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ORIGINAL ARTICLE

Polygenic Hyperlipidemias and Coronary Artery Disease Risk

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BACKGROUND: Hyperlipidemia is a highly heritable risk factor for coronary artery disease (CAD). While monogenic familial hypercholesterolemia associates with severely increased CAD risk, it remains less clear to what extent a high polygenic load of a large number of LDL (low-density lipoprotein) cholesterol (LDL-C) or triglyceride (TG)-increasing variants associates with increased CAD risk.

METHODS: We derived polygenic risk scores (PRSs) with ≈6M variants separately for LDL-C and TG with weights from a UK Biobank–based genome-wide association study with ≈324K samples. We evaluated the impact of polygenic hypercholesterolemia and hypertriglyceridemia to lipid levels in 27 039 individuals from the National FINRISK Study (FINRISK) cohort and to CAD risk in 135 638 individuals (13 753 CAD cases) from the FinnGen project (FinnGen).

RESULTS: In FINRISK, median LDL-C was 3.39 (95% CI, 3.38–3.40) mmol/L, and it ranged from 2.87 (95% CI, 2.82–2.94) to 3.78 (95% CI, 3.71–3.83) mmol/L between the lowest and highest 5% of the LDL-C PRS distribution. Median TG was 1.19 (95% CI, 1.18–1.20) mmol/L, ranging from 0.97 (95% CI, 0.94–1.00) to 1.55 (95% CI, 1.48–1.61) mmol/L with the TG PRS. In FinnGen, comparing the highest 5% of the PRS to the lowest 95%, CAD odds ratio was 1.36 (95% CI, 1.24–1.49) for the LDL-C PRS and 1.31 (95% CI, 1.19–1.43) for the TG PRS. These estimates were only slightly attenuated when adjusting for a CAD PRS (odds ratio, 1.26 [95% CI, 1.16–1.38] for LDL-C and 1.24 [95% CI, 1.13–1.36] for TG PRS).

CONCLUSIONS: The CAD risk associated with a high polygenic load for lipid-increasing variants was proportional to their impact on lipid levels and partially overlapping with a CAD PRS. In contrast with a PRS for CAD, the lipid PRSs point to known and directly modifiable risk factors providing additional guidance for clinical translation.

Key Words: coronary artery disease ■ humans ■ hypercholesterolemia ■ hypertriglyceridemia ■ risk factors

Hypercholesterolemia, particularly high LDL (low-density lipoprotein) cholesterol (LDL-C), is an established, heritable, and treatable risk factor for coronary artery disease (CAD).[1,2] Additionally, accumulating evidence suggests that increased triglycerides (TGs; hypertriglyceridemia) are causally linked to CAD.[3–5]

Increased levels of both LDL-C and TGs result from a combination of genetic and nongenetic factors.[6,7] Genetic factors include rare highly penetrant variants and a long tail of common variants with smaller effect sizes. While pathogenic variants in the *LDLR*, *PCSK9*, and *APOB* genes cause familial hypercholesterolemia, it has also been suggested that similarly high LDL-C levels could result from a high polygenic burden of LDL-C–increasing variants.[8,9] Monogenic familial hypercholesterolemia with an identified mutation associates with

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†A list of all FinnGen study participants is given in the Data Supplement.

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Nonstandard Abbreviations and Acronyms

CAD	coronary artery disease
HDL	high-density lipoprotein
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
OR	odds ratio
PRS	polygenic risk score
TG	triglyceride

a higher CAD risk than expected on the basis of a single LDL-C measurement.[10] While previous studies have linked a handful of common variants to both increased LDL-C and CAD risk, the contribution of an accumulation of a large number of LDL-C–increasing alleles to CAD risk has remained unknown.[11]

Similarly to hypercholesterolemia, both polygenic burden and highly penetrant variants contribute to hypertriglyceridemia.[6] However, highly penetrant variants underlying hypertriglyceridemia are much fewer and rare (estimated population prevalence, 1:1 000 000).[6] On the contrary, many individuals with hypertriglyceridemia have a high polygenic burden of TG-increasing variants.[6] Unlike LDL-C, it is unknown whether genetically increased TGs confer higher CAD risk than nongenetic hypertriglyceridemia. Genetics supporting a causal link between hypertriglyceridemia and CAD, and the evidence for beneficial therapeutic reducing of TGs to reduce cardiovascular disease risk, however, highlight the potential also for association between polygenic load of TG elevating alleles and CAD risk.[3–5,12,13]

