetic variants of the *ABCA1* gene might contribute to the individual difference of lipid levels [6]. One polymorphism of this gene, arg219-to-lys (R219K, namely rs2230806) in exon 7, has been extensively studied. The relationship between R219K and lipid levels is often used as an endophenotype of patients, and is combined with clinical diagnosis to help identify the causal genetic factors of human diseases (e.g., hypercholesterolemia [7], heart disease [7, 8], coronary artery disease (CAD) [9], etc). However, their correlation is still inconsistent and even becomes more ambiguous when considering the influence of race, gender, age and samples' clinical condition. For instance, three studies [10–12] reported that the K allele showed a significant positive correlation with HDLC levels in control or general populations, but this relationship was not observed in other studies [13–19]. The inconsistency also appeared in other three variables, namely LDLC, TC and TG levels, and the sample size, race, age, gender and other external elements are suspected as potential influences. Four meta-analyses were performed to address these issues [20–23], but all of them only emphasised the genetic variants of R219K and the risk of diseases (including ischaemic stroke, coronary heart disease, and type 2 diabetes mellitus diseases) but did not discuss the consistency of their relationship between patients and general populations.

Here, an update meta-analysis for the correlations between R219K polymorphism and HDLC, LDLC, TC and TG levels was conducted. This work aims to: i) investigate the relationship between R219K polymorphism and individual lipid levels within both the general population and patients with common diseases, ii) assess the consistency of this relationship between different populations and iii) estimate the influence of other external factors on this correlation.

Methods

Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed for this review [24]. A completed PRISMA checklist is available as an online supplementary material (Additional file 1).

Search strategy and criteria

The two authors (Shi and Tian) searched for studies published before January 2020 and extracted useful data from the ISI Web of Science [25] and PubMed databases [26] for papers in English and from the Chinese National Knowledge Infrastructure (CNKI) [27] and Wanfang databases [28] for papers in Chinese. The full search strategy and literature terms used for searching the above databases are available as an online supplementary material (Additional file 2).

Inclusion criteria were as follows: i) the mean lipids and standard deviations (SD) and/or standard errors (SE) were available for each group according to R219K genotypes; ii) at least one of the four variables (HDLC, LDLC, TC and TG) was available; iii) the frequency of genotype of R219K was also described; and vi) other related information that can be used to calculate the effect size of R219K on the four lipid variables or the required data could be collected from other publications.

Data extraction and quality assessment

Exclusion criteria were as follows: i) meeting summary; ii) no relevance of the *ABCA*1 gene; and iii) the original document was unavailable. Additionally, the quality of all articles was evaluated by two authors according to the Newcastle-Ottawa Scale (NOS) assessment scale, in which a study with NOS grade less than six was excluded to ensure quality. Information extracted from the eligible literatures included the following: i) name of the first-author, time of publication and number of samples; ii) health condition, ethnicity and mean age of subjects and proportion of females in the sample; iii) mean lipid levels, standard deviation and/or standard error for different groups according to R219K genotype; and vi) other format data that can be used to calculate the effect size value. The required data were extracted and formatted as described in the online supplementary material (Additional file 3).

Statistical analysis

Comprehensive Meta-Analysis V3 (CMA 3.0, Biostat, Inc. Englewood, USA) software was used to calculate the effect size of each study in a standardized mean difference (SMD) and 95% confidence interval (95% CI) format. Pooled effect size and sub-population analyses were also performed with CMA 3.0. Cochran's *Q*-statistic and I^2 statistics were used to assess the heterogeneity among eligible studies. If $P < 0.05$ and $I^2 > 50\%$, then the heterogeneity was defined as significant. To minimize the influence of the heterogeneity of the included studies and detect the outliers with low quality and extreme effect size, *meta* and *metafor* packages for R were used. The outliers were removed from the total studies in the following analyses. Considering the recommendation of P Cuijpers [29], the present meta-analysis was conducted using the random-effects pooling model which assumes that all studies stem from more than one hypothesised "population" and the true effects are normally distributed.

For categorical variables, the following two-step analysis was performed to explore the sources of observed significant heterogeneity and assess their influence on the relationship between the genetic variants R219K of *ABCA*1 and the lipid profile: i) pooling the effect of each subgroup as for a simple meta-analysis and ii) comparing the effects of the subgroups as recommended by Borenstein et al. [30]. For all variables including continuous ones, a regression-meta analysis was also conducted to estimate the influence of each variable on the correlation between R219K and lipid profile. Publication bias was examined with Begg's rank correlation [31], Egger's weighted regression tests [32] and a "trim and fill" test [33] and visualised by funnel plots. All significance tests were two-tailed, and the significance threshold was set to < 0.05.

