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ORIGINAL RESEARCH

GENETICS, OMICS, AND TISSUE REGENERATION

Polygenic Background Modifies Risk of Coronary Artery Disease Among Individuals With Heterozygous Familial Hypercholesterolemia

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ABSTRACT

BACKGROUND Heterozygous familial hypercholesterolemia (HeFH) is a monogenic disorder characterized by increased circulating low-density lipoprotein cholesterol and accelerated atherosclerosis. Even among this high-risk group, prior studies note considerable variability in risk of coronary artery disease (CAD).

OBJECTIVES The purpose of this study was to evaluate the cumulative impact of many common DNA variants—as quantified by a polygenic score—on incident CAD among individuals carrying a HeFH variant.

METHODS We analyzed data from a prospective cohort study of 1,315 individuals who carried a HeFH variant and 1,315 matched family noncarriers derived from a nationwide screening program in the Netherlands, with subsequent replication in 151,009 participants of the UK Biobank.

RESULTS Despite identification and lipid management within the Dutch screening program, 84 (6.4%) of HeFH variant carriers developed CAD as compared to 45 (3.4%) of matched family members (median follow-up 10.2 years, HR 1.88, 95% CI: 1.31-2.70). Among HeFH variant carriers, a polygenic score was associated with CAD with an effect size similar to low-density lipoprotein cholesterol - HR of 1.35 (95% CI: 1.07-1.70) and 1.41 (95% CI: 1.17-1.70) per standard deviation increase, respectively. When compared to noncarriers, CAD risk increased from 1.24-fold (95% CI: 0.64-2.34) to 3.37-fold (95% CI: 2.11-5.36) across quintiles of the polygenic score. A similar risk gradient, 1.36-fold (95% CI: 0.65-2.85) to 2.88-fold (95% CI: 1.59-5.20), was observed in 429 carriers in the UK Biobank.

CONCLUSIONS In 2 cohort studies involving 1,744 individuals with genetically confirmed HeFH - the largest study to date - risk of CAD varied according to polygenic background, in some cases approaching the risk observed in noncarriers. (JACC Adv 2023;2:100662) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

HeFH = heterozygous familial hypercholesterolemia

LDL-C = low-density lipoprotein cholesterol

LDLR = low-density lipoprotein receptor

Heterozygous familial hypercholesterolemia (HeFH) is a monogenic disorder with a prevalence of approximately 1 in 250 individuals caused by a DNA variant in any of 3 causal genes-low-density lipoprotein receptor (*LDLR*), apolipoprotein B (*APOB*), and proprotein convertase subtilisin/kexin 9 (*PCSK9*).[1] Perturbation of these genes lead to impaired clearance of atherogenic low-density lipoprotein cholesterol (LDL-C) from the circulation and accelerated atherosclerosis, with an estimated 3- to 4-fold increased risk of coronary artery disease.[2,3]

Although individuals who inherit a HeFH variant are known to be at increased risk when considered in aggregate, clinicians have long recognized considerable variability in risk of coronary artery disease (CAD), with up to 65% of patients free of clinical disease by age 75 years.[4] Prior studies have identified multiple drivers of this interindividual variability, including the specific DNA variant, degree of LDL-C elevation, intensity and duration of lipid-lowering therapy, adherence to a healthy lifestyle, presence of coronary calcium, and presence of traditional risk factors such as hypertension or diabetes.[4-6]

Beyond monogenic variants impacting CAD risk such as those underlying HeFH, recent advances in human genetics have uncovered a "polygenic" basis for common complex diseases.[7-11] In this model, the cumulative impact of many common DNA variants scattered across the genome and affecting a large number of biologic pathways can be quantified using a genome-wide polygenic score. Prior studies have noted a considerable gradient in risk of CAD according to polygenic score, including identification of up to 8% of the population with risk comparable to a HeFH variant.[12]

