A systematic review and meta-analysis on the association between CD36 rs1761667 polymorphism and cardiometabolic risk factors in adults

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The cluster of differentiation 36 (CD36) is one of the main receptors implicated in the pathogenesis of the cardiovascular disease. This study aimed to assess the association between CD36 rs1761667 polymorphism and cardiometabolic risk factors including body mass index (BMI), waist circumference (WC), total cholesterol (TC), triglyceride, HDL-C, LDL-C, blood pressure and fasting blood glucose (FBG). PubMed, EMBASE, Scopus, web of science, and Google Scholar were searched up to December 2021. Subgroup and meta-regression analyses were conducted to explore sources of heterogeneity. Eighteen eligible studies (6317 participants) were included in the study. In the overall analysis, a significant association was found between rs1761667 polymorphism of CD36 and TG in allelic (p < 0.001), recessive (p = 0.001) and homozygous (p = 0.006) models. A relationship between this polymorphism and HDL-C and FBG level was observed in the recessive genetic model. In the subgroup analysis, the A allele was associated with impaired lipid profiles (TC, LDL-C and HDL-C) in the Asian population. The influences of health status, design of the study, confounders, and other sources of heterogeneity should be considered when interpreting present findings. Cohort studies with large sample size and in different ethnicities are needed to confirm the relationship between rs1761667 SNP and cardiometabolic risk factors.

Abbreviations

CVD  Cardiovascular disease
CD36  Cluster of differentiation 36
LCFA  Long-chain fatty acids
GWAS  Genome-wide association study
SNPs  Single-nucleotide polymorphisms
T2DM  Type 2 diabetes mellitus
BMI  Body mass index
HWE  Hardy–Weinberg equilibrium
SD  Standard deviation
WMD  Weighted mean difference

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Cardiovascular diseases (CVD) are the most life-threatening conditions which have negative impacts on development and economic growth. Cardiometabolic risk factors including obesity, dyslipidemia, dysglycemia, and elevated blood pressure, increase the risk of cardiometabolic diseases. Impaired cardiometabolic risk factors can be present for years before the clinical symptoms become apparent; therefore, their management is difficult for physicians. It has been demonstrated that genetic factors play a role in the development of cardiometabolic risk independent of environmental factors. The cluster of differentiation 36 (CD36), also known as platelet glycoprotein IV or IIb, is one of the most important membrane proteins presents on the surface of a wide variety of cell types including adipocytes, macrophages, skeletal and cardiac myocytes, hepatocytes, microvascular endothelial cells, breast, kidney, platelets, microvascular endothelial cells, and epithelial cells in the gut. It has been shown that CD36 plays a role in inflammatory reactions, angiogenesis, orosensory perception of dietary lipid and fat preference, regulating the metabolic pathways of insulin-resistance, transporting long-chain fatty acids (LCFA) into adipose and muscle tissues, chylomicron synthesis, and energy metabolism. As a consequence of its functions, CD36 might be associated with a wide range of disorders such as CVD, dyslipidemia, hypertension, diabetes, metabolic syndrome, and cancer.

A genome-wide association study (GWAS) of the four large cohorts (19,602 white people in whom 1544 cases of stroke) showed that CD36 rs3211928 was significantly associated with stroke. Several studies have been conducted on the association between single-nucleotide polymorphisms (SNPs) in the CD36 gene including rs1761667 (A/G substitution) with CVD, type 2 diabetes mellitus (T2DM), consumption of total fat and fat taste perception, obesity, and metabolic syndrome. These studies have been performed in various ethnic populations around the world. However, ambivalent results were obtained regarding the association between genotype distribution of rs1761667 and cardiometabolic risk factors. For instance, Bayoumy et al. demonstrated that individuals with AA genotype of the CD36 rs1761667 had a significantly lower degree of dyslipidemia, systolic blood pressure (SBP), and waist circumference (WC) compared to individuals with AG and GG genotype. Boghdady et al. also showed that the AG genotype may be involved in the pathogenesis of coronary artery disease, raised body mass index (BMI), metabolic syndrome, and T2DM. On the other hand, Pioltine et al. reported that the SNP rs1761667 in the CD36 gene was not associated with obesity risk.

To the best of our knowledge, there is no systematic review and meta-analysis trying to examine the possible relationship between CD36 rs1761667 polymorphism and cardiometabolic risk factors. Thus, the current study aimed to examine the association between this polymorphism and cardiometabolic risk factors including BMI, WC, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), systolic and diastolic blood pressure, and fasting blood glucose (FBG).

**Results**

**Literature search and study characteristics.** In total, 297 publications were identified in the initial search; from which 106 studies were duplicates, and 153 articles did not meet the eligibility criteria after screening titles/abstracts. The full texts of thirty-eight articles were assessed for further consideration and twenty articles were excluded for the following reasons: reported duplicate data (n = 2), had no data on the outcome variables (n = 12), conducted on pregnant women (n = 2), children and adolescents aged below 18 years (n = 2) and did not provide the sufficient data (n = 2) (Supplementary Table S1). The article selection procedure is illustrated in Fig. 1. Eventually, 18 studies with 6317 participants were included in the systematic review. One study reported BMI before pregnancy; thus, it was included for this variable and this article was not used for other risk factors.

General characteristics of the 18 eligible studies are provided in Table 1. Six studies were from Asia, five from Africa, and six from Europe, and one study was from the USA/Italy. The majority of eligible studies included both sexes and only two and one were performed on women and men, respectively. The participants were aged 18–75.73 years and the mean body mass index was ranged from 21.66 to 34.60 kg/m². Seven studies were conducted on healthy individuals, three studies targeted patients with heart diseases, one study included individuals with T2DM, metabolic syndrome, and the six remaining studies included adults with other health status. In the majority of studies, genotype distributions were in Hardy-Weinberg equilibrium (HWE) and HWE was not reported in six studies and in one publication which reported the results in four different groups, HWE were not in equilibrium in three groups. Of the total 18 studies that assessed the relationship between CD36 rs1761667 genotypes and cardiovascular risk factors, nine studies were case–control (five studies reported only the data of the case group and two studies combined the data of two...
The rest of the studies revealed the result separately in the case and control groups\(^\text{18,19}\), nine studies were cross-sectional, \(^\text{13–17,20–23}\) of which 2 were baseline assessment of clinical trials\(^\text{14,17}\) (Table 1).