In this cohort study of 27 039 individuals from the Finnish National FINRISK Study (FINRISK) population cohort with lipid measurements, and 135 638 individuals including 13 753 CAD cases from the FinnGen project (FinnGen), we evaluated the impact of high polygenic LDL-C and TG to CAD risk. We developed separate genome-wide polygenic risk scores (PRSs) for both LDL-C and TG to define polygenic hypercholesterolemia and hypertriglyceridemia. First, we tested to what extent PRSs for LDL-C and TG associate with measured lipid levels. Second, we tested to what degree polygenic hypercholesterolemia and polygenic hypertriglyceridemia associate with increased risk for CAD.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be submitted through the Finnish Biobanks' FinnBB portal (https://finbb.fi/) for FinnGen at https://www.ukbiobank.ac.uk/researchers/ for the UK Biobank (UKBB) and at https://www.thl.fi/biobank/researchers for the GeneRISK study (GeneRISK) and FINRISK.

The Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District approved the FinnGen project (No. HUS/990/2017), the GeneRISK study, and the 2007 and 2012 FINRISK surveys. Earlier FINRISK surveys were approved by various ethics committees.[14] The North West Multi-Centre Research Ethics Committee approved the UKBB study. Written informed consent was obtained from all participants except the 1992 FINRISK survey, for which verbal informed consent was obtained as required by legislation and ethics committees at the time.

The full Methods are available as the Data Supplement.

Table 1. Clinical and Metabolic Characteristics of Individuals

	FINRISK		FinnGen	
Characteristics	n	Mean±SD	n	Mean±SD
n (men/women)	27 039 (12 884/14 155)		135 638 (59 252/76 386)	
CAD, n (%)	2750 (10.2%)		13 753 (10.1%)	
Lipid-lowering medication usage, n (%)	1658 (6.1%)		42 193 (31.1%)	
Smoking, n (%)	6739 (25%)		19 690 (22.1%)	
Age,* y	27 039	48.9±13.5	135 638	60.6±16.5
BMI, kg/m^2	26 941	26.8±4.69	95 528	27.2±5.6
Total cholesterol, mmol/L	27 024	5.49±1.08		
LDL-C, mmol/L	26 568	3.47±1.01		
Triglyceride, mmol/L	27 024	1.47±1.00		
HDL-C, mmol/L	27 024	1.44±0.381		
Apolipoprotein B, g/L	22 464	0.965±0.248		
Non–HDL-C, mmol/L	27 024	4.05±1.10		
Remnant-C, mmol/L	26 568	0.630±0.340		

LDL-C was calculated using the Friedewald formula; the effect of lipid-lowering therapy in those using medication at the time of lipid measurement was adjusted for by dividing LDL-C by 0.7 as utilized previously.[10] FinnGen lacks lipid measurements and lipid-lowering medication usage information. BMI indicates body mass index; CAD, coronary artery disease; FinnGen, The FinnGen project; FINRISK, The National FINRISK Study; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and Remnant-C, remnant cholesterol.

*Age at recruitment for FINRISK and age at end of follow-up for FinnGen.

RESULTS

Polygenic Hyperlipidemias and Lipid Levels

We tested the association between PRSs for LDL-C and TG derived from a genome-wide association study of lipid measurements in the UKBB and lipid levels in the Finnish FINRISK study. FINRISK comprises 27 039 individuals randomly drawn from the Finnish population (Table 1). Median LDL-C was 3.39 (95% CI, 3.38–3.40) mmol/L and TG, 1.19 (95% CI, 1.18–1.20) mmol/L in the whole cohort with slightly lower values in the more recent collections (Figure I in the Data Supplement).

