Associations of Polymorphisms in the Peroxisome Proliferator-Activated Receptor Gamma Coactivator-1 Alpha Gene With Subsequent Coronary Heart Disease: An Individual-Level Meta-Analysis

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Background: The knowledge of factors influencing disease progression in patients with established coronary heart disease (CHD) is still relatively limited. One potential pathway is related to peroxisome proliferator–activated receptor gamma coactivator-1 alpha (PPARGC1A), a transcription factor linked to energy metabolism which may play a role in the heart function. Thus, its associations with subsequent CHD events remain unclear. We aimed to investigate the effect of three different SNPs in the PPARGC1A gene on the risk of subsequent CHD in a population with established CHD.

Methods: We employed an individual-level meta-analysis using 23 studies from the GENetIcs of sUbSequent Coronary Heart Disease (GENIUS-CHD) consortium, which included participants (n = 80,900) with either acute coronary syndrome, stable CHD, or a mixture of both at baseline. Three variants in the PPARGC1A gene (rs8192678, G482S; rs7672915, intron 2; and rs3755863, T528T) were tested for their associations with subsequent events during the follow-up using a Cox proportional hazards model adjusted for age and sex. The primary outcome was subsequent CHD death or myocardial infarction (CHD death/myocardial infarction). Stratified analyses of the participant or study characteristics as well as additional analyses for secondary outcomes of specific cardiovascular disease diagnoses and all-cause death were also performed.

Results: Meta-analysis revealed no significant association between any of the three variants in the PPARGC1A gene and the primary outcome of CHD death/myocardial infarction among those with established CHD at baseline: rs8192678, hazard ratio (HR): 1.01, 95% confidence interval (CI) 0.98–1.05 and rs7672915, HR: 0.97, 95% CI 0.94–1.00; rs3755863, HR: 1.02, 95% CI 0.99–1.06. Similarly, no significant associations were observed for any of the secondary outcomes. The results from stratified analyses showed null results, except for significant inverse associations between rs7672915 (intron 2) and the primary outcome among 1) individuals aged ≥65, 2) individuals with renal impairment, and 3) antiplatelet users.

Conclusion: We found no clear associations between polymorphisms in the PPARGC1A gene and subsequent CHD events in patients with established CHD at baseline.

Keywords: polymorphisms, PPARGC1A, meta-analysis, SNPs, coronary heart disease, cohort studies
INTRODUCTION

Coronary heart disease (CHD) is a multifactorial disease caused by a complex interplay between genetic, behavioral, and environmental factors, with atherosclerosis as the main underlying component (Tirt, 2002). Several processes important for atherosclerosis, such as lipid homeostasis (Zhang et al., 2004; Lin et al., 2005), endothelial function, and inflammation, are potentially modulated by the peroxisome proliferator–activated receptor gamma coactivator-1 alpha (PPARGC1A), encoded by the PPARGC1A gene (Kadlec et al., 2016). PPARGC1A co-activates several transcription factors involved in energy metabolism and oxidative stress including peroxisome proliferator–activated receptors (PPARs) and nuclear respiratory factors (NRFs) (Liang and Ward, 2006).

Animal studies have shown the evidence of PPARGC1A involvement in cardiac energy metabolism (Arany et al., 2005; Rowe et al., 2010) during development (Lai et al., 2008a) and aging (Whitehead et al., 2018). Furthermore, PPARGC1A is dysregulated in heart failure (Sihag et al., 2009; Oka et al., 2020) and plays a role in endothelial regulation (Craigie et al., 2016), athero-sclerotic lesions (Kadlec et al., 2016), and may be involved in endogenous protective mechanisms (i.e., ROS and mitochondrial biogenesis) (Chen et al., 2011). Human studies have shown associations between a non-synonymous coding variant single nucleotide polymorphism (SNP) in PPARGC1A (G482S; rs1892678) and metabolic outcomes (Vandenbeek et al., 2016), atherosclerotic lesions (Kadlec et al., 2016), atherosclerosis as the main cause mortality, as well as the possible effect modification by age, sex, co-morbidities, and medication use.

METHODS

The Consortium

The GENIUS-CHD consortium is an international collaboration, established in 2014 to investigate the impact of genetics on secondary CHD events (http://www.genius-chd.com/). Details about the consortium and inclusion criteria are published elsewhere (Patel et al., 2019a; Patel et al., 2019b). In brief, it mainly includes prospective cohort studies where participants with established CHD at baseline were followed for secondary CHD events. The cases are defined as those experiencing a subsequent CHD event. Participating studies received the local institutional review board approval and included patients who had/provided the informed consent at the time of enrollment.