**Study quality assessment.** Based on the Newcastle–Ottawa Scale, four\(^\text{8,18,24,26}\), and five\(^\text{7,11,19,25,27}\) case–control studies had a high and moderate methodological quality, respectively. All cross-sectional studies were categorized to be very good or good regarding their quality\(^\text{13–16,18,22,23}\), except for two studies\(^\text{17,21}\) (Supplementary Table S2).

**The results of quantitative analysis.** In this meta-analysis, five common genotype models of CD36 (rs1761667) were considered: allelic model (A vs. G), dominant model (AA + GA vs. GG), recessive model (AA vs. GA + GG), homozygous model (AA vs. GG) and heterozygous model (GA vs. GG).
| Author (year) | Country | Study design | Number and sex (F/M) | BMI (Kg/cm²) | Genotypes frequencies | Mean age (years) | Notes about participants | Ethnicity | Method of genotype measured | Reported data | Hardy–Weinberg |
|--------------|---------|--------------|---------------------|--------------|----------------------|-----------------|-------------------------|-----------|---------------------------|--------------|---------------|
| Bayoumy et al.11 | Egypt | Case-control, case assessment included | 33 F/67 M | 33.40 ± 3.20 | GG: 5 AG: 70 AA: 25 | GG: 45.00 AG: 44.00 AA: 47.00 | Meta-bolic syn-drome | Arabs | Real-time PCR | WC, TC, TG, HDL-C, LDL-C, SBP, DBP | Equilibrium |
| Boghdady et al.8 | Egypt | Case-control, case assessment included | 16 F/31 M | 29.40 ± 3.40 | GG: 9 AG: 30 AA: 8 | GG: 54.80 AG: 53.80 AA: 54.60 | Coronary artery disease (CAD) | African Americans | Real-time PCR | BMI, WC, TC, TG, HDL-C, LDL-C | NM |
| Dalton et al.13 | UK | Cross-sectional | 85 F&M | 23.51 ± 4.18 | AG: 25.02 ± 4.30 AA: 24.31 ± 3.69 | GG: 28 AG: 39 AA: 18 | 26.10 | Individuals susceptible to overeating | Caucasian | Sequenom Mass Array system | BMI | Equilibrium |
| Dawcynski et al.14 | Germany | Clinical trial, baseline assessment included | 45 F&M | 26.31 ± 3.77 | GG: 8 AG: 24 AA: 13 | 60.00 | Milder hypertriacyl-glycerolemia | NM | Sequencing | TG, HDL-C | NM |
| Fujii et al.15 | Japan | Cross-sectional | 267 F/228 M | 23.60 ± 3.40 | AG: 23.70 ± 3.40 AA: 23.40 ± 2.80 | GG: 268 AG: 190 AA: 37 | 62.90 AG: 64.00 AA: 64.90 | Community-dwelling individuals (hyper-tension, dyslipidemia, diabetes, obesity) | Asians | PCR-CTPP | BMI, WC, TC, HDL-C, LDL-C, SBP, DBP, FBG | Equilibrium |
| Ma et al.16 | USA/ Italy | Cross-sectional | 328 F/214 M | 30.67 ± 5.54 | GG: 115 AG: 273 AA: 154 | GG: 35.00 AG: 36.00 AA: 38.00 | Healthy individuals of Caucasian origin | Caucasian | Acy-cloPrime-FP SNP Detection System | TC, TG, HDL-C, SBP, DBP, FBG | Equilibrium |
| Madden et al.17 | UK | Clinical trial, baseline assessment included | 108 M | 27.54 ± 4.20 | AG: 27.75 ± 3.91 AA: 26.90 ± 4.02 | GG: 27 AG: 51 AA: 30 | 57.00 AG: 55.80 AA: 54.00 | Healthy middle-aged men | Caucasian | Real-Time PCR | BMI, TG, HDL-C, LDL-C, FBG | NM |
| Melis et al.18 | Italy | Case-control | 37 F/25 M | 28.56 ± 7.52 | Case GG: 16/ AG: 31/ AA: 15 | NM | Healthy obesity | Caucasian | PCR-RFLP | BMI | NM |
| Momeni-Moghaddam et al.19 | Iran | Case-control | 25 F&27 M | 24.20 ± 4.38 | AA: 24.10 ± 4.35 | Case GG: 6/ AG: 40/ AA: 6 | 55.50 AG: 54.90 AA: 52.50 | HTN without CAD | Dis-equilibrium | Dis-equilibrium | Dis-equilibrium |
| | | | 13 F&44 M | 25.54 ± 5.26 | AG: 25.35 ± 4.88 AA: 24.10 ± 4.35 | Case GG: 12/ AG: 45/ AA: 8 | 56.18 AG: 56.69 AA: 54.13 | CAD | Asians | PCR-RFLP | BMI, TC, TG, HDL-C, LDL-C, SBP, DBP, FBG | Dis-equilibrium |
| | | | 11 F&54 M | 28.56 ± 7.52 | Case GG: 26/ AG: 30/ AA: 9 | 52.65 AG: 55.93 AA: 50.71 | Coronary angiography (without HTN and CAD) | NM | Sequencing | TC, TG, HDL-C, LDL-C, FBG | Equilibrium |
| | | | 26 F&39 M | 28.56 ± 7.52 | Case GG: 26/ AG: 30/ AA: 9 | 52.65 AG: 55.93 AA: 50.71 | Coronary angiography (without HTN and CAD) | NM | Sequencing | TC, TG, HDL-C, LDL-C, FBG | Equilibrium |
| | | | 203 F | 34.60 ± 4.20 | GG: 42/ AG: 102/ AA: 59 | 38–43 | Healthy obesity | African | PCR-RFLP | TC, LDL-C | NM |
| Ramos-Lopez et al.21 | Mexico | Cross-sectional | 157 F/75 | 21.66 ± 2.26 | GG: 46 AG: 104 AA: 82 | 18–25 | Healthy normal-weight | Admixed population | PCR-RFLP | TC, TG, HDL-C, LDL-C | Equilibrium |
| Ramos-Lopez et al.22 | Mexico | Cross-sectional | 40 F/33 M | 24.40 ± 4.31 | AG: 24.90 ± 4.20 AA: 26.60 ± 4.10 | GG: 11 AG: 40 AA: 22 | 53.70 AG: 51.40 AA: 48.10 | Chronic hepatitis C virus infection | Amerindian, Caucasian and African | Real-Time PCR | BMI, TC, TG, HDL-C, LDL-C, FBG | Equilibrium |
| Shen et al.23 | UK | Cross-sectional | 95 F/41 M | 22.9 ± 3.96 | GG: 37 AG: 66 AA: 33 | 18–55 | Healthy adults | Caucasian, African, West Asian and East Asian | Fluorogenic 5' nucleotide assay (Taq-Man) | BMI | NM |
| Solakvi et al.24 | Finland | Case-control | 736 F&M (Case: 314 + Control: 422) | Case: 28.80 ± 5.20 Control: 25.50 ± 3.60 | GG: 158 AG: 376 AA: 202 | 50.00 | Hypertension & non-hypertensive healthy subjects | Caucasian | Competitive Allele Specific PCR (KASP) technique | BMI, TC, SBP, DBP, FBG | Equilibrium |
| Yang et al.27 | China | Case-control, case assessment included | 209 F | 21.95 ± 2.76 | GG: 88 AG: 99 AA: 22 | 32.99 | Healthy women with GDM* | Asians | Taq-man allelic discrimination assay | BMI | Equilibrium |