Results

Characteristics of eligible studies and samples

A total of 80 studies met the inclusion criteria (see Fig. 1 for PRISMA flowchart). As described in the online supplementary materials (Additional file 4), 116 samples and 56,161 subjects were involved. Approximately 44.27% were women (24,860/56,161), and less than half were Asians (for Asian: 42.41%, samples = 75, n = 23,820 [34–80]; for Caucasian: 53.36%, samples = 37, n = 29,967 [9, 16, 18, 81–101]; and one African [102] and two mixed populations [103, 104] were defined as the mixed group: 4.23%, samples = 4, n = 2,374). The samples could also be categorised into patients (23.96%, samples = 45, n = 13,456), random (37.14%, samples = 44, n = 21,861) and mixed (38.9%, samples = 27, n = 21,844) groups according to their clinical information. More than 12 kinds of diseases were included in collected studies' samples.

Relationship between R219K and HDLC level

Overall pooled effect of R219K on HDLC

Pooled data revealed a significantly lower HDLC level in the RR genotype group than that in the K allele carrier group (*SMD* = -0.28 mmol/L, 95%CI: -0.36 ~ -0.20, z = -6.85, P < 0.001) in a random model. Extreme heterogeneity among all studies was observed, I^2 = 94.62% (Q = 2138.42, df = 115, P < 0.001) among these eligible studies. Four of the included samples (Abellán [93] data1, Sun [45] data 2, Ya [105] data1 and data 2) were identified as outliers with low-quality data and extreme effect size (see online supplementary materials, Fig. S5-1 and Fig. S5-2). The trend of the RR genotype population having a significantly lower HDLC level (*SMD* = -0.17 mmol/L, 95%CI: -0.22 ~ -0.12, z =-6.39, P < 0.001, and I^2 = 85.43%, Q = 761.80, df = 111, P < 0.001) than that of the K allele carriers in a random model was still observed after removing the four outliers.

Effect of R219K on HDLC in Asian and Caucasian subgroups

For Asian populations (samples = 72, n = 22,959), the RR genotype group had significantly lower HDLC level than the K allele carriers (*SMD* = -0.25 mmol/L, 95%CI: -0.32 ~ -0.17, z = 6.60, P < 0.001), and I^2 = 82.34% (Q = 401.98, df = 71, P < 0.001) in the heterogeneity test (Fig. 2). For Caucasian populations (samples = 36, n = 29,358), the difference in HDLC level between the RR genotype and K allele carriers did not reach statistical significance, *SMD* = -0.04 mmol/L, 95%CI: -0.11 ~ 0.02, z = -1.27, P = 0.20 in the random model, and I^2 = 85.00% (Q = 233.33, df = 35, P < 0.001) in the heterogeneity test. The relationship between different populations (e.g., Asian and Caucasian) was also significantly different (Q = 5.20, df = 1, P = 0.02), as estimated by the *metafor* package.

Effect of R219K on HDLC in different health-condition subgroups

Figure.3 shows that for clinical patients (samples = 43, n = 13,235), individuals with RR genotype had significantly lower HDLC level than the K allele carriers (*SMD* = -0.16 mmol/L, 95%CI: -0.23 ~ -0.09, *z* = -4.32, *P* < 0.001) in the random model, and I^2 = 68.78% (*Q* = 131.32, *df* = 41, *P* < 0.001) was obtained in the heterogeneity test. For the random population (samples = 43, n = 19,812), the RR genotype carriers also had significantly lower HDLC level than the K allele carriers (*SMD* = -0.15 mmol/L, 95%CI: -0.25 ~ -0.05, *z* = -2.89, *P* = 0.004), and I^2 = 89.30% (*Q* = 392.65, *df* = 42, *P* < 0.001) was acquired in the heterogeneity test. The same trend was observed in the mixed population (samples = 27, n = 21,844, *SMD* = -0.20 mmol/L, 95%CI: -0.29 ~ -0.11, *z* = -4.28, *P* < 0.001) with extreme heterogeneity of I^2 = 88.77% (*Q* = 231.59, *df* = 26, *P* < 0.001). Additionally, no any significant difference of the estimated effect of R219K on HDLC level was observed among the three subgroups.