Inclusion and Exclusion Criteria

Studies were included in the GENIUS-CHD consortium according to the following criteria: First, recruitment of participants with established CHD, defined as acute coronary syndrome or coronary artery disease (any revascularization procedures such as percutaneous coronary intervention, coronary bypass surgery, or a significant (50%) coronary artery plaque at angiography that affects any major epicardial vessel) at baseline or with a history thereof; second, availability of prospective follow-up and ascertainment of at least one clinical cardiovascular outcome (including all-cause mortality); and third, availability of samples, biomarkers, or in silico genotyping data. In the present study, we only included studies if SNP data in the PPARGC1A gene were available (Figure 1, flow-chart).

Data Extraction and Quality Assessment

We examined three lead SNPs: rs8192678, rs7672915, and rs3755863. If those variants were not available, proxies in high linkage disequilibrium (r^2 > 0.8) were considered: rs7683406, rs9966943, rs1873532, rs10938963, and rs12650562 (Figure 1, flow-chart). All proxy SNPs are intronic variants.

The quality control of the genotype data was performed by each study prior to analysis. Minor allele frequencies (MAFs) and Hardy–Weinberg equilibrium (HWE) were examined by each study.
Outcomes
The primary outcome was defined as myocardial infarction (MI) or CHD death during follow-up. Secondary outcomes were MI, coronary revascularization, heart failure, ischemic stroke, any stroke, any CVD (including MI, stroke, coronary revascularization, and CVD death), CHD death, CVD death, and all-cause death.

Statistical Analysis
The associations between SNPs and cardiovascular outcomes were evaluated in individual studies assuming an additive genetic model and using time-to-event Cox proportional hazards models adjusted for age and sex. Analyses were performed using shared statistical scripts and harmonized datasets across the consortium (Patel et al., 2019a; Patel et al., 2019b).

The study-level effect estimates and their corresponding standard errors were entered in an inverse variance weighted fixed-effect meta-analysis model. The \( \chi^2 \) test for heterogeneity and the \( I^2 \) statistic were used to quantify heterogeneity. Stratified analyses were performed for CHD subtypes at baseline: acute coronary syndrome (ACS) and coronary artery disease (CAD) with prior MI and CAD without prior MI. Stratification was also performed for the baseline patient-level characteristics of age (< or \( \geq 65 \) years), sex, hypertension (physician-diagnosed or under treatment), T2D (physician-diagnosed or under treatment), body mass index (BMI) (18.5–24.9; 25–29.9; \( \geq 30 \) kg/m2), statin use, antiplatelet use, renal impairment (eGFR<60 ml/kg/min), and left-ventricular impairment (left-ventricular ejection fraction<45% or diagnosed heart failure with impaired systolic function). Furthermore, sensitivity analyses were performed by stratifying two study-specific factors: European ancestry (a European study where >95% of the participants were of European ancestry versus non-European) and duration of the follow-up (< versus \( \geq 5 \) years).

In addition, we repeated the main analysis excluding cohorts departing from HWE (\( p < 0.05 \)). Effect sizes and confidence intervals (CI) were calculated using the two-sided \( \alpha \) of 0.05, and results are presented as hazard ratios (HRs). Analyses at the coordinating centers were conducted by R software (version 3.4.1) (R Development Core Team), and the meta-analysis was performed using the EpiSheet tool (K. Rothman, www.krothman.org).

RESULTS
Study Characteristics
In total, 23 studies from the GENIUS-CHD consortium with established CHD and available SNP data in the PPARGC1A gene were selected, with the lead SNPs available in 22, 17, and 19 studies and highly correlated (\( r^2 > 0.8 \) in Europeans) proxies available in 0, 2, and 2 studies for rs8192678 (non-synonymous variant G482S), rs7672915 (single nucleotide variant in intron 2), and rs3755863 (synonymous variant T528T), respectively (Figure 1). The participant characteristics and genotyping details (MAF and HWE p-value) of the SNPs under investigation are presented in Tables 1, 2.

Meta-Analysis Results
We found null associations for all three SNPs with the primary outcome of CHD death or MI (Figure 2). Similarly, null associations were found for all three SNPs with all secondary outcomes (Figure 3).