Continued
Table 1. Characteristics of studies that were included in this systematic review and meta-analysis. F female, M male, NM HNW, Healthy normal weight, HO Healthy obesity, not mention, HTN hypertension, T2DM type 2 diabetes mellitus, GDM gestational diabetes mellitus, PCR polymerase chain reaction, PCR–CTPP Polymerase chain reaction with confronting two-pair primers, PCR–RFLP polymerase chain reaction-restriction fragment length polymorphism, BMI body mass index, WC waist circumference, TC total cholesterol, TG triglyceride, HDL-C high-density lipoproteins cholesterol, LDL-C low-density lipoprotein cholesterol, SBP systolic blood pressure, DBP diastolic blood pressure, FBG fasting blood glucose. a BMI was calculated before gestation. b Insufficient data to calculate changes in SBP.

| Author (year) | Country | Study design | Number and sex (F/M) | BMI (Kg/cm²) | Genotypes frequencies | Mean age (years) | Notes about participants | Ethnicity | Method of genotype measured | Reported data | Hardy–Weinberg |
|---------------|---------|--------------|----------------------|--------------|-----------------------|-----------------|--------------------------|-----------|-----------------------------|--------------|--------------------------|
| Yuan et al. 25 | China   | Case–control, case assessment included | 42 F/70 M | GG: 23.80 ± 2.70 AG: 24.40 ± 3.30 AA: 23.50 ± 2.60 | GG: 41 AG: 49 AA: 22 | 57.10 | T2DM | Asians | PCR–RFLP | BMI, TC, HDL-C, LDL-C, DBP, FBG | Equilibrium |
| Zhang et al. 27 | China   | Case–control, case assessment included | 43 F/69 M | 23.78 ± 2.85 | GG: 43 AG: 60 AA: 9 | 64.04 | Coronary artery heart disease | Asians | PCR–RFLP | BMI, TC, HDL-C, LDL-C | Equilibrium |
| Zhang et al. 28 | China   | Case–control | 1359 F&M (Case: 367 + Control: 992) | Case: 25.52 ± 3.42 Control: 25.29 ± 3.48 | GG: 543 AG: 631 AA: 185 | 75.73 | Atherosclerotic stroke & without stroke | Asians | ligation detection reaction (LDR) probe sequences | TC, HDL-C, LDL-C | Equilibrium |

Table 2. The association between CD36 rs1761667 polymorphism and anthropometric indices. All analyses were conducted using a random-effects model. a All analyses were done using the random-effects model. b There was no evidence of publication bias by observing the funnel plots. WMD, weighted mean difference; 95% CI, 95% confidence interval.
Anthropometric measures. Twelve articles7,13,15,17–19,22–25,27 (n = 2478) reported the data on BMI and five articles11,13,18,24 with 1859 subjects were included in quantitative analysis for WC. As shown in Table 2, there was no significant association between CD36 rs1761667 genotypes and BMI in allic (WMD = 0.092 kg/m², 95% CI: −0.25, 0.31, p = 0.84, I² = 31.20%), dominant (WMD = 0.23 kg/m², 95% CI: −0.14, 0.61, p = 0.23, I² = 17.90%), recessive (WMD = −0.29 kg/m², 95% CI: −0.84, 0.25, p = 0.29, I² = 41.20%), homozygous (WMD = 0.10 kg/m², 95% CI: 0.00, 0.23, p = 0.07, I² = 15.70%) models (Supplementary Figure S5). According to the subgroup analysis, the association was significant for BMI in patients with heart disease (WMD = −1.36 kg/m², 95% CI: −2.53, −0.20, p = 0.02, I² = 0.00%) and in the heterozygous model, in studies with medium quality (WMD = 0.58 kg/m², 95% CI: 0.07, 1.09, p = 0.02, I² = 0.00%) (Supplementary Table S3).

