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Polygenic Risk Score and Statin Relative Risk Reduction for Primary Prevention of Myocardial Infarction in a Real-World Population

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Abstract

Genetic substudies of randomized controlled trials demonstrate that high coronary heart disease (CHD) polygenic risk score modifies statin CHD relative risk reduction; it is unknown if the association extends to statin users undergoing routine care. We sought to determine how statin effectiveness is modified by CHD polygenic risk score in a real-world cohort of participants without previous myocardial infarction. We determined CHD polygenic risk scores in participants of the Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort. Covariate-adjusted Cox regression models were used to compare the risk of cardiovascular outcomes between statin users and matched nonusers. Statin effectiveness on incident myocardial infarction showed no gradient with increasing 10-year Pooled Cohort Equations atherosclerotic cardiovascular disease (ASCVD) risk across low, borderline, intermediate, and high ASCVD risk

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AUTHOR CONTRIBUTIONS

A.O.-O., T.H., R.M.K., and N.R. wrote the manuscript. A.O.-O. designed the research. T.H. performed the research. A.O.-O., T.H., M.A.S.C., D.K.R., T.J.H., C.I., R.M.K., and N.R. analyzed the data. T.H. contributed an analytical tool.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

score groups. In contrast, statin effectiveness by polygenic risk was largest in the high polygenic risk score group (hazard ratio (HR) 0.41, 95% confidence interval (CI), 0.31–0.53; *P* = 1.5E-11), intermediate in the intermediate polygenic risk score group (HR 0.56, 95% CI, 0.47–0.66; *P* = 8.4E-12), and smallest in the low polygenic risk score group (HR 0.67, 95% CI, 0.47–0.97; *P* = 0.03; *P* for high vs. low = 0.01). ASCVD risk and statin low-density lipoprotein cholesterol (LDL-C) lowering did not differ across polygenic risk score groups. In patients undergoing routine care, CHD polygenic risk modified statin relative risk reduction of incident myocardial infarction independent of LDL-C lowering. Our findings extend prior work by identifying a subset (i.e., self-identified White individuals with low CHD polygenic risk scores) with attenuated clinical benefit from statins.

Statin therapy has shown substantial benefit in preventing atherosclerotic cardiovascular disease (ASCVD) events including coronary heart disease (CHD) and other vascular events.[1] The magnitude of this observed benefit was found to be directly proportional to the degree of statin-induced low-density lipoprotein cholesterol (LDL-C) lowering.[1,2] Although clinical and demographic factors (age, sex, diabetes, hypertension, etc.) were not found to modify this relationship,[1,2] the discovery of modifiers could improve current practice guidelines regarding eligibility for statin treatment.

Recent genetic substudies of statin randomized controlled trials have demonstrated that factors other than the degree of LDL-C lowering can modify statin CHD relative risk reduction. In particular, high CHD polygenic risk (derived from variants previously found to be associated with CHD in genome-wide association studies[3-5]) was associated with a greater statin benefit compared with low and intermediate polygenic risk score groups.[6,7] In addition to statin-induced LDL-C lowering, this association was also found to be independent of other traditional ASCVD risk factors, including strong family history.

Although these results suggest that polygenic risk scores may be able to better identify candidates predicted to receive substantial benefit from statin therapy beyond those who qualify for treatment based on current practice guidelines, results from randomized controlled trials may not generalize to the broad population of statin users undergoing routine clinical care.[8] Thus, it is unknown if the association between CHD polygenic risk and statin CHD relative risk reduction extends to statin users outside of a clinical trial setting. The primary objective of this study was to validate that this previously established CHD polygenic risk score modifies statin CHD risk reduction in a cohort of real-world, primary prevention participants. Furthermore, results from the aforementioned studies (both the statin randomized controlled trial substudies as well as the genome-wide association studies that derived the polygenic risk scores) are based on participants almost entirely self-identified as White race or of European descent (depending on the study).[3-7] Therefore, we also explored how this polygenic risk score modifies statin effectiveness in participants with substantial proportions of sub-Saharan African, Native American, and East Asian ancestry.

METHODS

Data source

We used data from participants in Genetic Epidemiology Research on Adult Health and Aging (GERA), a resource of the Research Program on Genes, Environment and Health (RPGEH) within the Kaiser Permanente Northern California (KPNC) health system that links electronic health record, genome-wide variant, and demographic survey data[9,10] as described in the Supplementary Methods.