Stratified Meta-Analysis
Stratification by the CHD subtype at baseline resulted in borderline significant direct associations for rs8192678 (G482S) with the primary outcome for baseline CAD without MI and borderline inverse associations for rs7672915 (intron 2) for baseline ACS (Figure 4). A significant inverse association was found for...
| Cohort                        | Study (country)                                                                 | Design, CHD type                  | Year       | Mean follow-up time, years (SD) | N recruited with CHD | Sex, % male | Mean age, years (SD) | European ancestry (%) | PubMed ID |
|------------------------------|---------------------------------------------------------------------------------|-----------------------------------|------------|---------------------------------|----------------------|-------------|---------------------|-----------------------|-----------|
| AGNES Arrhythmia Genetics in  | Cohort, ACS                                                                      | 2001–2005                         | 6.73 (4.75)| 1,459                           | 79.2                 | 57.8 (10.7) | 100                 |                       | 20622880 |
| the Netherlands              |                                                                                  |                                   |            |                                 |                      |             |                     |                       |           |
| ANGNES Angiography and Genes | Cohort, mixed                                                                    | 2002–2005                         | 8.20 (4.47)| 588                             | 65.5                 | 64.1 (9.6)  | 100                 |                       | 21640993 |
| Study (Finland)              |                                                                                  |                                   |            |                                 |                      |             |                     |                       |           |
| CDCS                         | Coronary Disease Cohort Study (New Zealand)                                     | 2002–2009                         | 5.21 (2.15)| 2,139                           | 71.3                 | 67.4 (12.0) | 91.4                |                       | 20400779 |
| CTMM                         | CTMM Circulating Cells (Netherlands)                                            | 2009–2011                         | 0.97 (0.37)| 713                             | 69.0                 | 62.6 (10.1) | 96.5                |                       | 23975238 |
| FINCAVAS Finnish Cardiovascular Study | Cohort, mixed                                                                 | 2001–2008                         | 8.57 (3.99)| 1,671                           | 69.4                 | 60.9 (11.0) | 100                 |                       | 16515696 |
| GoDARTS prevalent Genetics  | Population, CAD                                                                  | 2004–2012                         | 3.47 (2.95)| 1,261                           | 61.1                 | 71.5 (10.9) | 99.8                |                       | 29025058 |
| of Diabetes Audit and        |                                                                                  |                                   |            |                                 |                      |             |                     |                       |           |
| Research in Tayside Scotland |                                                                                  | 8.57 (3.99)                       |            |                                 |                      |             |                     |                       |           |
| (I)                          |                                                                                  |                                   |            |                                 |                      |             |                     |                       |           |
| GoDARTS incident Genetics    | Population, CAD                                                                  | 2004–2012                         | 6.48 (3.06)| 2,514                           | 65.9                 | 69.1 (8.4)  | 99.7                |                       | 29025058 |
| of Diabetes Audit and        |                                                                                  |                                   |            |                                 |                      |             |                     |                       |           |
| Research in Tayside Scotland |                                                                                  | 10.47 (4.45)                      |            |                                 |                      |             |                     |                       |           |
| (P)                          |                                                                                  |                                   |            |                                 |                      |             |                     |                       |           |
| IATVB Italian Atherosclerosis| Cohort, ACS                                                                      | 1997–2006                         | 1.77 (0.27)| 546                             | 73.8                 | 65.6 (11.1) | 100                 |                       | 21757122 |