Also, no association was found for WC in allic (WMD = −0.92 cm, 95% CI: −2.20, 0.35, p = 0.15, I² = 57.70%), dominant (WMD = −0.70 cm, 95% CI: −2.76, 1.36, p = 0.50, I² = 52.30%), recessive (WMD = −2.32 cm, 95% CI: −4.71, 0.06, p = 0.056, I² = 66.30%), homozygous (WMD = −2.25 cm, 95% CI: −5.48, 0.98, p = 0.17, I² = 65.70%), heterozygous (WMD = −0.29 cm, 95% CI: −2.04, 1.45, p = 0.74, I² = 32.40%) models (Table 2 and Supplementary Figure S6).

Lipid profile. Total cholesterol (TC). The overall meta-analysis of eleven studies with 3755 participants8,11,16,19,22–26 showed no significant association between CD36 rs1761667 polymorphism and serum TC levels (allelic: WMD = 0.41 mg/dl, 95% CI: −1.60, 2.44, p = 0.68; dominant: WMD = 0.66 mg/dl, 95% CI: −2.96, 4.30, p = 0.71; recessive: WMD = 0.83 mg/dl, 95% CI: −5.61, 3.95, p = 0.73; homozygous: WMD = 2.18 mg/dl, 95% CI: −1.24, 5.61, p = 0.21; heterozygous: WMD = −1.37 mg/dl, 95% CI: −6.53, 3.79, p = 0.60) models and heterogeneity between included studies was moderate to high (Table 3 and Supplementary Figure S7). In the subgroup analysis, the association was significant in studies conducted in the Asian population in allelic (WMD = 1.04 mg/dl, 95% CI: 0.88, 1.20, p < 0.001, I² = 0.00%) and homozygous (WMD = 1.17 mg/dl, 95% CI: 0.76, 1.58, p < 0.001, I² = 0.00%) models and healthy individuals (AA vs. GG: WMD = 5.52 mg/dl, 95% CI: 1.60, 9.43, p = 0.006, I² = 18.50%). Furthermore, serum TC level was significantly higher in adjusted studies under allic, dominant and heterozygous models (Supplementary Table S4).

Triglyceride (TG). The analysis of eleven studies7,8,11,14–17,19,21,22,25,26 (n = 2105) revealed that in overall, there was a significant association between rs1761667 polymorphism and TG values in allelic (WMD = −7.11 mg/dl, 95% CI: −11.06, −3.16, p < 0.001, I² = 58.50%) models, the TG level in the AA genotype group was significantly lower than that in G allele carriers, and the same difference was also observed in the above-mentioned models (Table 3 and Supplementary Figure S8). Subgroup analysis revealed that rs1761667 polymorphism was associated with decreased TG in the healthy population and HWE studies with AA genotype and A allele group, compared to the GG genotype and G allele group in homozygous (healthy participants: WMD = −5.46 mg/dl, 95% CI: −8.92, −2.00, p = 0.002, I² = 0.00%; equilibrium subgroup: WMD = −11.85 mg/dl, 95% CI: −23.02, −0.68, p = 0.03, I² = 67.60%) and allelic models (healthy participants: WMD = −4.26 mg/dl, 95% CI: −6.12, −2.40, p < 0.001, I² = 0.00%; equilibrium subgroup: WMD = −6.65 mg/dl, 95% CI: −11.20, −2.11, p = 0.004, I² = 58.80%), respectively. Further details about the subgroup analysis are provided in Supplementary Table S5.

High-density lipoprotein cholesterol (HDL-C). Based on the results of twelve datasets with 3464 individuals7,8,11,14–17,19,21,22,25,26,28 AA genotype population had a significantly higher HDL-C level (WMD = 1.36 mg/dl, 95% CI: 0.08, 2.64, p = 0.03, I² = 62.10%) than G allele carriers in the recessive model (Table 3 and Supplementary Figure S9), with regard to subgroup analysis, this relationship was seen in the studies with HWE (WMD = 1.62 mg/dl, 95% CI: 0.23, 3.01, p = 0.02, I² = 68.60%). Lower serum HDL-C levels were observed in the studies with the Asian population in allelic (WMD = −0.09 mg/dl, 95% CI: −0.18, −0.01, p = 0.02, I² = 0.00%), dominant (WMD = −0.29 mg/dl, 95% CI: −0.43, −0.14, p < 0.001, I² = 0.00%) and heterozygous (WMD = −0.38 mg/dl, 95% CI: −0.52, −0.23, p < 0.001, I² = 0.00%) models (Supplementary Table S6).