Institutional Review Board (IRB) approval was obtained from both Kaiser Permanente and the University of California. Participants gave written informed consent.

Genotyping

To maximize coverage of genome-wide variants, study participants were previously genotyped on one of four Axiom arrays (Affymetrix, Santa Clara, CA) based on self-identified race/ethnicity.[11] Imputation was performed to the 1000 Genomes Project (Phase I integrated release, March 2012, with August 2012 chromosome X update and singletons removed).[12] Individual genetic ancestry admixture proportions were generated using the same algorithm as previously reported,[13] except using ADMIXTURE v1.3.0[14] (a faster implementation of the same algorithm); we refer readers to the Supplementary Methods or Banda *et al.*[13] for further details on how race/ethnicity and genetic ancestry were characterized in participants.

Phenotyping

A participant met the definition of a statin user if (i) they were considered to be adherent from the date of statin initiation to the date of event or censor; (ii) they appeared to be a new initiator of statin therapy within the time frame of follow-up; (iii) their last statin dispensing record window ended ≤30 days before the date of event or censor; and (iv) their date of statin initiation occurred >30 days before the date of event or censor (time-to-event and censoring analyses described in more detail below). We used proportion of days covered to estimate adherence and set 80% as the adherence threshold.[15] To reduce the likelihood of including participants who were not new initiators of statins, we defined a new initiator of statin therapy as a participant whose initial statin dispensing record was >6 months after entering KPNC membership.[10]

A participant met the definition of a statin nonuser if they had no statin dispensing records before the date of event or censoring unless statin initiation was considered to be too recent to impact outcomes (i.e., ≤30 days before event or censoring).

To identify statin nonusers with similar ASCVD risk as statin users at index, we matched each user to two nonusers by age (within 3 years at a maximum), sex, cigarette smoking, diabetes, hypertension, and race/ethnicity as described in the Supplementary Methods.

To obtain a primary prevention population, we included participants with no evidence of myocardial infarction prior to index. This definition for primary prevention was based on a

prior genetic substudy of a statin randomized controlled trial that investigated the association between the same polygenic risk score and statin CHD benefit.[6]

As the main complication of CHD, we prespecified first-time myocardial infarction (fatal + nonfatal) to be the primary outcome. A major adverse cardiovascular event (MACE) was defined as a composite of myocardial infarction (fatal + nonfatal), ischemic stroke (fatal + nonfatal), or any other cardiovascular disease death. MACE was prespecified as the secondary outcome, consistent with the known benefit of statin therapy on all-cause cardiovascular mortality.[16,17]

CHD polygenic risk score

We selected the 164 variants independently associated with CHD (and corresponding odds ratios) in prior genome-wide association studies from the UK Biobank and Coronary Artery Disease Genome-Wide Replication and Meta-Analysis plus The Coronary Artery Disease (CARDIoGRAMplusC4D) (Table S1).[18-20] To calculate a polygenic risk score for each participant, the count of each variant allele (or allelic dosage for imputed variants) was weighted (log of the odds ratios for the prior strength of association between each variant and CHD) and summed. See Supplementary Methods for more details.

Data analysis

One common proposal for analysis in genetic studies of multiethnic cohorts is to ignore population descriptors and analyze groups as a single pooled sample.[21] However, any results from an analysis in a combined cohort will likely represent participants with the largest sample size and mask findings of underrepresented groups. Thus, this approach is limited for the vast majority of biobank-linked multiethnic cohorts worldwide (including GERA) since they lack diversity in sample size by self-identified race/ethnicity.[22] Furthermore, despite its limitations,[23] self-identified race is considered a “master status variable”[24] capturing important environmental (e.g., structural racism) and nonenvironmental (e.g., self-identified Black individuals in the United States often have substantial genetic ancestry from West and Central Africa[25]) factors that could be lost if not accounted for. For these reasons, and in accord with the previously mentioned objectives of the study, we categorized participants by self-identified race/ethnicity groups: participants were stratified into race/ethnicity groups before subsequent analyses. Mean genetic ancestry proportions were calculated and reported within each race/ethnicity group, similar to previous studies,[13] to ensure that ancestry from underrepresented populations were appropriately included in the study. Race/ethnicity groups with fewer than 250 statin users were not included in the study population due to inadequate statistical power.