Heterogeneity sources

Meta-regression analysis was also performed to explore all potential moderators including categorical (e.g., ethnicity and healthcondition) and continuous (publication data, gender, and age) variables. The racial factor which is responsible for more than 13% of the sample variance (for Asian population, β = -0.32, 95% CI: -0.72 to 0.08, R^2 = 0.15; for Caucasian, β = -0.12, 95% CI: -0.52 to 0.28, R^2 = 0.13) was significantly associated with the effect of R219K (*Q* = 17.00, *df* = 2, *P* < 0.001. Table 1). Meanwhile, the other four variables including publication date, mean sample age, percentage of females in each sample, and clinical status were not associated with the pooled effect (all *P*s > 0.05).

Table 1
The meta-regressions of moderators for the estimated effect of R219K

Moderator	No. of studies	*β*	95%CI	*z*	*P*	*R*-square
Intercept		15.68	-7.54 to 38.90	1.32	0.186	0.00
Publication data	108	-0.01	-0.02 to 0.00	-1.31	0.189	0.00
Race[a]						
Asian	72	-0.32	-0.72 to 0.08	-1.56	0.119	0.15
Caucasian	36	-0.12	-0.52 to 0.28	-0.61	0.543	0.13
		Q = 17.00, *df* = 2, P **< 0.001**				
Health condition [b]						
Patients	42	0.05	-0.08 to 0.18	0.78	0.435	0.10
Random	43	-0.03	-0.18 to 0.12	-0.40	0.688	0.08
		Q = 1.09, *df* = 2, *P* = 0.581				
Mean sample age	100	0.10	-0.10 to 0.29	0.96	0.339	0.06
Percentage of females	101	0.00	-0.01 to 0.00	-0.61	0.545	0.06

[a] Samples which consisted multiple ethnic subjects set as reference;

[b] Samples including patients and controls set as reference;

[c] Bold type denotes P < 0.05.

Publication bias analysis

A publication bias analysis was performed and is available in the online supplementary materials (Additional file 5). Both *Begg*'s rank correlation (tau = -0.24, $z = 3.83$, $P < 0.001$) and *Egger*'s weighted regression ($t_{110} = 3.82$, $P < 0.001$) detected a significant publication selection bias in this meta-analysis. The funnel plot (Fig. S5-3) also showed a considerable asymmetry distribution among the included studies. Meanwhile, the trim-and-fill test estimated approximately 23 missing studies on the left side of the mean effect, and the overall initial effect was significantly changed (SMD_{adj} = -0.26 mmol/L, 95%CI: -0.31 ~ -0.20; $t_{245} = 2.34$, $P = 0.02$) after the adjustment for the missing data.

Meta-analysis for genetic variant R219K and LDLC

Relationship between R219K and LDLC levels

The pooled effect of the genetic variant R219K on LDLC levels was estimated with 65 eligible studies (samples = 94) including 34,901 participants. The meta-analysis showed that the RR genotype population had significantly higher LDLC level than K allele carriers (*SMD* = 0.12 mmol/L, 95%CI: 0.04 ~ 0.20, $z = 2.83$, $P = 0.005$) in the random model. Extreme heterogeneity among all studies was observed with $I^2 = 91.56\%$ ($Q = 1101.80$, $df = 93$, $P < 0.001$). The same correlation trend (*SMD* = 0.05 mmol/L, 95%CI: 0.01 ~ 0.10, $z = 2.25$, $P = 0.02$, and $I^2 = 72.08\%$, $Q = 329.46$, $df = 92$, $P < 0.001$ for heterogeneity test) between R219K and LDLC levels was observed after removing the outliers of Abellán's sample [93] identified by the *metafor* software package.

In Asian populations (samples = 66, n = 17,180), the LDLC level was clearly higher in the RR genotype group than in the K allele carrier group (*SMD* = 0.06 mmol/L, 95%CI:-0.01 ~ 0.12, and $I^2 = 69.45\%$, $Q = 212.76$, $df = 65$, $P < 0.001$ for the heterogeneity test. Fig. S6-2), but the difference did not reach statistical significance ($z = 1.81$, $P = 0.07$). For Caucasian populations (samples = 25, n = 16,015), the difference also disappeared (*SMD* = 0.06 mmol/L, 95%CI: -0.02 ~ 0.13, $z = 1.43$, $P = 0.15$, and $I^2 = 76.37\%$, $Q = 101.55$, $df = 24$, $P < 0.001$ for heterogeneity test; Fig. S6-3). No significant difference was found in the comparison of the effects of R219K estimated in Asian and Caucasian populations. The same result trend was observed when analysing other subgroups categorised by subjects' health condition (Fig. S6-4). Furthermore, the meta-regression analysis indicated that no moderators were significantly associated with the relationship between *ABCA*1 R219K polymorphism and individual LDLC levels (Table S6-1).