| Thrombosis and Vascular      |                                                                                  |                                   |            |                                 |                      |             |                     |                       |           |
| Biology Group                |                                                                                  |                                   |            |                                 |                      |             |                     |                       |           |
| LIFE-Heart Leipzig (LIFE)    | Cohort, mixed                                                                    | 2006–2014                         | 1.62 (2.03)| 5,564                           | 77.2                 | 63.9 (11.1) | 100                 |                       | 32747942 |
| Heart Study (Germany)        |                                                                                  |                                   |            |                                 |                      |             |                     |                       |           |
| LURIC                         | The Ludwigshafen Risk and Cardiovascular Health Study (Germany)                   | 1997–2000                         | 8.58 (3.18)| 2,320                           | 76.6                 | 63.8 (9.9)  | 100                 |                       | 11258203 |
| OHGS Oslo Heart Genomics     | Cohort, mixed                                                                    | 2010–2013                         | 1.77 (0.27)| 546                             | 73.8                 | 65.6 (11.1) | 100                 |                       | NA        |
| Study (Canada)               |                                                                                  |                                   |            |                                 |                      |             |                     |                       |           |
| PLATO                         | The Study of Platelet Inhibition and Patient Outcomes (International)             | RCT, ACS                          | 2006–2008 | 0.86 (0.24)                      | 18,624               | 69.5        | 62.6 (11.0)        | 98.3                  | 19332184 |
| PMI                           | Post Myocardial Infarction Study (New Zealand)                                    | Cohort, ACS                       | 1994–2001 | 8.56 (3.58)                      | 1,057                | 78.0        | 62.8 (10.6)        | 91.1                  | 12771003 |
| PROSPER                       | Prospective Study of Pravastatin in the Elderly at Risk (Netherlands)             | RCT, CAD                          | 1997–1999 | 3.15 (0.71)                      | 893                  | 70.3        | 75.4 (3.4)         | 100                  | 10569329 |
| SHEEP                         | Stockholm Heart Epidemiology Program (Sweden)                                     | Cohort, ACS                       | 1992–1995 | 14.87 (5.91)                     | 1,150                | 70.7        | 59.3 (7.2)         | 100                  | 17667644 |
| SMART Second Manifestations   | Cohort, mixed                                                                    | 1999–2010                         | 6.77 (3.86)| 3,057                           | 81.7                 | 60.5 (9.3)  | 98.2                |                       | 10468526 |
| of Arterial Disease (Netherlands) |                                                                                  |                                   |            |                                 |                      |             |                     |                       |           |
| STABILITY                     | Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy trial (International) | RCT, CAD                          | 2008–2010 | 3.60 (0.57)                      | 10,786               | 82.0        | 64.7 (9.1)         | 86.1                  | 24678955 |
| UCP                           | Utrecht Cardiovascular Pharmacogenetic Study (Netherlands)                        | Cohort, mixed                     | 1985–2010 | 8.00 (4.16)                      | 1,508                | 75.4        | 64.1 (10.0)        | 100                  | 25652526 |
| UKB                           | United Kingdom Biobank (United Kingdom)                                          | Population, CAD                   | 2006–2010 | 6.39 (1.72)                      | 12,045               | 80.6        | 69.9 (8.1)         | 94.2                  | 1001779  |
| VIVIT                         | Vorarlberg Institute for Vascular Investigation and Treatment Study (Austria)     | Cohort, CAD                       | 1999–2008 | 7.43 (2.91)                      | 1,447                | 72.0        | 64.5 (10.5)        | 99.8                  | 24265174 |
| GENE Maths                   | Cleveland Clinic Genebank Study (United States)                                  | Cohort, mixed                     | 2001–2007 | 3.00 (0.00)                      | 2,345                | 74.3        | 61.5 (11.1)        | 100                  | 21475195 |
| INVEST                        | International Verapamil SR TranslomiPrey Study Genetic Substudy INVEST-GENES (United States) | RCT, CAD                          | 1997–2003 | 2.83 (0.82)                      | 5,979                | 44.0        | 66.1 (9.7)         | 38.0                  | 21372283, 17700361 |
| UCorBio                       | Utrecht Coronary Biobank (Netherlands)                                           | Cohort, mixed                     | 2011–2014 | 1.6 (0.9)                        | 1,493                | 75.6        | 65.4 (10.3)        | 72.4                  | NA        |