Cox proportional hazards regression models were generated using time-to-event (from index) data with right-censoring for the primary and secondary outcomes. Participants who did not experience an outcome were censored at the time of death, the last LDL-C measurement in their records, or at age 90 (due to lack of detailed data in this subgroup as previously described[10]), whichever occurred first. Model covariates included sex, age, hypertension, diabetes, and cigarette smoking status at the time of index date.

For the primary analysis, first we generated Cox proportion hazards regression in the matched statin nonusers alone to compare the primary and secondary prespecified cardiovascular outcomes across polygenic risk score groups. The low polygenic risk score group served as the reference. Second, Cox proportional hazards regression was used for statin effectiveness to compare the risk of each outcome between statin users and matched nonusers. Statin effectiveness for each outcome was determined overall, within polygenic risk score groups, and within 10-year ASCVD risk groups (using the Pooled Cohort Equations).[26]

We conducted a secondary analysis to again investigate the risk of incident myocardial infarction across polygenic risk score groups in statin nonusers alone; however, in this case, we accounted for sample size differences between self-identified White participants and each of the other race/ethnicity groups (the sample size of other race/ethnicity groups that met the criteria for study inclusion were significantly smaller than White participants) as described in the Supplementary Methods. The purpose of this analysis was to determine if sample size alone explains the differences in the association between polygenic risk and incident myocardial infarction across race/ethnicity groups. The purpose of this analysis was not to treat the findings in the White participants as the reference.

All analyses were conducted using R software (R Foundation for Statistical Computing, version 3.5.1, https://www.R-project.org/; Vienna, Austria).

RESULTS

Clinical characteristics and statin effectiveness in self-identified White participants

There were 10,912 self-identified White statin users who met the criteria for study inclusion. Clinical characteristics were similar between statin users and matched nonusers (Table S2) at time of index. This includes factors that were not matched for, including 10-year ASCVD risk (mean risk was 13.5% (median 11.8%) and 13.2% (median 10.4%) in statin users and nonusers, respectively) and body mass index (median body mass index was 27.5 and 26.5 kg/m^2 in statin users and nonusers, respectively). At a median follow-up of 8.5 years (9.3 and 8.2 years in statin users and nonusers, respectively), the primary outcome occurred 1,625 times (440 and 1,185 times in statin users and nonusers, respectively) and the secondary outcome occurred 3,406 times (978 and 2,428 times in statin users and nonusers, respectively). Statins were effective in lowering LDL-C (45% relative and 70 mg/dL absolute from index levels) compared with statin nonusers (4% relative and 4 mg/dL absolute from index levels). Statins significantly reduced the primary outcome of myocardial infarction (hazard ratio (HR) 0.54, 95% confidence interval (CI), 0.47–0.61; P = 1.7E-20; Figure S1A) and the secondary outcome of MACE (HR 0.80, 95% CI, 0.73–0.87; P = 7.0E-7; Figure S1B) compared with statin nonusers.

Polygenic risk score and cardiovascular outcomes in self-identified White participants

Clinical characteristics at index were similar in statin nonusers across polygenic risk score groups (Table 1; Table S3). Higher CHD polygenic risk was associated with higher risk of myocardial infarction (HR 1.59 per polygenic risk score standard deviation, 95% CI,

1.42–1.78; P = 2.2E-15; Figure 1) and MACE (HR 1.35 per polygenic risk score standard deviation, 95% CI, 1.25–1.46; P = 2.2E-13; Figure S2) in a linear fashion.

Statin effectiveness by 10-year ASCVD risk score group in self-identified White participants

The HR for statin effectiveness on incident myocardial infarction showed no gradient with increasing 10-year ASCVD at 0.52 (95% CI, 0.28–0.98; P = 0.04), 0.46 (95% CI, 0.25–0.83; P = 0.01), 0.58 (95% CI, 0.48–0.71; P = 2.8E-8), and 0.46 (95% CI, 0.37–0.56; P = 3.7E-14) for low, borderline, intermediate, and high ASCVD risk, respectively (Figure 2a).