The PRSs consisted of 6 million markers and explained 5.4% (adjusted r^2) of variation in LDL-C and 5.1% in TG. In FINRISK, median LDL-C was 2.87 (95% CI, 2.82–2.94) mmol/L in the lowest and 3.78 (95% CI, 3.71–3.83) mmol/L in the highest 5% of the LDL-C PRS distribution (Figure 1A). Similarly, median TG was 0.97 (95% CI, 0.94–1.00) mmol/L in the lowest and 1.55 (95% CI, 1.48–1.61) mmol/L in the highest 5% of the TG PRS distribution (Figure 1B). The increases in LDL-C and TG levels were similar in all FINRISK subcollections (Figure II in the Data Supplement). The correlation between the LDL-C PRS and the TG PRS was low (r=0.15). Subsequently, the cross-trait pleiotropy between the LDL-C and TG PRSs was small as the LDL-C PRS explained 0.7% (adjusted r^2) of TG levels and the TG PRS 0.3% of LDL-C levels (Figure III in the

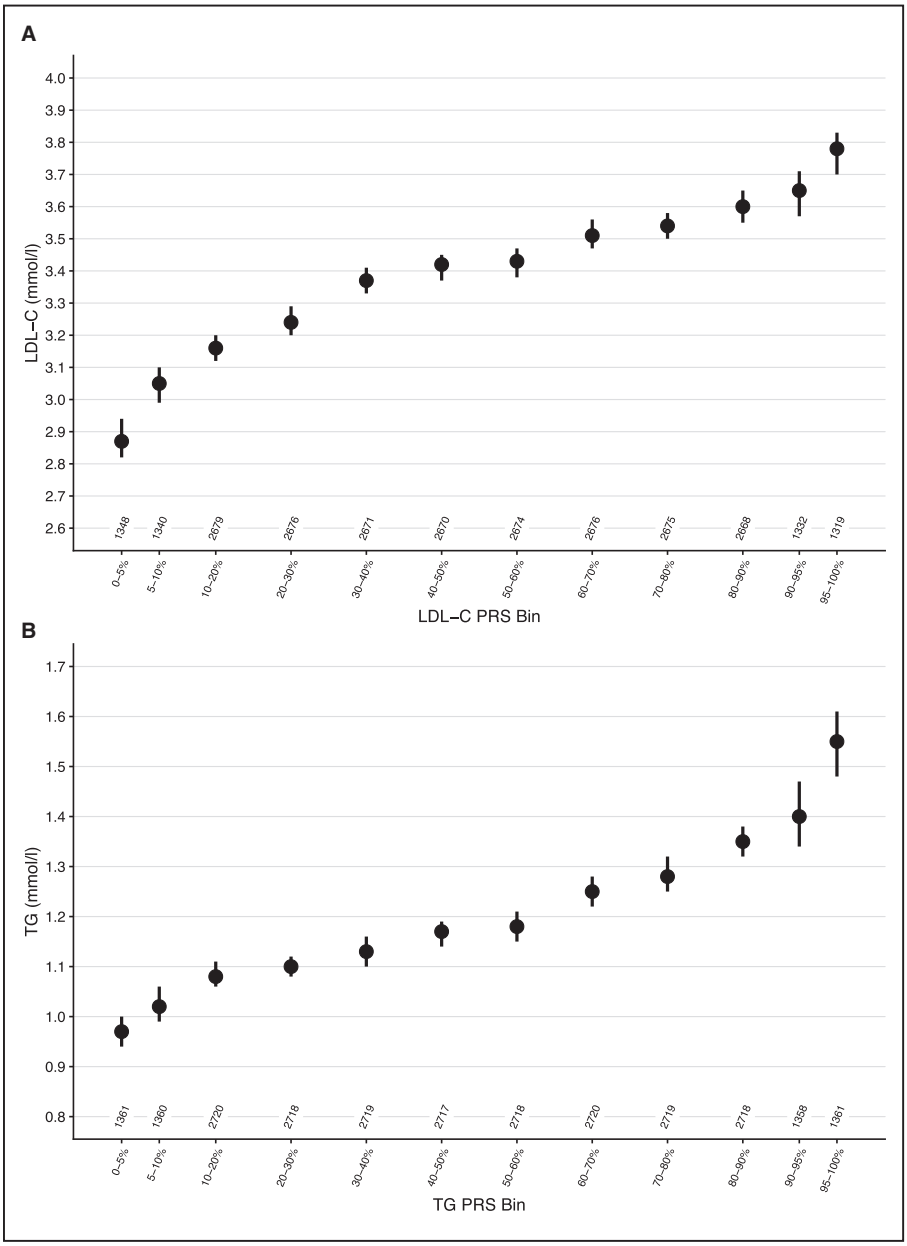

Figure 1. Median lipid levels across the distributions of the lipid polygenic risk scores (PRSs) in the National FINRISK Study (FINRISK) cohort. Numbers of individuals in the PRS bins are reported. Vertical lines represent 95% CIs.