Preliminary evidence suggests that polygenic background may be an important driver of risk for CAD even among patients with HeFH. In 2 studies, among 233 and 138 carriers of a HeFH variant respectively, LDL-C was shown to vary according to a polygenic score designed to predict cholesterol levels.[13,14] More recently, we studied 56 carriers of a HeFH variant in a cross-sectional analysis and observed that CAD risk was 1.3- to 12.6-fold higher in carriers as compared to noncarriers across quintiles of a CAD polygenic score.[15] Extrapolating to a broader HeFH population using regression analysis, this result suggested a gradient in risk of developing CAD by age 75 years ranging from 17% to 78% across percentiles of the polygenic score.[15]

Here, we set out to study the relationship between polygenic background and risk of incident CAD during >10 years of follow-up in much larger populations of individuals with genetically confirmed HeFH, including 1,315 individuals from a national HeFH screening program in the Netherlands and an additional 429 individuals from the UK Biobank prospective cohort study. Moreover, we study the interplay between a polygenic score - which quantifies inherited risk from a range of causal pathways - and circulating LDL-C concentrations among HeFH variant carriers.

METHODS

STUDY POPULATIONS. The Dutch National HeFH cascade-screening program enrolled participants between 1994 and 2013.[16] For the current study, adult heterozygous carriers of a HeFH variant and free of atherosclerotic cardiovascular disease (defined as stroke and/or coronary artery disease) at time of enrollment, and who provided written informed consent for additional genetic analysis and linkage of health records, were included (n = 1,343) (Supplemental Figure 1).[17] In order to compare CAD risk in HeFH variant carriers to noncarriers, a control group consisting of relatives confirmed to be noncarriers and derived from the same families as the carriers, was matched based on age and sex in a 1:1 ratio. Polygenic score assessment in these noncarriers was not available owing to lack of stored DNA and/or informed consent required. This reuse of anonymized data was approved by the Institutional Review Board of Amsterdam UMC (W20_033 # 20.061). Detailed information on HeFH variant ascertainment, data collection, LDL-C measurements, and genotyping can be found in the Supplemental Appendix.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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To replicate observations in the Dutch HeFH cohort, we studied an additional 151,009 participants of the UK Biobank prospective cohort study with whole exome sequencing data available, and fully independent of those that contributed to the training of the polygenic score.[18] According to a combination of previously published criteria, HeFH causing variants were defined as follows: a loss-of-function variant in *LDLR*, a likely pathogenic or pathogenic annotation in the online ClinVar database, or variants that were previously determined to be HeFH causing by a clinical geneticist based on 2 cohort studies in the UK Biobank.[3,15,19] See Supplemental Table 1 for a breakdown of HeFH variant carriers according to these criteria. Details on gene sequencing, quality control of genetic data, and HeFH variant ascertainment are provided in the Supplemental Appendix.

Polygenic score derivation and calculation. A previously published genome-wide polygenic score (GPS_{CADEUR}) of 1.2 million common DNA variants was calculated in participants of both the Dutch screening program and the UK Biobank.[20] This score was derived from a recent genome-wide association study led by the CARDIOGRAMplusC4D Consortium that studied over 1 million individuals.[21] In brief, a range of tuning parameters within the LDPred2 algorithm were used to select the best-performing polygenic score among 116,649 individuals (4,412 CAD cases and 112,237 controls) of European ancestry in the UK Biobank study.[20,22] Among these individuals, the GPS_{CADEUR} associated with an odd ratio for CAD per standard deviation increase of 1.98 (95% CI: 1.94-2.02). To prevent any inflation in effect size due to overfitting, all 116,649 UK Biobank participants included in the GPS_{CADEUR} score selection were excluded from the current study. The polygenic score weights for GPS_{CADEUR} used in this publication are available for download from the Polygenic Score Catalog through accession ID PGS003727.

The raw calculated polygenic score was ancestry-adjusted and normalized using the first 5 principal components of ancestry as detailed in the Supplemental Methods as performed previously.[19,23] A low, intermediate, and high polygenic score for CAD was defined as a polygenic score in the first quintile (low), second to fourth quintile (intermediate), and fifth quintile (high), respectively, using cohort-specific cutoffs as performed previously.[24,25]

STATISTICAL ANALYSES. The primary outcome of this study was CAD (defined in the Supplemental Appendix). Cox proportional hazards modeling with covariates for age at enrollment, sex, and the first 5 principal components of ancestry were used in all analyses (detailed in the Supplemental Appendix). The performance of the models was evaluated using Harrell's c-statistics.[26] Ten-year event rates according to LDL-C groups were standardized by fitting a Cox proportional hazards model on the average age, sex, and the first 5 principal components of ancestry. Similar to previous studies, the polygenic score conformed to an approximately normal distribution in this study (Supplemental Figure 2).[12,19] All analyses were performed in R (version 4.0.2, R Foundation).[27] Two-sided *P* values were used and a value of $P < 0.05$ was considered statistically significant.