Publication bias analysis

For the publication bias analysis, *Begg*'s rank correlation suggested no significant publication selection bias ($z = 1.12$, $P = 0.26$) and *Egger*'s weighted regression showed a weak bias ($t_{91} = 2.16$, $P = 0.033$). The funnel plot also showed no considerable asymmetry distribution of the effect of R219K of each eligible study, with 10 missing studies estimated by the trim-and-fill method (Fig. S6-5).

Meta-analysis for genetic variant R219K and TC

The effect size of the genetic variant R219K on TC levels was pooled from 66 studies (samples = 96, n = 34,814). The meta-analysis showed no significant difference in the TC level between the RR genotype population and the K allele carriers in the random model, and significant heterogeneity was found among all studies. After four outliers (Abellán [93] data1, Ya [105] data1, 2 and 3) detected by the *meta* and *metafor* packages were removed (Fig. S7-1 and 2), a consistent result was obtained (*SMD* = 0.01 mmol/L, 95%CI:-0.06 ~ 0.08, $z = 0.20$, $P = 0.846$; $I^2 = 88.37\%$, $Q = 782.18$, $df = 91$, $P < 0.001$. Fig. S7-3). Hierarchical and meta-regression analyses were also performed to explore the heterogeneity among samples, but no variable was identified. Furthermore, no significant publication bias was found among the current selected studies (Table S7-1).

Meta-analysis for genetic variant R219K and TG

Sixty-five eligible studies (samples = 95, n = 34,478) were collected in this study to explore the relationship between R219K polymorphism and individual TG levels. Pooled results showed that the RR genotype population had significantly higher TG level than the K allele carriers (*SMD* = 0.15 mmol/L, 95%CI: 0.05 ~ 0.25, $z = 2.92$, $P = 0.003$) in the random model, and $I^2 = 94.54\%$ ($Q = 1721.66$, $df = 94$, $P < 0.001$) for the heterogeneity test. However, this significant effect disappeared when four outlier data (Delgado-Lista [19], Sun [45] data1 and data 2, Ya [105] data1) were removed from all samples (Fig. S8-1 and 2).

Additionally, no significant effect between R219K genotype and TG level was observed in the inter- and intra-population of Asians and Caucasians (Fig. S8-3). Neither the following subgroup analysis (Fig. S8-4) nor meta-analysis (Table S8-1) revealed that the variable was associated with the effect of R219K or responsible for the extreme heterogeneity of the current study.

Begg's rank correlation and *Egger*'s weighted regression methods showed no publication bias in all studies. However, looking through the effect distribution of each study in the funnel plot and considering the adjustment for missing studies estimated by trim-and-fill method, the initial effect of R219K on TG level was significantly changed (the estimatedright missing studies n = 21, $SMD_{adj} = 0.14$, 95%CI: 0.08 ~ 0.21; $t = 2.37$, $P = 0.019$).

Discussion

According to the results of the present meta-analysis, only one consistent association was observed between the genetic variant of R219K and the level of HDLC both in the total samples and in the subgroups categorised by ethnicity and health condition. While, the results of subgroup analysis and meta-regression also indicated that their relationship was more consistent in the Asian population and not sensitive to the samples' health condition. R219K polymorphism had no remarkable influence on LDLC, TC and TG levels.

As an updated meta-analysis, compared with previous meta-analyses (samples = 22, n = 21,966 in Ma et al [106]; and samples = 62, n = 48,452 in Lu et al. [20]), the current study used a larger sample size (samples = 116, n = 56,161). From this perspective, the current results are more robust. In addition, in this study, not only HDLC, LDLC, TC and TG were all analyzed, but also the effect of the heterogeneity of the included studies was minimised, and the outliers with lower quality and extreme effect size were detected using R software.