Additional studies not included in primary outcome analysis but included in secondary outcome analyses of all-cause mortality.

| Study                        | Design, CHD type                  | Year       | Mean follow-up time, years (SD) | N recruited with CHD | Sex, % male | Mean age, years (SD) | European ancestry (%) | PubMed ID |
|------------------------------|-----------------------------------|------------|---------------------------------|----------------------|-------------|---------------------|-----------------------|-----------|
| COROGENE Corogene Study      | Cohort, ACS                        | 2006–2008 | 7.7 (0.5)                       | 1,489                | 70.9        | 64.7 (11.9)        | 100                  | 21642350 |
| (Finland)                    |                                   |            |                                 |                      |             |                     |                       |           |
| MDCS                         | Cohort, mixed                      | 1991–1996 | 8.3 (8.0)                       | 4,546                | 60.2        | 58.0 (7.6)         | 100                  | 19936945 |

(Continued on following page)
TABLE 1 | (Continued) Characteristics of studies included in the meta-analysis.

| Cohort                  | Study (country)               | Design, CHD type          | Year                  | Mean follow-up time, years (SD) | N recruited with CHD | Sex, % male | Mean age, years (SD) | European ancestry (%) | PubMed ID |
|-------------------------|--------------------------------|---------------------------|-----------------------|---------------------------------|----------------------|-------------|----------------------|------------------------|-----------|
| TRIUMPH                 | Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patient’s Health Status (United States) | Cohort, ACS              | 2005–2008             | 0.97 (0.15)                    | 2,062                | 72.2        | 59.8 (12.1)          | 100                    | 21772003  |
| WTCCC (BHF)             | WTCCC CAD Study (United Kingdom) | Cohort, mixed            | 1998–2003             | 10.05 (2.81)                   | 1,926                | 79.3        | 60.0 (8.1)           | 100                    | 16380912, 17634449 |

More detailed information is available in Reference number 28: Patel RS et al. (2019) Circ Genom Precic Med.

CHD, coronary heart disease; ACS, acute coronary syndrome; CAD, coronary artery disease; RCT, randomized controlled trial; SD, standard deviation.

TABLE 2 | Minor allele frequencies (MAFs) and p-values for Hardy–Weinberg equilibrium (P_HWE) for the three SNPs in the studies included in the meta-analysis.

| Cohort | MAF rs8192678 (G482S) | PHWE rs8192678 (G482S) | MAF rs7672915 (intron 2) | PHWE rs7672915 (intron 2) | MAF rs3755863 (T528T) | PHWE rs3755863 (T528T) |
|--------|------------------------|------------------------|--------------------------|--------------------------|------------------------|-----------------------|
| AGNES  | 0.331                  | 0.106                  | 0.404*                   | 0.842*                   | 0.395                  | 0.550                 |
| ANGENES| 0.316                  | 0.075                  | 0.385                    | 0.265                    | 0.343                  | 0.280                 |
| CDCS   | 0.345                  | 0.880                  | 0.465                    | 0.254                    | 0.402                  | 0.741                 |
| CTMM   | 0.345                  | 0.720                  | 0.430                    | 0.242                    | 0.402                  | 0.237                 |
| FINCAVAS| 0.320                | 0.261                  | 0.355                    | 0.0008*                  | 0.350                  | 0.162                 |
| GoDARTSprevalent         | 0.348             | 0.784                  | 0.466                    | 0.485                    | 0.409                  | 0.572                 |
| GoDARTSincident          | 0.325             | 0.523                  | 0.444                    | 0.064                    | 0.382                  | 0.416                 |
| IATVB              | 0.363             | 0.909                  | -                        | -                        | 0.441*                 | 0.672*                 |
| LIFE-Heart               | 0.323             | 0.135                  | 0.432                    | 0.950                    | 0.367                  | 0.109                 |
| LURIC                         | 0.345             | 0.776                  | 0.448                    | 0.571                    | 0.395                  | 0.654                 |
| OHGS                           | 0.287             | 0.806                  | 0.424*                   | 0.215*                   | 0.355                  | 0.097                 |
| PLATO                         | 0.325             | 0.698                  | 0.451                    | 0.374                    | 0.374                  | 0.701                 |
| PMI                             | 0.348             | 0.015*                 | 0.435                    | 0.093                    | 0.404                  | 0.032                 |
| PROSPER                        | 0.338             | 0.582                  | 0.442                    | 0.510                    | 0.399                  | 0.420                 |
| SLEEP                          | 0.339             | 0.948                  | 0.399                    | 0.804                    | 0.391                  | 0.416                 |
| SMART                          | 0.339             | 0.965                  | -                        | -                        | -                     | -                     |
| STABILITY                      | 0.334             | 0.778                  | 0.469                    | 0.026*                   | 0.385                  | 0.714                 |
| UGP                             | 0.353             | 0.734                  | 0.435                    | 0.434                    | 0.411*                 | 1.0*                  |
| UKB                             | 0.342             | 0.982                  | 0.061                    | 0.909                    | 0.005                  | 0.848                 |
| VIVIT                           | -                | -                      | -                        | -                        | 0.477*                 | 0.270*                 |
| GENEBANK                       | 0.348             | 0.716                  | 0.423                    | 0.472                    | 0.4                   | 0.931                 |
| INVEST                          | 0.301             | 0.034*                 | 0.498                    | 0.554                    | 0.374                  | 0.385                 |
| UCORBIO                         | 0.337             | 0.643                  | -                        | -                        | -                     | -                     |
| Additional studies are not included in primary outcome analysis but included in secondary outcome analyses of all-cause mortality. |

*Indicates the use of a highly correlated proxy (AGNES, rs9996943; OHGS, rs7683406; IATVB, rs10938963; UCP, rs1873532; and VIVIT, rs12650562).