Statin effectiveness by polygenic risk score group in self-identified White participants

On-treatment LDL-C and statin LDL-C lowering did not differ across polygenic risk score groups (Table 2; Table S4). Statin effectiveness for the primary outcome was largest in the high polygenic risk score group (HR 0.41, 95% CI, 0.31–0.53; P = 1.5E-11), middle in the intermediate polygenic risk score group (HR 0.56, 95% CI, 0.47–0.66; P = 8.4E-12), and smallest in the low polygenic risk score group (HR 0.67, 95% CI, 0.47–0.97; P = 0.03; P for high vs. low = 0.01; Figure 2b; Table 2; Table S4). Number-needed-to-treat to prevent the primary outcome corresponded to the pattern of statin relative risk reduction with values of 25, 41, and 84 for high, intermediate, and low polygenic risk score groups, respectively. We observed a similar stepwise gradient in statin effectiveness for MACE (P for high vs. low = 4.5E-4; Figure S3; Table 2; Table S4). Within the intermediate polygenic risk score group (quintiles 2 to 4), however, statin effectiveness did not show a clear gradient (Table S4).

Cardiovascular outcomes and statin effectiveness by polygenic risk score group in self-identified Black, Latinx, and East Asian participants

There were 270 self-identified Black statin users, 749 East Asian statin users, and 769 Latinx statin users meeting study inclusion criteria. There were not enough eligible statin users (fewer than 250) within each of the remaining race/ethnicity categories (Pacific Islander, South Asian, or Native American) for study inclusion. Mean genetic ancestry proportions by race/ethnicity are presented in Table S5. Clinical characteristics at the time of index and overall statin effectiveness results are presented in Tables S6-S8. Polygenic risk score distributions by race/ethnicity groups are shown in Figure S4.

The relationship between polygenic risk score and the primary outcome of incident myocardial infarction in statin nonusers varied by race/ethnicity: the HR for this outcome was 0.77 (95% CI, 0.32–1.85; P = 0.55) in Black participants, 2.05 (95% CI, 1.27–3.31; P = 0.003) in East Asian participants, and 1.87 (95% CI, 1.19–2.95; P = 0.007) in Latinx participants per polygenic risk score standard deviation (Figures S5-S7). Similarly, our exploratory analyses accounting for sample size differences showed that the beta (HR) characterizing the association between polygenic risk score and time-to-event for the primary outcome in statin nonusers deviated most from the mean beta of White participants in Black (−1.84 standard deviations; P = 0.03) compared with East Asian and Latinx participants (Figure S8). The standard error characterizing the association between polygenic risk score and time-to-event for the primary outcome deviated furthest from the mean standard error of White statin nonusers in Black statin nonusers (1.33

standard deviations; $P = 0.09$). For the standard error characterizing the association between polygenic risk score and time-to-event, deviation from the mean standard error in White statin nonusers was 1.16 standard deviations ($P = 0.12$) in East Asian statin nonusers and 0.64 standard deviations ($P = 0.26$) in Latinx statin nonusers (Figure S9). Accordingly with the polygenic risk score-incident myocardial infarction association, the relationship between polygenic risk score and statin effectiveness also varied by race/ethnicity (Table S9).

DISCUSSION

Previous studies have reported a strong association between CHD polygenic risk score and statin relative risk reduction of cardiovascular outcomes independent of statin-induced LDL-C lowering in primary prevention.[6,7] The polygenic risk score and its association with statin benefit was respectively generated from and studied in predominantly participants of European descent.[6,7] The current study is the first to validate these results in a real-world cohort. Furthermore, this is the first study to demonstrate attenuated statin benefit in low polygenic risk score participants. Finally, this is the first to study this relationship in participants with substantial proportions of sub-Saharan African, Native American, and East Asian ancestry.

The evidence establishing statin treatment as first-line for the prevention of myocardial infarction through randomized controlled trials are numerous, but lack diversity. For example, meta-analyses of statin trials since the 1990s reveal that <8% of composite study participants are >75 years of age[27] and only 27% are women.[28] Moreover, among prior genetic substudies of statin trials investigating CHD polygenic risk scores, the cumulative total of White participants is >97%. On the other hand, with 57% women, 34% >75 years of age (at some point during follow-up), and 14% participation from individuals who do not identify as White, the current study population has substantially more diversity than those from statin randomized controlled trials. Thus, our findings may have more transferability to the full population of patients eligible for statin therapy in the United States.