Data Supplement). All in all, the LDL-C and TG PRSs had a clear impact on their respective lipid levels.

Polygenic Hyperlipidemias and CAD Risk

To assess how polygenic hyperlipidemia associates with CAD risk, we analyzed 135 638 individuals including 13 753 registry-based CAD cases from the Finnish FinnGen project (Table 1). FinnGen is an aggregation of Finnish prospective epidemiological and disease-based cohorts and hospital biobank samples and, therefore, includes the FINRISK participants. Polygenic hypercholesterolemia associated with increased CAD risk. Compared with the remainder of the population, individuals with the LDL-C PRS in the highest 10% had 1.4-fold increased CAD risk (odds ratio [OR], 1.41 [95% CI, 1.32–1.50]), and individuals in the highest 5% also had 1.4-fold increased risk (OR, 1.36 [95% CI, 1.24–1.49]; Figure 2A). CAD prevalence was 52% higher (12.5% versus 8.2%) between the highest and the lowest 5% of the LDL-C PRS distribution (Figure 3A). OR for CAD per SD unit increase of the LDL-C PRS was 1.17 (95% CI, 1.15–1.20; Table 2).

For polygenic hypertriglyceridemia, compared with the remainder of the population, individuals with the TG PRS in the highest 10% had 1.3-fold increased CAD risk, and individuals in the highest 5% also 1.3-fold (OR, 1.31 [95% CI, 1.19–1.43]) increased CAD risk (OR, 1.31 [95% CI, 1.22–1.40]; Figure 2B). CAD prevalence was 36% higher (11.8% versus 8.7%) between the highest and the lowest 5% of the TG PRS distribution (Figure 3B). OR for CAD per SD unit increase of the TG PRS was 1.12 (95% CI, 1.09–1.14; Table 2).

We tested whether the lipid PRSs improve CAD risk prediction beyond a similarly derived CAD PRS. Comparing the highest 5% to the remainder of the population, the effects of the lipid PRSs on CAD risk were attenuated only modestly when adjusted for the CAD PRS (LDL-C PRS OR, 1.26 [95% CI, 1.16–1.38] and TG PRS OR, 1.24 [95% CI, 1.13–1.36]; Figure 4). The area under the receiver operating characteristic curve of a model with the lipid and CAD PRSs was high (0.879; Table 2). It was, however, similar to a model with only the CAD PRS (0.879; Table 2).

DISCUSSION

By developing genome-wide PRSs for LDL-C and TG, we evaluated the impact of high genetic risk for these established and causal risk factors of CAD. We showed that high polygenic burden for both LDL-C or TG associated with considerably increased LDL-C and TG levels, respectively. Similarly, polygenic hypercholesterolemia and triglyceridemia associated with significantly increased CAD risk. Furthermore, PRSs for LDL-C and TG were partially overlapping with a PRS for CAD.

Polygenic hypercholesterolemia, in our study, conveyed 0.41 mmol/L higher LDL-C levels and 36% higher