Studies with p_HWE < 0.05 were excluded in sensitivity analyses for the primary outcome.

rs7672915 (intron 2) with the primary outcome among the ≥65 years of age category as well as for renal impairment and antiplatelet use (Figure 5B). There were no significant associations between any of the SNPs and the primary outcome in the models stratified by sex, hypertension, T2D, BMI, statin use, and left-ventricular impairment (Figures 5A-C). Sensitivity analyses only indicated marginal differences. Neither exclusion of cohorts deviating from HWE nor
FIGURE 2 | Meta-analyses of the associations between three SNPs in the PPARGC1A gene and primary outcome (CHD death or myocardial infarction) in participants with baseline CHD within GENIUS-CHD using an additive, fixed-effect model adjusted for age and sex.
stratification by European ancestry changed associations with the primary outcome (data not shown). Stratification by follow-up time also resulted in null associations, except for significant inverse associations for rs7672915 (intron 2) and the primary outcome in the stratum with follow-up <5 years (HR: 0.93, 95% CI 0.88–0.99).

DISCUSSION

This meta-analysis resulted in overall null associations between three polymorphisms in the PPARGC1A gene studied in relation to the risk of subsequent CHD events (primary outcome) in a population with established CHD. The polymorphism rs7672915 (intron 2) was, however, observed to be borderline inversely associated with subsequent CHD events.

The results were generally consistent across the strata of CHD subtypes at baseline as well as of patient- and study-level characteristics. However, inverse associations with the primary outcome were seen for rs7672915 (intron 2) amongst those with age ≥65, renal impairment, and use of antiplatelets. In addition, inverse associations with the primary outcome were seen for rs7672915 (intron 2) among studies having a follow-up <5 years.

Human Studies on Polymorphisms in the PPARGC1A Gene

Our results suggested that the PPARGC1A gene in patients with established CHD does not play an important role in disease progression, leading to subsequent CHD events. Previous research study has not investigated this relationship. However, there are studies that indicate that the PPARGC1A gene is important for the development of CAD (Zhang et al., 2008; Yongsakulchai et al., 2016; Maciejewska-Skrendo et al., 2019) and cardiometabolic disease phenotypes (Ek et al., 2001; Barroso et al., 2006; Xie et al., 2007; Lai et al., 2008b; Vimalakshetra et al., 2008; Yang et al., 2011; Franks et al., 2014; Jemaa et al., 2015; Kruzliak et al., 2015). The PPARGC1A gene (rs8192678; G482S) was associated with an increased risk of CAD in a Chinese