In our self-identified White participants, over a median follow-up of ~ 8.5 years, we generated a statin response phenotype of 46% relative risk reduction for the primary outcome with a net mean LDL-C lowering effect of 66 mg/dL compared with the statin nonusers. Furthermore, we showed that this statin effect does not vary across guideline-based 10-year ASCVD risk score groups. These results are consistent with findings from meta-analyses of statin randomized controlled trials, which reported a ~ 23% relative risk reduction (in 5-year incidence of a major coronary event) for every 1 mmol/L (39 mg/dL) of statin-induced LDL-C lowering and demonstrated that this statin risk reduction–cholesterol lowering relationship is not modified by traditional ASCVD risk factors.[1] Our replication of these well-established statin effects illustrate the robustness of our phenotype as we moved forward in interrogating the impact of the CHD polygenic risk score.

We found that participants within the highest quintile of polygenic risk for CHD had a more than twofold increased chance of incident myocardial infarction compared with the lowest quintile when not receiving statin therapy and an enhanced statin benefit (59% relative risk reduction for incident myocardial infarction) when receiving therapy. Genetic substudies

of prior primary prevention randomized controlled trials also demonstrate high baseline CHD risk and enhanced statin CHD relative risk reduction in the highest CHD polygenic risk score group (Table 3).[6,7,29] For example, in a *post hoc* meta-analysis of two statin primary prevention trials, top quintile polygenic risk participants had enhanced CHD risk (1.72-fold among placebo-treated participants) and statin efficacy (50% statin relative risk reduction) compared with the lowest quintile.[7] Thus, our findings suggest that data from prior randomized controlled trials can be extrapolated to patients undergoing routine care.

Participants in the lowest CHD polygenic risk score quintile received an attenuated statin relative risk reduction (33%). This was found to be a weaker statin effect than for participants from the intermediate (44% risk reduction) and high (59% risk reduction) polygenic risk score groups; these differences were observed despite an overall pretreatment risk profile (12% median 10-year ASCVD risk) and statin LDL-C response (45% lowering from baseline) that did not differ by genetic background. In contrast, prior genetic randomized controlled trial substudies in primary prevention populations did not find attenuated statin efficacy in the low polygenic risk score group compared with intermediate polygenic risk (Table 3). For example, in a *post hoc* analysis of the JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) trial, both low and intermediate polygenic risk participants experienced a statin relative risk reduction of 32% compared with placebo.[7] Larger sample size and longer follow-up in the current study may have facilitated our elucidation of this association. Indeed, our sample size of 32,736 self-identified White, primary prevention participants is larger than the combined population of previous randomized controlled trial genetic substudies investigating this topic. Additionally, the present real-world population may be more heterogenous (considering the strict inclusion/exclusion criteria of randomized controlled trials), increasing the possibility of detecting this difference. For instance, elevated C-reactive protein and low LDL-C (< 130 mg/dL) was required for enrollment in JUPITER,[7] narrowing the generalizability of results from that genetic substudy. Overall, further studies are necessary to confirm this novel finding of the current study.

If replicated, the current results extend these prior data by demonstrating an additional potential clinical use of polygenic risk scores: to identify patients for whom statin therapy may not offer sufficient cardiovascular benefit relative to potential harm (e.g., an individual with borderline ASCVD risk, high likelihood of a statin-induced adverse drug reaction, and low CHD polygenic risk score). The benefits of deprescribing (or never initiating) regardless of drug—in populations vulnerable to the impact of polypharmacy—continue to gain traction.[30] Thus, there is a need for precision medicine tools that can optimize the risk and benefit of therapies. However, the current evidence must be interpreted with caution and followed up with future investigations before translation to the bedside.

We found variation in the relationship between polygenic risk score and both cardiovascular outcomes (statin nonusers alone) as well as statin risk relative reduction (statin users and nonusers) across populations. Unsurprisingly, the association between the CHD polygenic risk (derived from participants of European ancestry) and cardiovascular outcomes was strongest (i.e., smallest *P* value) in our White participants. We conducted bootstrap analyses to determine the role of sample size in this observation: we measured the deviation

among the other race/ethnicity groups from a distribution of parameters (betas and standard errors) characterizing the association between polygenic risk score and incident myocardial infarction in White participants (mean European ancestry of 96.5%). Our results show that even after accounting for sample size differences, deviation existed in parameters characterizing the polygenic risk score-incident myocardial infarction relationship from White participants. This is congruent with prior data showing that polygenic risk scores may be most precise in the populations from which they were derived.[31] Thus, it is of no surprise that the observed point estimates for statin relative risk reduction within each polygenic risk score group were also not consistent across populations.