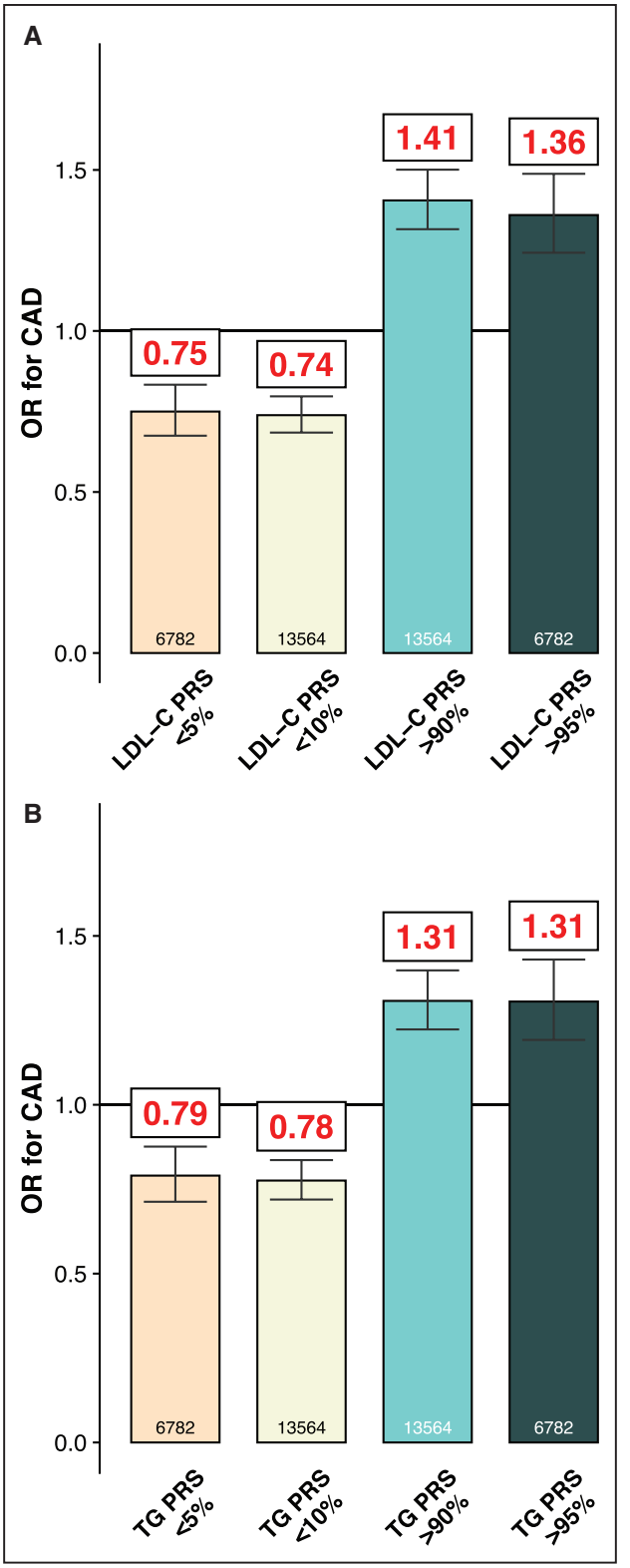

Figure 2. Odds ratios (ORs) for coronary artery disease (CAD) across the lipid polygenic risk score (PRS) distributions in the FinnGen project (FinnGen).

Total numbers of individuals in PRS bins are reported. ORs were estimated using logistic regression adjusted for age, sex, first 10 principal components, and genotyping batch. PRS bins were compared with the remainder of the population. Error bars represent 95% CIs.