Given the important role of *ABCA1* in the formation of nascent HDLC [107, 108], its mutations and genetic variants are suspected relating to high-density lipoprotein deficiency [109] and other diseases related to abnormal HDLC levels. Although its function is still unclear, R219K polymorphism in *ABCA*1 gene was extensively studied. However, its correlation with individual lipid profiles still presents some controversies. In this meta-analysis, 116 eligible samples were pooled, and the significant influence of R219K variant on individual HDLC levels was observed. The combination of outlier sample detection and subgroup analysis revealed that this effect was more credible and consistent in the Asian population.

LDLC, colloquially known as “badcholesterol”, is suspected of being an independent risk factor of human diseases (e.g., CAD) [110]. Here, the weak influence of R219K on LDLC level was observed based on 65 (samples = 94) previous studies, but the relationship disappeared in the subgroup analyses. Considering the critical influence of sample size for statistical power, sensitivity and detection in one hypothesis, this weak association we observed in the total sample compared with the subgroups was more likely due to the increased type II error that occurs in large sample sizes [111]. Similarly, a weak association was also observed in the total sample in Lu et al. [20] study, and this association only remained in one subgroup (Chinese population, samples = 33, n = 9,588) under categorisation by ethnicity or gender. For analyses on the TC and TG levels, the present results indicated no substantial effect from R219K polymorphism.

Regarding the remarkable racial difference in genetic variants reported in the Third National Health and Nutrition Examination Survey (NHANES) [112], a racial difference in lipid levels was also suspected to some extent due to genetic variability [113]. In the current study, the regression-meta analysis revealed that the racial factor significantly influenced the correlation between R219K polymorphism and HDLC level ($Q = 17.00$, $df = 2$, $P < 0.001$. Table 1). The pooled effect of R219K on HDLC levels in Asian populations was significantly higher than in Caucasian populations (SMD_{Asian} *v* $SMD_{\text{Caucasian}}$ = -0.24 *v* -0.04, $Q = 5.20$, $df = 1$, $P = 0.023$). Many reports also mentioned the racial/ethnic difference in lipid levels and related diseases [114, 115]. Thus, investigating the observed racial difference would help determine whether this phenomenon results from the real influence of R219K polymorphism on HDLC level or from the distinctive allele distribution of R219K in different ethnicities.

As mentioned above, simultaneously investigating the correlation between R219K, diagnostic results and lipid profile of subjects, increasing studies have reported the association between R219K polymorphism and the class of CVD diseases and other dyslipidaemia-related diseases. Consequently, within the healthy population and the patients with dyslipidemia-related diseases, the correlation of R219K and lipid profiles should also be different. However, the present work revealed that neither the result of subgroup analyses nor that of meta-regression confirmed the difference in the effect of R219K on lipid levels among patients, random populations and mixed populations. Additionlly, the health condition of the samples was not the main source of heterogeneity of our pooled samples (all Ps > 0.05, $R_{\text{max}}^2 \leq 0.10$, see the online supplementary materials Additional files 5–8).These results might reinforce the uncertainty about the utilisation of genetic variants (e.g., R219K in *ABCA*1 gene) to improve the diagnosis, monitoring and clinical decision-making of lipid testing.

This review has several strengths: i) it used a robust, systematic and transparent approach in accordance with the Cochrane Handbook, the PRISMA statement and ii) regarding the robustness of our pooled effect, the *metafor* package was used to detect and remove the outliers from the total studies. In addition to the subgroup analyses for categorical variables (i.e., ethnicity and health condition), the difference in the pooled effects between each group was assessed by hypothesis testing. On the other hand, The limitations of this review must also be mentioned. Firstly, a systemic meta-analysis should collect as much literatureas possible, even unpublished studies. However, only studies published in English or Chinese were included. Publication bias analyses also suggested that the missing studies may cause the

significant bias observed in the current review (Fig. S5-1 and Fig. S8-5). Secondly, the random-effect model was predominantly adopted to address the extreme significant heterogeneity among the total samples. Hierarchical and regression meta-analyses were also performed to explore the source of heterogeneity, but the source of most of the variance in the effect remains unknown (R_{max}^2 = 0.15, see online supplementary materials Additional files 5–8). Finally, the health condition of the subjects was introduced as a categorical variable to explore its influence on R219K effect, and all patients with six kinds of CVD diseases, diabetes, and other diseases were classified into one group. However, this "unified" approach may have caused the sample heterogeneity in this study. Given sufficient eligible studies for each disease, a network meta-analysis should be performed to determine the comparative effects of all included diseases [116].