Study limitations

First, to characterize our study population and determine cardiovascular outcomes we relied on International Classification of Diseases (ICD) codes, which are not always accurate. However, using ICD codes to classify myocardial infarction generally yields positive predictive values >90%.[32] Furthermore, we used an algorithm for diabetes that had been previously validated.[33]

Second, another potential reason for discrepant results from prior studies is the differing number of variants in each polygenic risk score used (Table 3). However, the polygenic risk scores from each of the studies including the current study are from the same data source (CARDIoGRAMplusC4D) and only differ in number of variants because the sample size has gotten larger over time (each subsequent polygenic risk score contains the variants from the previous scores).[18] Furthermore, a prior study investigating multiple CHD polygenic risk scores determined that across the full range of scores ranging from < 100 all the way to >6 million, there was only a 2% difference in strength of association between the least and most predictive score.[34] Thus, the differing number of variants in each polygenic risk score is unlikely to have impacted results.

Third, these analyses in diverse populations are underpowered and exploratory in nature, but results may underscore the need for ancestry-specific or trans-ancestry CHD polygenic risk scores (e.g., not derived only from participants of predominantly European ancestry) to advance statin precision medicine; efforts to generate CHD polygenic risk scores for minoritized populations are ongoing.[35] The majority of human genomic research has been conducted in participants of European descent despite making up a relatively smaller proportion of the global population.[31] There is a moral imperative to advance genomic studies in historically excluded populations. Thus, although limited in sample numbers, our data in participants from underrepresented populations provide a much-needed foundation for future larger studies investigating this topic in statin users.

CONCLUSION

In a large cohort of primary prevention patients undergoing routine care, CHD polygenic risk modified the effectiveness of statin therapy. Our findings (i) extend prior work by identifying a subset of patients (i.e., self-identified White individuals with low CHD polygenic risk scores) receiving attenuated clinical benefit from statins and (ii) confirm results from genetic substudies of randomized controlled trials in high polygenic risk

individuals, who receive enhanced statin benefit. More research is needed in larger, diverse cohorts to ensure that advances in polygenic risk scores will improve the health of all populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Recent genetic substudies of statin randomized controlled trials have demonstrated that high coronary heart disease (CHD) polygenic risk is associated with a greater statin benefit compared with low and intermediate risk independent of statin-induced low-density lipoprotein cholesterol lowering and traditional atherosclerotic cardiovascular disease (ASCVD) risk factors.

WHAT QUESTION DID THIS STUDY ADDRESS?

The primary objective of this study was to validate that this previously established CHD polygenic risk score modifies statin CHD risk reduction in a cohort of real-world, primary prevention participants.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Our findings confirm enhanced statin benefit in high polygenic risk score patients, but also identifies a subset of patients less likely to receive clinical benefit from statins.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Our results add to the current evidence base rationalizing CHD polygenic risk scores as a precision medicine tool to further optimize risk and benefit of statin therapy in combination with traditional ASCVD risk factors.

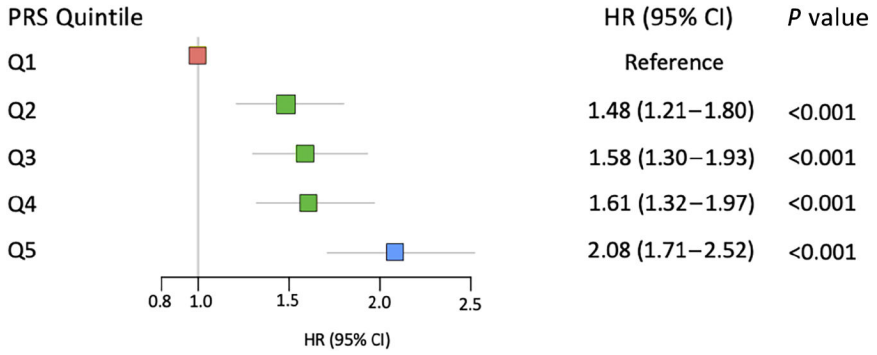

Figure 1.