TABLE 1 Clinical Characteristics of HeFH Variant Carriers and Matched Family Noncarriers the Dutch HeFH Cohort

	HeFH Variant Carrier (n = 1,315)	Family Noncarriers (n = 1,315)	*P* Value
Females	695 (52.9)	695 (52.9)	matched
Age at start follow-up, y	42.1 ± 14.6	42.1 ± 14.5	matched
BMI, kg/m	25.7 ± 4.4	25.5 ± 4.2	0.42
Smoker	478 (36.7)	535 (40.7)	0.04
Alcohol use	763 (58.0)	802 (61.0)	0.13
Hypertension	179 (13.7)	182 (13.8)	0.82
Diabetes	54 (3.4)	49 (3.7)	0.57
Affected gene			-
LDLR	1,064 (80.9)	0 (0)	
APOB	248 (18.9)	0 (0)	
PCSK9	3 (0.2)	0 (0)	
Total cholesterol, mg/dL	230 ± 56	188 ± 39	<0.01
Estimated untreated LDL-C, mg/dL	214 ± 73	120 ± 37	<0.01
Measured LDL-C, mg/dL	160 ± 54	114 ± 34	<0.01
HDL-C, mg/dL	46 ± 15	48 ± 15	<0.01
Triglycerides, mg/dL	101 (68-152)	108 (71-163)	0.02
Statin use	889 (67.6)	197 (15.0)	<0.01
Other lipid-lowering therapy use	310 (23.6)	21 (1.6)	<0.01
Any lipid-lowering therapy use	899 (68.4)	205 (15.6)	<0.01

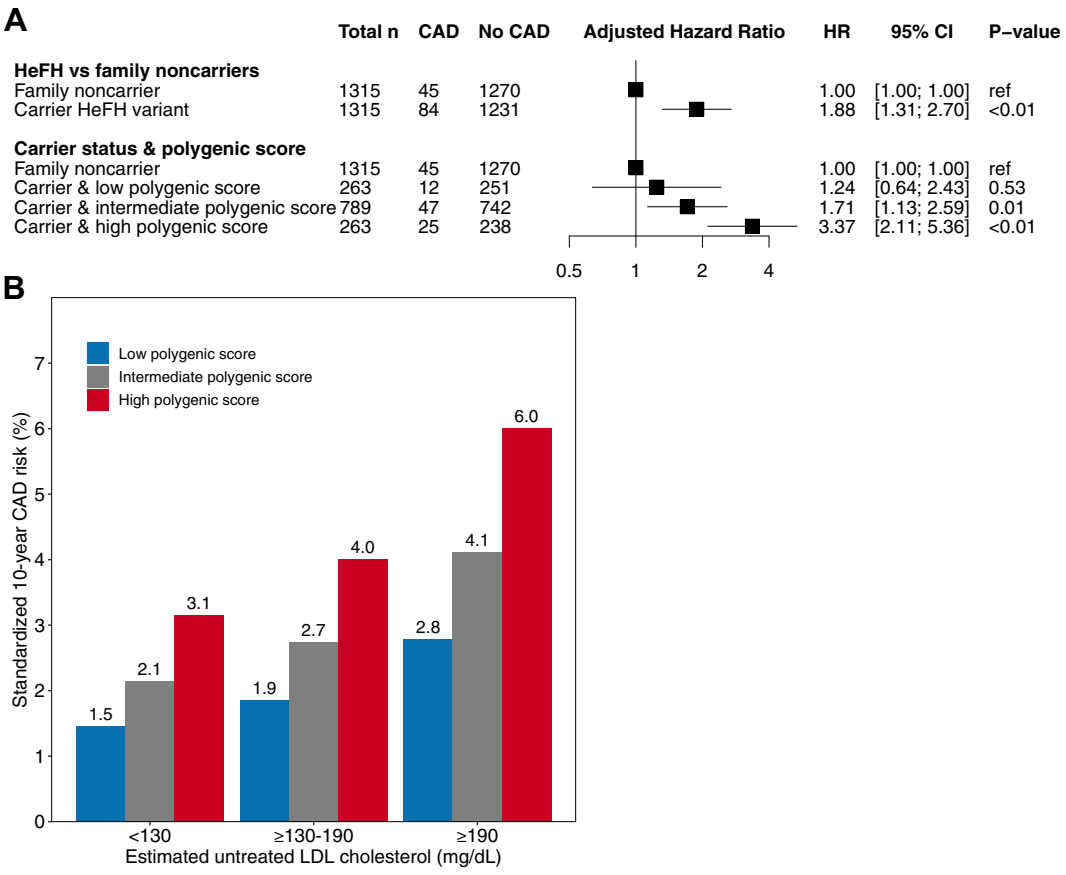
Values are n (%), mean ± SD, or median (IQR).