Conclusions

R219K genetic variant showed a solid association with individual HDLC levels. R219K individuals with the genotype RR had lower HDLC levels than K allele carriers in the Asian subgroup regardless of the gender, age and health condition. The influence of ethnicity and health condition on the pooled effects must be considered when interpreting the current findings and/or accepting the recommendation for R219K clinical utilisation.

Abbreviations

ABCA1: adenosine triphosphate-binding cassette exporter A1; CMA: Comprehensive Meta-Analysis; CNKI: Chinese National Knowledge Infrastructure; CVD: cardiovascular diseases; HDLC: high-density lipoprotein cholesterol; LDLC: low-density lipoprotein cholesterol; NOS: Newcastle-Ottawa Scale; PRISMA: Systematic Reviews and Meta-analyses; SD: standard deviations; SE: standard errors; SMD: the standard mean difference; TC: total cholesterol; TG: triglycerides

Declarations

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

KJZ and JLL Conceived and designed the study; YJT and YFW Collected the data; KJZ and ZYS analysed the data; KJZ, YJT and QLC interpreted the results and edited the article. All authors read and approved the final manuscript.

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Figures

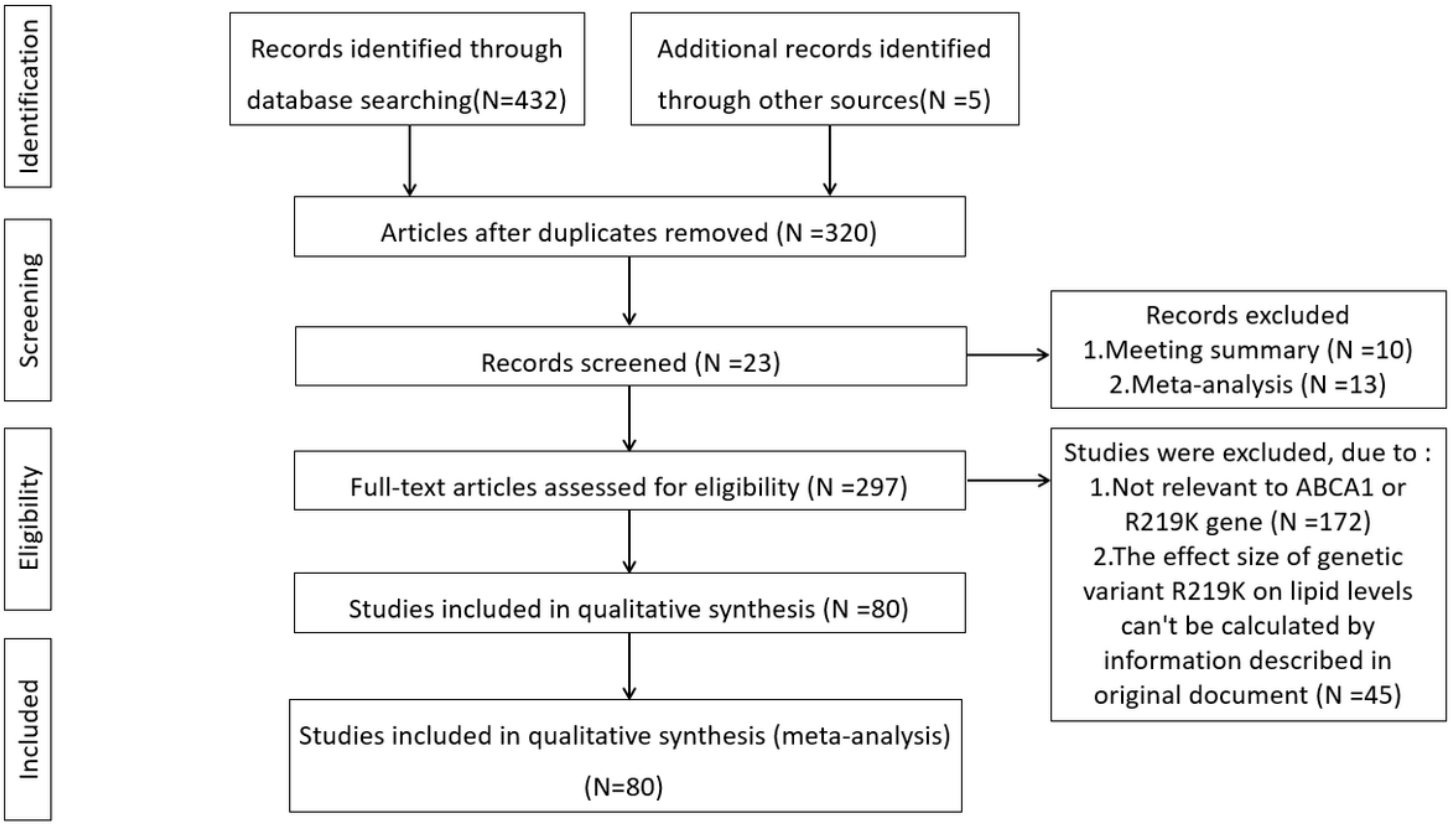

Figure 1

Flow chart for the literatures included in the systematic review and meta-analysis.