Low-density lipoprotein cholesterol (LDL-C). Meta-analysis of ten studies7,8,11,17,18,22,25,26 (n = 2585) revealed, no significant association between CD36 rs1761667 polymorphism and LDL-C levels in different genetic models (allelic model: WMD = −0.62 mg/dl, 95% CI: −4.40, 3.14, p = 0.74; dominant model: WMD = −0.36 mg/dl, 95% CI: −3.80, 3.07, p = 0.83; recessive model: WMD = −2.68 mg/dl, 95% CI: −11.53, 6.15, p = 0.55; homozygous model: WMD = −2.07 mg/dl, 95% CI: −9.79, 5.64, p = 0.59; heterozygous model: WMD = −3.98 mg/dl, 95% CI: −8.77, 0.80, p = 0.10) (Table 3 and Supplementary Figure S10). Allelic (WMD = 5.43 mg/dl, 95% CI: 0.16, 10.70, p = 0.04, I² = 69.90%), recessive (WMD = 12.77 mg/dl, 95% CI: 1.99, 23.55, p = 0.02, I² = 84.30%) and homozygous (WMD = 9.10 mg/dl, 95% CI: 0.29, 17.91, p = 0.04, I² = 54.60%) models were associated with an increase in LDL-C levels in healthy participants and there was moderate to high heterogeneity between the included studies. Under the allelic (WMD = 1.32 mg/dl, 95% CI: 1.18, 1.45, p < 0.001, I² = 0.00%) and homozygous (WMD = 1.92 mg/dl, 95% CI: 1.57, 2.28, p < 0.001, I² = 0.00%) genetic models, rs1761667 had a significant association with the LDL-C levels in Asian population and there was no heterogeneity between the included studies. The results of subgroup analysis based on the study design and quality indicated that, the concentration of LDL in moderate quality and cross-sectional studies was lower in heterozygous model, whereas this variable was significantly higher in studies that adjusted the association for the potential confounders (WMD = 2.33 mg/dl, 95% CI: 2.17, 2.48, p < 0.001, I² = 0.00%) than studies with no adjustment (WMD = −5.14 mg/dl, 95% CI: −8.43, −1.84, p = 0.002, I² = 1.70%) (Supplementary Table S7).
| Meta-analysis | Heterogeneity | Publication bias |
|---------------|---------------|-----------------|
| No. of datasets | No. of subjects | WMD* (95%CI) | P_{effect} | Q statistic | P_{within} | I² (%) | Beggs's tests | Egger's tests |
| Meta-analysis | Heterogeneity | Publication bias |
| Total cholesterol (mg/dl) | | | | | | | | |
| Allelic model (A vs. G) | 7510 | 0.41 (−1.60, 2.44) | 0.68 | 28.23 | 0.002 | 64.60 | 0.35 | 0.33 |
| Dominant model (AA + GA vs. GG) | 3755 | 0.66 (−2.96, 4.30) | 0.71 | 29.09 | 0.001 | 65.60 | 0.87 | 0.46 |
| Recessive model (AA vs. GA + GG) | 3755 | −0.83 (−5.61, 3.95) | 0.73 | 91.91 | <0.001 | 89.10 | 0.35 | 0.77 |
| Homozygous model (AA vs. GG) | 1867 | 2.18 (−1.24, 5.61) | 0.21 | 20.59 | 0.02 | 51.40 | 0.21 | 0.82 |
| Heterozygous model (GA vs. GG) | 2962 | −1.37 (−6.53, 3.79) | 0.60 | 59.76 | <0.001 | 83.30 | 0.53 | 0.57 |
| Triglyceride (mg/dl) | | | | | | | | |
| Allelic model (A vs. G) | 4210 | −7.11 (−11.06, −3.16) | <0.001 | 18.97 | 0.04 | 47.30 | 0.062 | 0.069 |
| Dominant model (AA + GA vs. GG) | 2105 | −7.25 (−14.64, 0.12) | 0.054 | 21.96 | 0.01 | 54.50 | 0.35 | 0.002 |
| Recessive model (AA vs. GA + GG) | 2105 | −14.54 (−22.74, −6.35) | 0.001 | 32.33 | <0.001 | 69.10 | 0.75 | 0.55 |
| Homozygous model (AA vs. GG) | 1061 | −13.94 (−23.82, −4.06) | 0.006 | 24.12 | 0.007 | 58.50 | 0.08 | 0.051 |
| Heterozygous model (GA vs. GG) | 1678 | −6.22 (−15.40, 2.96) | 0.18 | 30.66 | 0.001 | 67.40 | 0.75 | 0.004 |
| HDL-C (mg/dl) | | | | | | | | |
| Allelic model (A vs. G) | 6928 | 0.58 (−0.29, 1.45) | 0.19 | 39.64 | <0.001 | 72.20 | 0.73 | 0.29 |
| Dominant model (AA + GA vs. GG) | 3464 | 0.21 (−1.16, 1.58) | 0.76 | 28.30 | 0.003 | 61.10 | 1.00 | 0.54 |
| Recessive model (AA vs. GA + GG) | 3464 | 1.36 (0.08, 2.64) | 0.03 | 29.03 | 0.002 | 62.10 | 0.73 | 0.14 |
| Homozygous model (AA vs. GG) | 1789 | 1.64 (−0.41, 3.70) | 0.11 | 36.79 | <0.001 | 70.10 | 0.94 | 0.26 |
| Heterozygous model (GA vs. GG) | 2852 | −0.31 (−1.62, 0.99) | 0.64 | 24.45 | 0.01 | 55.00 | 0.73 | 0.87 |
| LDL-C (mg/dl) | | | | | | | | |
| Allelic model (A vs. G) | 5170 | −0.62 (−4.40, 3.14) | 0.74 | 55.82 | <0.001 | 83.90 | 0.15 | 0.75 |
| Dominant model (AA + GA vs. GG) | 2585 | −0.36 (−3.80, 3.07) | 0.83 | 15.54 | 0.07 | 42.10 | 0.15 | 0.02 |
| Recessive model (AA vs. GA + GG) | 2585 | −2.68 (−11.53, 6.15) | 0.55 | 138.25 | <0.001 | 93.50 | 0.72 | 0.90 |
| Homozygous model (AA vs. GG) | 1295 | −2.07 (−9.79, 5.64) | 0.59 | 51.61 | <0.001 | 82.60 | 0.10 | 0.64 |
| Heterozygous model (GA vs. GG) | 2118 | −3.98 (−8.77, 0.80) | 0.10 | 27.70 | 0.001 | 67.50 | 0.37 | 0.01 |

Table 3. The association between CD36 rs1761667 polymorphism and lipid profile. All analyses were conducted using a random-effects model. Significant values are in bold. All analyses were done using the random-effects model. These values were unchanged using the trim and fill method. WMD, weighted mean difference; 95% CI, 95% confidence interval.
Table 4. The association between CD36 rs1761667 polymorphism and blood pressure and fasting blood glucose. All analyses were conducted using a random-effects model. Significant values are in bold. All analyses were done using the random-effects model. aThere was no evidence of publication bias by observing the funnel plots. WMD, weighted mean difference; 95% CI, 95% confidence interval.