Risk of incident myocardial infarction across coronary heart disease polygenic risk score quintiles in self-identified White statin nonusers. Higher polygenic risk score was associated with an increasing risk gradient for incident myocardial infarction across low (quintile 1), intermediate (quintiles 2–4), and high (quintile 5) polygenic risk score groups. CI, confidence interval; HR, hazard ratio; PRS, polygenic risk score.

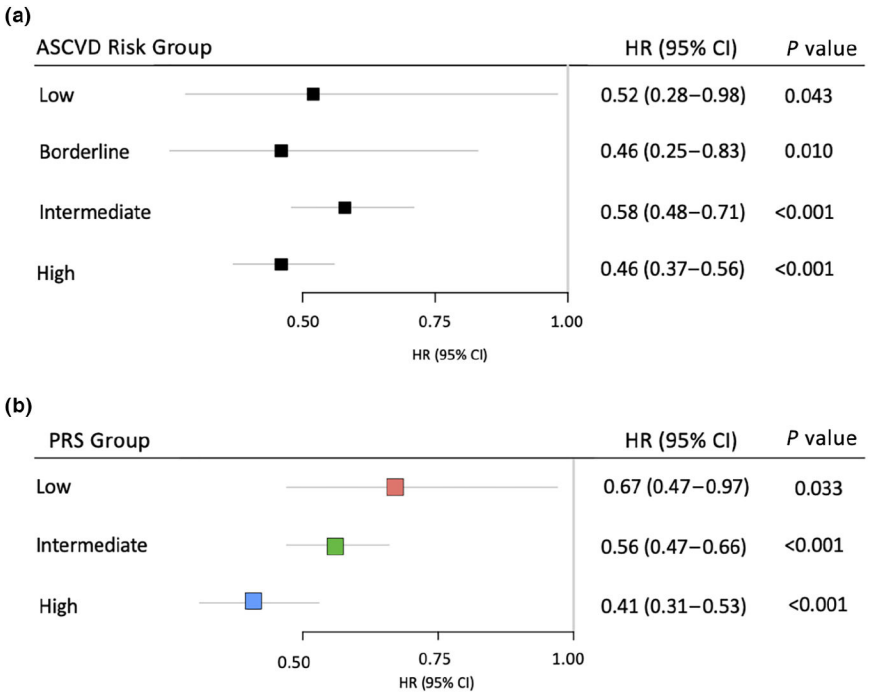

Figure 2.

Statin effectiveness on incident myocardial infarction in self-identified White participants. (**a**) Statin effectiveness did not show a strong relationship with increasing 10-year Pooled Cohort Equations ASCVD risk score groups in self-identified White participants. (**b**) In contrast, the magnitude of statin effectiveness in these same participants became progressively stronger across low (quintile 1), intermediate (quintiles 2–4), and high (quintile 5) polygenic risk score groups with smallest statin benefit in the low polygenic risk score group and largest benefit in the high polygenic risk score group (P for high vs. low = 0.01). ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; HR, hazard ratio; PRS, polygenic risk score.

Table 1

Clinical characteristics at index date across coronary heart disease polygenic risk score groups[a]

	Low PRS (*n* = 4,672)	Intermediate[b] PRS (*n* = 13,140)	High PRS (*n* = 4,012)	*P* value
Age, years	63.6 (12.0)	62.9 (12.3)	62.4 (12.6)	<0.001
Female	56.0%	56.7%	57.0%	0.619
BMI[c], kg/m^2	26.8 (5.9)	26.5 (5.9)	26.4 (5.6)	0.004
Current or former cigarette use	47.0%	46.3%	44.4%	0.040
Diabetes mellitus	1.4%	1.6%	1.8%	0.322
Hypertension	46.1%	47.6%	49.1%	0.020
ASCVD Risk score[d], %	10.5 (12.4)	10.5 (12.8)	9.8 (12.7)	0.067
Lipid panel[c], mg/dL				
TC	200 (43)	203 (43)	203 (43)	<0.001
LDL-C	118 (36)	120 (36)	121 (36)	<0.001
HDL-C	57 (23)	56 (23)	56 (24)	0.073
TG	102 (69)	103 (71)	103 (72)	0.023

Data presented as median (interquartile range) or percentage. One-way analysis of variance across the polygenic risk score group was performed for continuous variables and χ^2 test was performed for categorical variables.