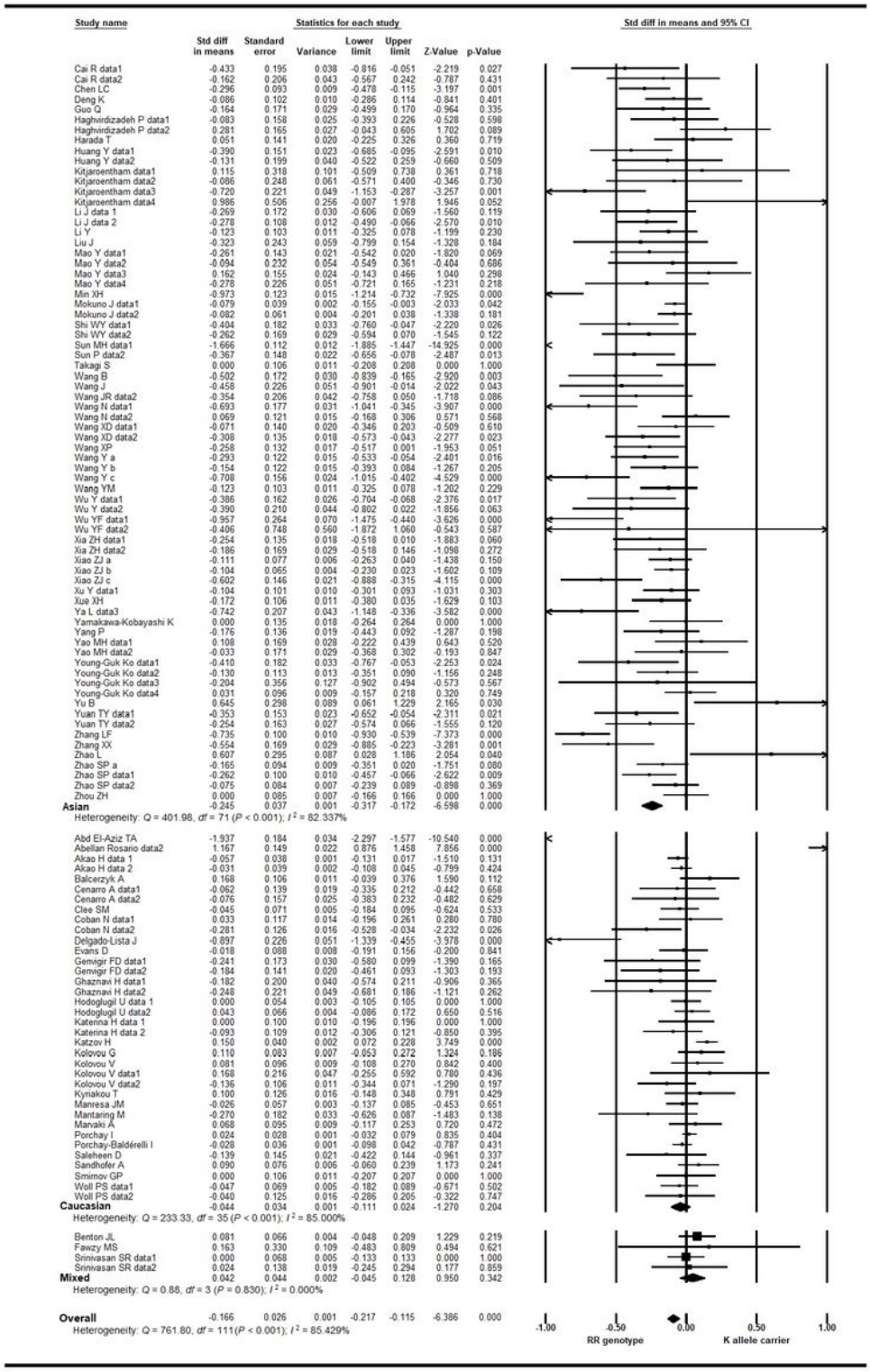

Figure 2

The relationship between R219K and the level of HDLC in Asian, Caucasian, and overall population. The effect of the genotype was measured by the mean differences (95% CI). Horizontal lines represent 95% CIs.