**Blood pressure.** The analysis results for five studies (n = 2112)\(^1\)\(^{11,15,16,19,24}\) for systolic (SBP) and six studies with 2224 participants\(^1\)\(^{11,15,16,19,22,24}\) for diastolic blood pressure (DBP) are illustrated in Table 4. No significant association was detected between genetic models of CD36 rs1761667 polymorphism and blood pressure (Table 4 and Supplementary Figure S11–S12). In the recessive model, the average DBP in the AA genotype group was significantly lower than that of G allele carriers in studies which did not adjust the association for confounders (Table 4 and Supplementary Figure S11–S12). In the recessive model, the average DBP in the AA genotype group was significantly lower than that of G allele carriers in studies which did not adjust the association for confounders (Table 4 and Supplementary Figure S11–S12). In the recessive model, the average DBP in the AA genotype group was significantly lower than that of G allele carriers in studies which did not adjust the association for confounders (Table 4 and Supplementary Figure S11–S12).

**Fasting blood glucose (FBG).** Seven studies\(^1\)\(^{15–17,19,22,24,25}\) which included a total of 2305 individuals assessed the serum FBG in different genotypes of CD36 rs1761667. According to the pooled analysis, under the recessive genetic model, the homozygous A-allele carriers had a significantly higher FBG concentration compared with G allele carriers (WMD = 2.33 mg/dl, 95% CI: 0.92, 3.74, \(p = 0.001\), \(I^2 = 6.03\%\) ) and no heterogeneity was observed between included studies (Table 4 and Supplementary Figure S13). A significant relationship of rs1761667 polymorphism with the FBG level was observed under the recessive genetic model (\(\beta = 0.001, I^2 = 0.00\) ) and the between-study heterogeneity was not observed in these subgroups. The between-study heterogeneity was not observed in these subgroups (\(I^2 = 0.00\) ). The findings of other subgroup analyses were reported in Supplemental Table S9.

| Analysis                                   | No. of data-sets | No. of subjects | Meta-analysis          | Heterogeneity |
|--------------------------------------------|------------------|-----------------|------------------------|--------------|
|                                           |                  |                 | WMD2 (95%CI) P\(_{\text{effect}}\) Q statistic P\(_{\text{within}}\) I\(^2\) (%) |              |
| **Systolic Blood pressure (mmHg)**         |                  |                 |                        |              |
| Allelic model (A vs. G)                    | 4224             | 2.01 (−4.92, 0.90) 0.17 36.92 <0.001 89.20 |
| Dominant model (AA + GA vs. GG)           | 2112             | -4.17 (−9.22, 0.88) 0.10 38.98 <0.001 89.70 |
| Recessive model (AA vs. GA + GG)          | 2112             | -4.83 (−12.95, 3.28) 0.24 126.85 <0.001 96.80 |
| Homozygous model (AA vs. GG)              | 1050             | -8.42 (−18.09, 1.24) 0.08 85.03 <0.001 95.30 |
| Heterozygous model (GA vs. GG)            | 1669             | -3.30 (−7.84, 1.23) 0.15 28.79 <0.001 86.10 |
| **Diastolic Blood pressure (mmHg)**       |                  |                 |                        |              |
| Allelic model (A vs. G)                    | 4448             | -0.14 (−0.75, 0.46) 0.63 4.89 0.43 0.00 |
| Dominant model (AA + GA vs. GG)           | 2224             | -0.14 (−1.20, 0.92) 0.79 0.87 0.97 0.00 |
| Recessive model (AA vs. GA + GG)          | 2224             | -0.85 (−2.56, 0.85) 0.32 9.50 0.08 47.70 |
| Homozygous model (AA vs. GG)              | 3113             | -0.57 (−2.14, 1.00) 0.47 5.87 0.31 14.80 |
| Heterozygous model (GA vs. GG)            | 3759             | 0.001 (−1.11, 1.11) 0.99 0.35 0.99 0.00 |
| **Fasting blood glucose (mg/dl)**         |                  |                 |                        |              |
| Allelic model (A vs. G)                    | 4610             | 2.07 (−0.11, 4.25) 0.06 23.76 <0.001 74.70 |
| Dominant model (AA + GA vs. GG)           | 2305             | 3.64 (−0.89, 8.17) 0.11 49.96 <0.001 80.40 |
| Recessive model (AA vs. GA + GG)          | 2305             | 3.33 (0.92, 3.74) 0.001 6.03 0.42 0.40 |
| Homozygous model (AA vs. GG)              | 1173             | 4.28 (−1.02, 9.60) 0.11 30.42 <0.001 80.30 |
| Heterozygous model (GA vs. GG)            | 1813             | 3.07 (−1.17, 7.33) 0.15 39.95 <0.001 85.00 |