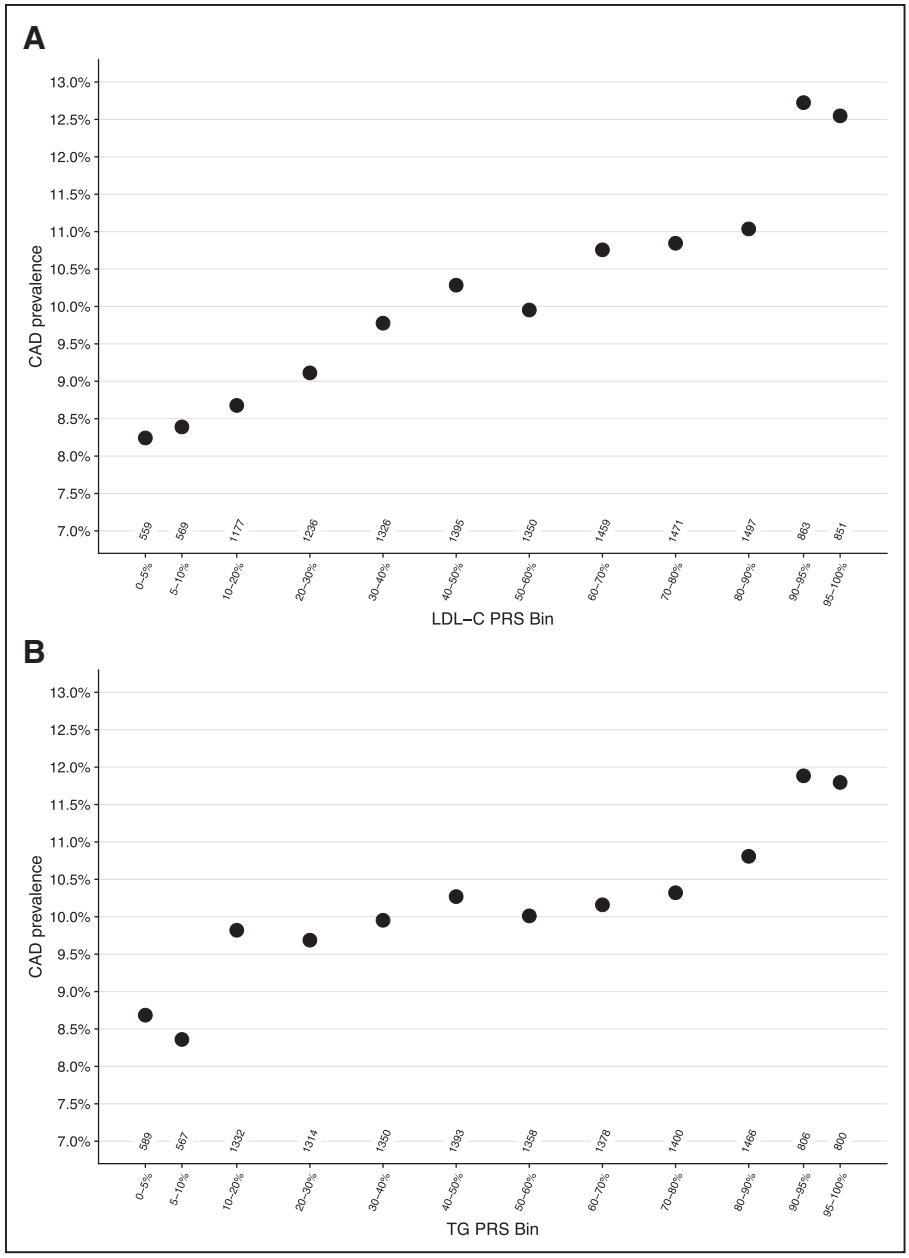

Figure 3. Coronary artery disease (CAD) prevalence across the lipid polygenic risk score (PRS) distributions in the FinnGen project (FinnGen).
Numbers of CAD cases in PRS bins are reported.

CAD risk in the highest 5% of the LDL-C PRS compared with the remainder of the population. This is considerably lower than the previous estimates of the effects of high-impact *LDLR* familial hypercholesterolemia mutation on LDL-C levels (2–3 mmol/L) and CAD risk (2.6- to 3.7-fold).[10,15,16] Going further from the highest 5% to the highest 1% of the LDL-C PRS conveyed still only 0.55 mmol/L higher LDL-C levels compared with the remainder of the population (Figure IV in the Data Supplement). While the established high-impact *LDLR* familial hypercholesterolemia mutations directly disrupt LDL receptor function causing lifelong high LDL-C levels, the effect sizes of the individual variants contributing to polygenic hypercholesterolemia are small, and they likely increase LDL-C via multiple indirect biological pathways. Whereas monogenic familial hypercholesterolemia is a severe disease with high CAD risk, polygenic hypercholesterolemia, as captured by the current PRSs, seems to have a smaller effect on LDL-C levels and CAD risk. The degree of benefit of lipid-lowering therapies in individuals with polygenic hypercholesterolemia has, therefore, remained largely unknown.

In our study, both LDL-C and TG PRSs associated with CAD risk also when adjusted for a CAD PRS. The key difference between intermediate biomarker PRSs (such as the lipid PRSs) and disease end point PRSs (such as a CAD PRS) is that biomarker PRSs have a more direct mechanism and effect on clinical outcomes. The CAD PRS was based on a case-control setting of individuals with or without a CAD diagnosis with a risk