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**FIGURE 3** | Meta-analyses pooled results of the associations between three SNPs in the PPARGC1A gene and secondary outcomes in participants with baseline CHD within GENIUS-CHD using an additive, fixed-effect model stratified for age and sex (pHeterogeneity >0.05 for all outcomes). Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction.
population (Zhang et al., 2008). Moreover, the PPARGC1A gene (rs8192678; G482S), alone as well as in combination with polymorphisms in PPAR and liver X receptor α (LXRA), associated with an increased risk and severity of CAD in a Thai population (Yongsakulchai et al., 2016). The PPARGC1A gene (rs8192678; G482S) was further associated with T2D in a Tunisian population (Jemaa et al., 2015), with waist circumference among Slovenian participants with T2D (Kruzliak et al., 2015) and with severe hypertension in a Chinese population (Xie et al., 2007). The PPARGC1A gene was also identified in a search for protein-level interactions with transcripts mapped nearest to T2D susceptibility loci (Morris et al., 2012). Although the rs8192678; G482S Ser482 allele appears to be associated with increased obesity and T2D susceptibility (Vandenbeek et al., 2017) as well as a poorer therapeutic efficacy of rosiglitazone (Zhang et al., 2010), its carriers also appear to respond better to caloric restriction (Goyenechea et al., 2008) and bariatric surgery (Geloneze et al., 2012). In the Boston Puerto Rican Health Study, they found associations between polymorphisms in the PPARGC1A gene and DNA damage, T2D, and CVD (Lai et al., 2008b). However, meta-analysis only indicated modest roles within specific ethnicity and age groups for polymorphisms in the PPARGC1A gene (rs8192678; G482S) with T2D (Barroso et al., 2006; Yang et al., 2011) and hypertension (Vimalaswaran et al., 2008). The Ser482 allele carried an increased risk for hypertrophic cardiomyopathy in a community-based cross-sectional study in China (Wang et al., 2007). However, another study in a Russian population did not find evidence for such an association (Nikitin et al., 2010). The two other SNPs under investigation were less studied but have been shown to associate with metabolic traits (Brito et al., 2009; Juang et al., 2010a; Mirzaei et al., 2012): rs7672915 (intron 2) associated with left-ventricular diastolic function in Caucasians (Juang et al., 2010) whereas rs3755863 (T528T) was found to be associated with waist circumference in European children (Brito et al., 2009) and with LDL cholesterol in an adult population consisting mostly of obese women (Mirzaei et al., 2012). Furthermore, rs3755863 (T528T) seemed to decrease PPARGC1A expression levels in cellular models (Mirzaei et al., 2012). Although results from subgroup analyses always should be interpreted with caution, it is possible that the significant association between rs7672915 (intron 2) and the primary outcome seen only in the subgroup of individuals aged 65 years or older in our study population may be relevant; age-related risk factors could interact with genetics and increase vulnerability to subsequent events. Based on similar reasoning, the significant associations we observed in subgroups with impaired renal function and users of antiplatelets, respectively, could be relevant. Also, the fact that rs7672915 (intron 2) was significantly associated with our primary outcome when the basis for the analysis was limited to including cohort data with less than 5 years of follow-up may indicate that the PPARGC1A gene plays a role in CHD progression, possibly in repair and recovery after an initial event in the short term.

Mechanistic Studies on PPARGC1A and Cardiometabolic Health

The PPARGC1A gene, located on chromosome 4, encodes for a protein consisting of 798 amino acids in humans. It is highly expressed in tissues abundant in mitochondria such as the liver (in fasting states) (Yoon et al., 2001), kidney, brown adipose tissue, skeletal muscle, brain, and heart (Puigserver et al., 1998). PPARGC1A activates transcription factors by inducing a conformational change after binding to them, which increases the affinity of the transcription complex to other coactivators that
have histone acetyltransferase activity. This increased affinity will then lead to the acetylation of histone proteins and conformational alterations that allow the increased accessibility of DNA to the transcription complex (Puigserver et al., 1999). Several pathways involving PPARGC1A and energy metabolism have been described, for example, mitochondria biogenesis, glucose/fatty acid metabolism, remodeling of fiber muscle composition, and adaptive thermogenesis (Liang and Ward, 2006). The effect of PPARGC1A on the mitochondrial metabolism, especially, can have implications for cardiac