\(^\text{a}\)There was no evidence of publication bias by observing the funnel plots. WMD, weighted mean difference; 95% CI, 95% confidence interval.
SBP, DBP, and FBG concentrations by visually observing the Begg’s funnel plots (Supplementary Figure S1–S4). of publication bias for studies evaluating the association between CD36 rs1761667 polymorphism and WC, tion was lower in these individuals compared with G/A and A/A individuals12,16,17. In addition, a study in North Indian population showed that the presence of the minor rs1761667-allele A was associated with elevating the risk of developing T2DM19. The results of the ethnicity subgroup showed that Caucasians with AA genotype had a higher FBG concentration than G carriers. This discrepancy in this finding might be owing to different ethnicity, sample sizes, gene-environment and gene–gene interactions, publication bias and clinical heterogeneity. Another possible reason for this contrary finding can be a varied selection of the health status in different populations. On the other hand, the majority of eligible studies had evaluated fasting glucose levels. It was better to apply other glucose indicators (glycated hemoglobin A1c) because fasting blood glucose is affected by many factors such as BMI, psychological stress, smoking habits, potassium intake, etc30,31. So, it seems that for a definitive interpretation of this result further studies are needed. The subgroup analysis demonstrated that the A allele was associated with elevated TC and LDL-C levels and decreased HDL-C levels in Asians. In line with the mentioned conclusion in the present study, some previous studies reported these outcomes and suggested A allele of rs1761667 as a susceptibility factor for high serum cholesterol levels, low HDL-C and atherothrombotic stroke11,26,32. The deficiency of CD36 occurs rarely in Caucasians and is relatively common (3–10%) in the population of Asian and African descent33. As mentioned before, CD36 deficiency is closely related to the elevated prevalence of metabolic abnormalities, including hyperlipidemia, and increased fasting glucose levels. Moreover, clinical investigations have shown that the rs1761667-A allele decreases the CD36 expression and is associated with upper recognition taste thresholds for fat and decreased lipid taste perception34,35. The significant relationship between the CD36 SNP rs1761667 variant and lipid levels were shown in Asians also highlights the interaction between the CD36 SNP rs1761667 variant and ethnicity in modulating the plasma lipids. Bayoumy et al.11 noted in an Egyptian population that the minor allele frequency (MAF) of rs1761667 polymorphism was merely 0.25, Noel et al.36 showed that the MAF was 0.46 in a Hispanic population. Previous studies have been reported the influence of interethnic differences in allele frequencies. These variations can contribute to the differences in gene expression and eventually, disease susceptibility. Therefore, it is important to consider the population variations in the allele frequency when trying to identify an association between a polymorphism and the risk of diseases37–39. Further studies with different ethnicities should be performed to confirm these conclusions. The analyses also showed a significant association between increased levels of LDL-C, FBG and A allele of CD36 rs1761667 in healthy participants. It is mentioned that the synthesis and translocation of CD36 are influenced by various stimuli. Modifications of CD36 affect cardiac function via altering the cellular uptake of fatty acids in the myocardium. The increased CD36-induced fatty acid uptake could be harmful or beneficial under various pathological conditions40. CD36 is decreased in pathological cardiac hypertrophy and increased in diabetic cardiomyopathy and atherosclerosis. In a healthy heart, insulin promotes CD36 transportation from the endosome to the cell membrane. Simultaneously, the forkhead box O1 (FOXO1) transcription factor promotes CD36 expression41. Long chain fatty acids (LCFAs) absorbed by CD36 are used for oxidation and storage as lipids in mitochondrial. Whereas in diabetes, the enhancement of insulin strongly activates the P13K–Akt (phosphatidylinositol 3-kinase–protein kinase B) pathway that leads to a robust CD36 expression. On the other hand, upregulated mir-320 and down-regulated mir-200b–3p accelerate the CD36 transcription and translation, uptake of LCFAs facilitates in cardiomyocytes eventually. Intracellular LCFAs either enter the mitochondria...
for producing energy and the by-products reactive oxygen species (ROS) or forms triglycerides. As we know, triglycerides accumulation can result in insulin resistance. The ROS assembly and insulin resistance deteriorate cardiac function and would trigger diabetic cardiomyopathy. Therefore, CD36 has different functions in diverse conditions and there is a need for more in-depth study with different health status. Moreover, a significant association with BMI was detected among subjects with heart diseases in the recessive model. The mechanisms underlying how modifications of CD36 affect fat metabolism and cardiometabolic risk factors still remain to be elucidated; however, some evidence has shown that CD36 plays a role in the metabolism of LDL-C and HDL-C and contributes directly to their regulation. A systematic review of studies that investigated the association between CD36 and the metabolic complications of obesity, reported that CD36 may be involved in obesity-related complications in humans. Moreover, CD36 deficiency might affect myocardial uptake of LCFAs, delay clearance of plasma fatty acid after an oral meal, and be associated with abnormalities in chylomicron formation.

The CD36 is a membrane transporter of long-chain polysaturated fatty acid in many tissues including skeletal muscles, adipocytes and the heart. Dysfunction of this protein might reduce the intramuscular fatty acid oxidation rate. Therefore the availability of fatty acid enhances their storage in adipocytes. Peroxisome proliferator-activated receptor (PPAR-γ) is a nuclear receptor that regulates adipocyte differentiation and adipogenesis and CD36 is regarded as a key factor in the activation of PPAR-γ and its change might influence PPAR-γ mediated adipocyte differentiation. It has been suggested that CD36 expression is reduced in circumvallate taste buds among high-fat diet-induced obese rats which leads to a decreased sensitivity to fat taste, as a result the intake of fatty foods increases as a compensatory response. Muthuswamy et al. reported that a lower CD36 expression (in AA and AG genotype at rs1761667) might be involved in reducing the release of PYY from taste bud cells. The presence of CD36 in gustatory papillae, the main LCFAs receptor in taste bud cells, contributes to dietary fat taste perception and fat preference. More preference and increased eating of fatty foods have been expressed, which may reflect a decline in oral and gastrointestinal fatty acid sensitivity in obesity. Based on the results obtained after subgroup analysis according to quality assessment, design of studies, adjustment for confounders, and Hardy–Weinberg equilibrium, high-quality cohort studies considering confounders such as age, sex, BMI, smoking, alcohol consumption and physical activity are needed to confirm the results.