Table 2. CAD Prediction With Lipid and CAD PRSs

Predictors	AUC Unadjusted	AUC Baseline	AUC Full	OR (95% CI) Full	*P* Value
PRS_{LDL-C}	0.758	0.874	0.875	1.17 (1.15–1.20)	$<2\times10^{-16}$
PRS_{TG}	0.757	0.874	0.875	1.12 (1.09–1.14)	$<2\times10^{-16}$
PRS_{CAD}	0.767	0.874	0.879	1.43 (1.40–1.46)	$<2\times10^{-16}$
PRS_{CAD}+PRS_{LDL-C}	0.769	0.874	0.879		
PRS_{CAD}				1.41 (1.38–1.44)	$<2\times10^{-16}$
PRS_{LDL-C}				1.13 (1.11–1.16)	$<2\times10^{-16}$
PRS_{CAD}+PRS_{TG}	0.768	0.874	0.879		
PRS_{CAD}				1.42 (1.39–1.45)	$<2\times10^{-16}$
PRS_{TG}				1.09 (1.07–1.12)	1.29×10^{-15}
PRS_{CAD}+PRS_{LDL-C}+PRS_{TG}	0.769	0.874	0.879		
PRS_{CAD}				1.41 (1.37–1.44)	$<2\times10^{-16}$
PRS_{LDL-C}				1.11 (1.09–1.14)	$<2\times10^{-16}$
PRS_{TG}				1.06 (1.03–1.08)	2.49×10^{-6}

ORs and AUCs for CAD with continuous LDL-C, TG, and CAD PRSs as predictors estimated using logistic regression. Unadjusted refers to a model with the PRSs as predictors, baseline to a model with age and sex as predictors, and full to a model with PRSs as predictors adjusted for age and sex. All models also include the technical covariates (first ten principal components and genotyping batch). AUC indicates area under the receiver operating characteristic curve; CAD, coronary artery disease; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; PRS, polygenic risk score; and TG, triglycerides.

of misclassifications and correlates little with known risk factors, complicating its interpretation and clinical implications.[17] As the genome remains constant throughout life, unlike measured individual lipid values, PRSs are independent of age, medical conditions, medication usage, diet, fasting state, and other constantly changing confounding factors.

Our study has several limitations. First, as FINRISK participants fasted for a minimum of 4 hours before measuring lipid profiles, our association estimates may have been attenuated particularly between the TG PRS and TG levels. The association between the TG PRS and CAD risk, however, remains unaffected by this. Second, because the Friedewald formula is invalid for individuals with TG >4.52 mmol/L, 456 (1.7%) FINRISK samples were excluded from LDL-C analyses.[18] Third, some variants included in the lipid PRSs are not specific to their primary lipids and have residual effects on others. Excepting a negative association between the TG PRSs and HDL (high-density lipoprotein) cholesterol, however, the PRSs had only minor associations with other than their primary lipids (Figure III in the Data Supplement). Fourth, our weights for the lipid PRSs came from the UK population and were tested in the Finnish population; our results may have limited accuracy in other ethnicities. Replication and validation in other cohorts with lipid measurements and populations is warranted in the future.

In summary, the CAD risk associated with a high polygenic load for LDL-C or TG -increasing genetic variants was proportional to their impact on lipid levels. In contrast with a PRS for CAD, the lipid PRSs point to a known and directly modifiable risk factor enabling more straightforward clinical translation. As PRSs can also be measured at any point in life, they provide powerful tools for prioritizing individuals for blood lipid panel screening and subsequent evidence-based intervention.

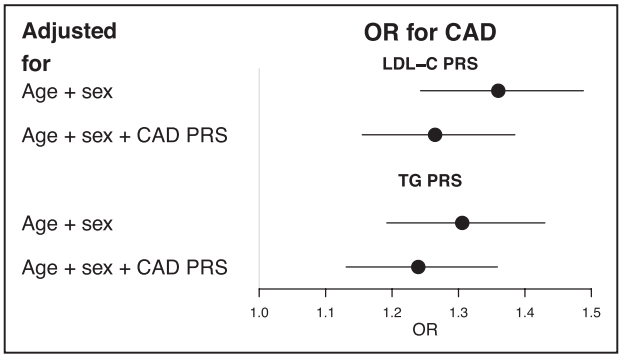

Figure 4. Odds ratios (ORs) for coronary artery disease (CAD) for those in the highest 5% of the polygenic risk scores (PRSs) compared with the remainder of the population with and without adjusting for the CAD PRS in the FinnGen project (FinnGen).
ORs were estimated using logistic regression. All models were additionally adjusted for age and sex. Horizontal lines represent 95% CIs. LDL-C indicates low-density lipoprotein cholesterol; and TG, triglyceride.

ARTICLE INFORMATION

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Disclosures

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