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PRS, polygenic risk score; TC, total cholesterol; TG, triglycerides.

[a]For the analyses of self-identified White statin nonusers.

[b]Intermediate polygenic risk score group defined as polygenic risk score quintiles 2–4.

[c]Lipid panel and BMI based upon measurements on or before index date.

[d]ASCVD Risk score calculated using Pooled Cohort's Equation, which estimates 10-year percent risk of first ASCVD event.[36]

Table 2

Statin effectiveness on incident myocardial infarction and major adverse cardiovascular events[a] across coronary heart disease polygenic risk score groups[e]

	Statin nonusers			Statin users			Statin effectiveness					
PRS group	*N*	Events	Event risk	*N*	Events	Event Risk	On-treatment LDL-C, mg/dL, median (IQR)	Absolute LDL-C reduction, mg/dL, median (IQR)	HR (95% CI)[b]	RRR[c]	ARR	NNT
MI												
Low	4,672	171	3.7%	1,876	55	2.9%	86 (30.5)	69 (38)	0.67 (0.47–0.97)	32.6%	1.19%	84
Intermediate[d]	13,140	734	5.6%	6,501	266	4.1%	87 (31)	70 (39)	0.56 (0.47–0.66)	43.9%	2.45%	41
High	4,012	280	7.0%	2,535	119	4.7%	89 (32)	70 (39)	0.41 (0.31–0.53)	59.2%	4.13%	25
MACE												
Low	4,727	430	9.1%	1,910	145	7.6%	87 (30)	68 (38)	0.97 (0.77–1.22)	2.8%	0.26%	387
Intermediate[d]	13,321	1,467	11%	6,588	583	8.8%	88 (30)	70 (39)	0.84 (0.75–0.94)	16.4%	1.81%	56
High	4,074	531	13%	2,563	250	9.7%	89 (32)	70 (39)	0.59 (0.49–0.71)	40.7%	5.31%	19

ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events, MI, myocardial infarction; NNT, number needed to treat; PRS, polygenic risk score; RRR, relative risk reduction.

[a]Major adverse cardiovascular events included myocardial infarction (fatal + nonfatal), ischemic stroke (fatal + nonfatal), and other cardiovascular death.

[b]Time-to-incident myocardial infarction in statin users vs. nonusers with age, sex, low-density lipoprotein cholesterol, diabetes, hypertension, and cigarette smoking included as covariates.

[c]RRR calculated as (1-HR) × 100.

[d]Intermediate polygenic risk score group defined as polygenic risk score quintiles 2–4.

[e]For analyses in self-identified White participants.

Table 3

Statin benefit for coronary events in primary prevention studies across low, intermediate, and high PRS groups[a]

	Data source	Total sample size	Number of variants in PRS score	Low PRS		Intermediate PRS		High PRS	
				HR[b]	95% CI	HR[b]	95% CI	HR[b]	95% CI
Mega *et al.*[7]	JUPITER	8,769	27	0.68	0.26, 1.78	0.68	0.42, 1.10	0.41	0.16, 0.91
	ASCOT-LLA	6,978	27	0.64	0.26, 1.56	0.68	0.44, 1.04	0.54	0.29, 0.94
Natarajan *et al.*[6]	WOSCOPS	4,892	57	0.65	0.44, 0.97	0.76	0.63, 0.92	0.56	0.40, 0.78
Current study	GERA	32,736	164	0.67	0.47, 0.97	0.56	0.47, 0.66	0.41	0.31, 0.53

ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm; CI, confidence interval; GERA, Genetic Epidemiology Research on Adult Health; HR, hazard ratio; JUPITER, Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin; PRS, polygenic risk score; WOSCOPS, West of Scotland Coronary Prevention Study.

[a]Low, intermediate, and high PRS groups correspond to quintile 1, quintiles 2–4, and quintile 5, respectively.

[b]Hazard ratio of statin relative risk reduction for incident coronary heart disease events following covariate adjustment (covariates for the current study: age, sex, low-density lipoprotein cholesterol, diabetes, hypertension, and cigarette smoking).