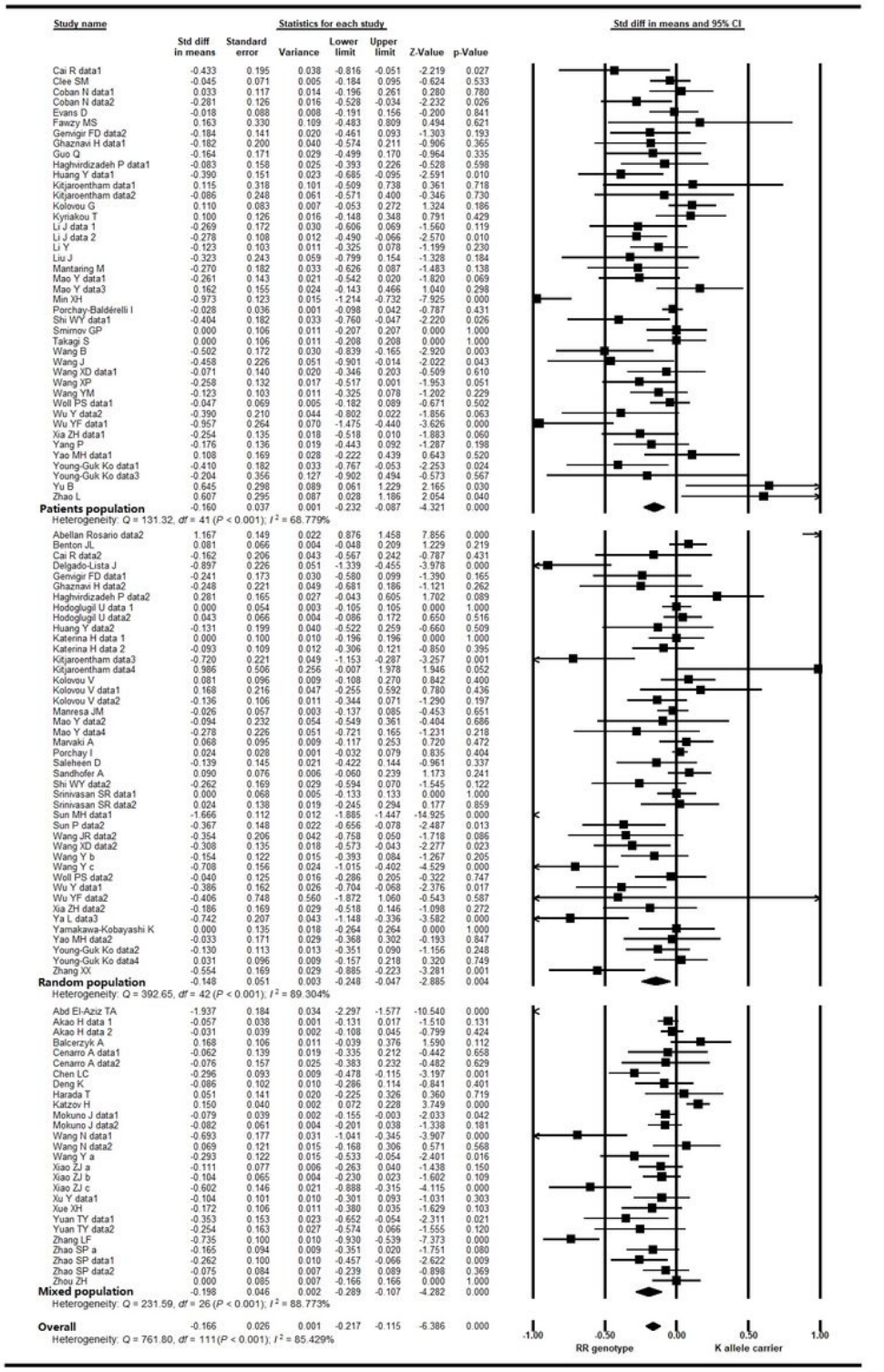

Figure 3

The relationship between R219K and the level of HDLC in patients, random, and overall population. The effect of the genotype was measured by the mean differences (95% CI). Horizontal lines represent 95% CIs.

Supplementary Files

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