FIGURE 5 | Panel (A): Meta-analyses of the associations between rs192673 (G482S) in the PPARGC1A gene and the primary outcome (CHD death or myocardial infarction) in participants with baseline CHD within GENIUS-CHD using an additive, fixed-effect model stratified for patient-level characteristics. LV, left ventricular. Panel (B): Meta-analyses of the associations between rs7672915 (intron 2) in the PPARGC1A gene and the primary outcome (CHD death or myocardial infarction) in participants with baseline CHD within GENIUS-CHD using an additive, fixed-effect model stratified for patient-level characteristics. LV, left ventricular. Panel (C): Meta-analyses of the associations between rs3755863 (T528T) in the PPARGC1A gene and the primary outcome (CHD death or myocardial infarction) in participants with baseline CHD within GENIUS-CHD using an additive, fixed-effect model stratified for patient-level characteristics. LV, left ventricular.
health by regulating the fuel availability and the amount of reactive oxygen species in the heart (Di et al., 2018). PPARGC1A target genes that are thought to play a role in cardiac health are estrogen-related receptors (ERRs; i.e., ERα, ERRβ, and ERRγ) and nuclear respiratory factor-1, which activate many mitochondrial genes, as well as PPARs (i.e., PPARα, PPARβ, PPARγ, and PPARδ), which play important roles in the fatty acid uptake and oxidation in the heart (Di et al., 2018). Any dysregulation in PPARGC1A may be detrimental; studies have shown that its downregulation increased vascular stress (Kadlec et al., 2016), oxidative stress and inflammation (Waldman et al., 2018; Rius-Pérez et al., 2020), impaired mitochondrial function, and reduced antiapoptotic and angiogenic responses (Mahmood et al., 2019), whereas its upregulation induced pathological changes in mitochondrial biogenesis, contributing to cardiac disease (Lehman et al., 2000; Le Chen and Knowlton, 2011; Caravia et al., 2018). One of the SNPs (rs8192678; G482S) was recently shown to decrease angiogenic responses (Mahmood et al., 2019), whereas its mitochondrial function, and reduced antiapoptotic and angiogenic responses (Mahmood et al., 2019), whereas its upregulation induced pathological changes in mitochondrial biogenesis, contributing to cardiac disease (Lehman et al., 2000; Le Chen and Knowlton, 2011; Caravia et al., 2018). One of the SNPs (rs8192678; G482S) was recently shown to decrease the stability, impact structural conformation, and catalytic function of the PPARGC1A protein, which could be detrimental for CAD (Taghvaei et al., 2021). However, this is not reflected in our findings of null associations for the three tested SNPs in the PPARGC1A gene with subsequent CHD events. Our findings of inverse associations of rs7672915, intron 2 in subgroups (older age, with renal impairment, and antiplatelet users) could be random findings or due to the role of PPARGC1A in mitochondria subsequently affecting the aging process (Wenz, 2011), kidney disease (Lynch et al., 2018), and platelet function (Melchinger et al., 2019).

Limitations and Strengths
There are several limitations which may have attenuated or diluted the effect estimates. First, when studying cohorts of patients, as in this study, there is always a possibility that the index event bias may influence the results (Dahabreh and Kent, 2013; Patel et al., 2019a). Our study population consists of CHD survivors subjected to varying types of preventive actions, including lifestyle changes and drug treatments, which may have impacted risks for recurrent events and death. In addition, there is a possibility that individuals who died early with the disease have a more severe phenotype and that the degree of severity is linked to the presence of the genetic variants we studied. However, in the previously published genome-wide studies of genetic variants in relation to the risk of first-time events of CHD, the current genetic variants were not included among the significant association findings (Peden et al., 2011; Schunkert et al., 2011; Deloukas et al., 2013; Nikpay et al., 2015; van der Harst and Verweij, 2018). Furthermore, if the index event is a consequence of a strong risk factor, there may be lower levels of exposure to other—individually weaker—-independent risk factors in the selected population, which could have attenuated associations between genetic variants and the risk of subsequent events in our study (Patel et al., 2019b). Second, we had no information on the age of onset of the index CHD event or on whether revascularization procedures were late-staged (belonging to the index event) or unplanned and symptom-driven (true secondary event). Third, the variability in the follow-up between studies could impact the findings through outcome misclassification. Fourth, it is possible that other SNPs, outside our selected three, in the PPARGC1A gene play a key role. Finally, in the present study, we only investigated single SNP associations within a single gene whereas it could be relevant to also address gene–gene interactions and polygenic scores. The major strength of this study, however, is the large number of studies and individuals included. This allowed us to make reasonably conclusive inferences.

CONCLUSION
The findings from this large individual-level meta-analysis do not indicate the involvement of the PPARGC1A gene in the progression to secondary CHD events amongst people who experienced an index CHD event. However, future research studies on the potential role of PPARGC1A in subgroups of patients with established CHD, in relation to the risk of recurrence, may be warranted.

DATA AVAILABILITY STATEMENT
The data analyzed in this study are subjected to the following licenses/restrictions: Individual participant-level data for each participating study were not collected for the present project and will, therefore, not be made available. Further details and contact information are available at http://krothman.hostbyet2.com/. Requests to access these datasets should be directed to www.genius-chd.org.

ETHICS STATEMENT
The studies involving human participants were reviewed and approved by the local institutional review board approval and included patients who had provided informed consent at the time of enrollment. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS
KL, RP, and FA: conceptualization. KL, TS, BM, FL, MV, SC, and BG: preparation of the analysis plan. TS: original manuscript draft preparation. VT and MV: data analysis. All authors contributed to data collection, either within the framework of a participatory study or at a more comprehensive level in terms of collecting results from participatory studies. All authors contributed to the editing of the manuscript and approved the submitted version.

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