The current evidence showed no significant association of this CD36 SNP with blood pressure; however, subgroup analysis based on adjustment of confounders demonstrated a significant association between decreased DBP and studies which did not consider confounding variables into account. Molecular studies suggested that CD36 contributes to the production of nitric oxide. Since reducing nitric oxide activity in the renal medulla is associated with hypertension, it is proposed that a decreased CD36 in renal cells may be related to hypertension. Furthermore, some studies in animals indicated that there is a relationship between CD36 genetic background and regulation of blood pressure. There are some reasons which may explain these inconsistencies. The conflicting results might be due to variations in the health status and the genotyping methods, differences in ethnicity of the populations and their sex, gene–gene interactions in various populations and interactions of rs1761667 polymorphism with other variants in the CD36 gene. Moreover, some environmental factors may affect CD36 expression, as alcohol and fatty acids are recognized to modify the epigenome that includes acetylation of histones, DNA methylation, etc. According to the factors mentioned, observations are still controversial and further studies are needed to arrive at a firm conclusion about the association with blood pressure. However, it is worth noting that studies on CD36 suggest that transcriptional activation, post-translational modification and localization alterations in this protein may create new approaches for the treatment of CVD.

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Methods
This systematic review and meta-analysis is reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement66. The study protocol was also registered in the prospective register of systematic reviews (PROSPERO) [protocol code: CRD42021253789].

Search strategy. Relevant articles were identified through online search of the literature in PubMed/MEDLINE, EMBASE, Scopus, ISI (Web of Science) and Google Scholar up to December 2021 without any publication date, language, and any other restrictions. The keywords used to search were: rs1761667 OR “− 31,118 G > A” OR “− 31,118 G > A” OR “− 31,118 G > A”. The research was also updated by adding the following keywords in the all fields “GWAS”, “Genome-wide association studies”, “Genome wide association studies”, “Genome wide association study”, “Geno- mine-wide association study”, “GWA study”, “Whole-genome association study”, “Whole-genome association studies”, “WGA”, “Whole Genome Association Analysis”, “Whole-Genome Association Analysis”, “Genome Wide Association Analysis”, “Genome-Wide Association Analysis” to did not lose any article (Supplementary Table S11). The references of the relevant study were also examined manually for any missing related literature.

Eligibility criteria. All published studies (cross-sectional, cohort, case–control designs and baseline of controlled clinical trials) that focused on CD36 rs1761667 polymorphism and cardiometabolic biomarkers such as anthropometric indices (BMI, and WC), lipid profile markers (TC, TG, HDL-C and LDL-C), blood pressure and FBG were included in the present review. Furthermore, articles with or without deviation from the Hardy–Weinberg equilibrium (HWE) were included. If the studies were done in pregnant, lactating women, children, adolescents aged < 18 years, and also if they had no outcomes of interest, were excluded from the review. In the case of repeated publications on the same study, we selected the one which included a higher number of participants.

Data extraction. For each eligible study, data were extracted on the author’s last name, publication year, country, participants’ characteristics (sample size, sex, age, health status and ethnicity), method of genotyping, HWE and mean ± standard deviation (SD) of desired outcomes. Two reviewers (ASA and ZY) independently screened the titles and abstracts, assessed the full text of the relevant articles, and extracted the data. Any possible disagreements or discrepancies were resolved by group discussion.

Risk of bias assessment. Two authors independently evaluated the methodological quality of eligible studies. The quality of each study was assessed by using the Newcastle–Ottawa (NOS) Scale for case–control (eight items)59 and its modified version adapted for cross-sectional studies (seven items)60 with a maximum score of 9 and 10, respectively. The NOS was used for assessing the risk of bias in clinical trials because their baseline assessments were considered in this meta-analysis. According to the obtained NOS scores, case–control studies were classified into three levels: low quality (0–4 points), medium quality (5–6) and high quality (7–9 points) and cross sectional studies were classified into four levels: unsatisfactory (0–4 points), satisfactory (5–6 points), good (7–8 points) and very good (9–10 points) (as previously performed61,62). Any discrepancies were addressed by discussion to reach a consensus.

Statistical analysis. The raw difference in means and its 95% confidence interval (CI) was calculated by using Cochran’s Q test and the I-squared (I²) statistic (which is an estimate ranging from 0 to 100%). The heterogeneity between studies was evaluated using Cochran’s Q test and the I-squared (I²) statistic (which is an estimate ranging from 0 to 100%). The heterogeneity was regarded as low, moderate, and high when the values of I² were 25%, 50%, and exceeded 75%, respectively63. Subgroups analyses according to ethnicity, health status (heart disease, healthy and others), Hardy–Weinberg equilibrium, quality score (high or medium quality), design of the study (case–control or cross-sectional) and adjustment of confounders were performed to detect sources of between-study heterogeneity and also meta-regression analysis was used to identify potential sources of heterogeneity. Sensitivity analysis was used to assess whether the overall association depended on a specific study64. The presence of the publication bias was investigated by visual inspection of the funnel plots in case there were < 10 studies in each analysis, and also through statistical asymmetry tests (Begg’s adjusted rank correlation and Egger’s tests) for meta-analysis of 10 or more effect sizes65. In the case of asymmetry, Duval and Tweedie’s trim and fill analysis was applied for more adjustment of publication bias66. All statistical analyses were performed by using STATA version 11.2 (StataCorp, College Station, TX). Two-tailed p ≤ 0.05 were considered statistically significant.

Data availability
All data analyzed during the current study are available in Supplementary 2.

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Author contributions

H.M.-Kh., A.S.A. and Z.Y. designed the research, conducted the electronic searches and study selection; A.S.A. and Z.Y. conducted data extraction and tabulated data; H.M.-Kh. and A.S.A. conducted the data analysis and interpretation of results; Z.Y. wrote the first draft of the manuscript; H.M.-Kh., A.S.A., M.M. and M.H.S. critically revised the manuscript. All authors read and approved the final version of the manuscript.

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Competing interests

The authors declare no competing interests.