APOB = apolipoprotein B gene; BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; *LDLR* = low-density receptor gene; *PCSK9* = proprotein convertase subtilisin/kexin type 9 gene.

RESULTS

ANALYSIS OF THE DUTCH HeFH COHORT. Of the 1,315 HeFH variant carriers included in the final analyses 695 (53%) were female, and mean age was 42.1 ± 14.6 years (Table 1). Although the majority of HeFH variant carriers were treated with statins (67.6%) and/or other lipid-lowering therapies (23.6%), measured LDL-C was significantly higher in variant carriers compared with 1,315 age and sex matched family noncarriers (160 ± 54 mg/dL vs 114 ± 34 mg/dL, $P < 0.01$). Consequently, estimated untreated LDL-C showed even higher differences between HeFH variant carriers and family noncarriers

FIGURE 1 Polygenic Risk and Incident CAD in the Dutch HeFH Cohort



HeFH variant carriers in the Dutch HeFH Cohort are at higher risk for CAD during follow-up compared to age- and sex matched family noncarriers (A, upper part). Moreover, a marked increase in risk is observed according to polygenic score compared to Family noncarriers (A, lower part). HeFH variant carriers with a high polygenic score and high estimated untreated LDL-C are at higher 10-year CAD risk compared to other combinations of polygenic score and LDL-C among participants with available LDL-C measurements (n = 1,248) (B). CAD = coronary artery disease; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol.

(214 ± 73 mg/dL vs 120 ± 37 mg/dL, $P < 0.01$) (Table 1, Supplemental Figure 3). According to a principal component analysis for ancestry, 1,231 (93.6%) of HeFH variant carriers were of European ancestry (Supplemental Figure 4).

During a median follow-up time of 10.2 (IQR: 7.5-15.1) years, an incident CAD event occurred in 84 (6.4%) HeFH variant carriers and 45 (3.4%) matched family relative noncarriers, corresponding to 6.0 (95% CI: 4.8-7.3) and 3.1 (95% CI: 2.3-4.1) events per 1,000 person-years, respectively. Despite early identification and early initiation of treatment in a national cascade screening program for HeFH, carriers were still characterized by an increased risk for incident CAD compared to family noncarriers (adjusted HR: 1.88, 95% CI: 1.31-2.70) (Figure 1A).

As expected, traditional CAD risk factors were associated with incident CAD among the HeFH variant carriers. The adjusted HR per LDL-C standard deviation increase was 1.41 (95% CI: 1.17-1.70), for hypertension 2.09 (95% CI: 1.26-3.48), obesity 2.24 (95% CI: 1.37-3.67), and diabetes 1.07 (95% CI: 0.46-2.50).

Next, we investigated the extent to which a polygenic score was associated with incident CAD among carriers of a HeFH variant. The median polygenic score percentile was significantly higher in HeFH variant carriers with incident CAD compared to those who remained free of CAD (58th vs 49th percentile respectively, $P = 0.02$). A 1 standard deviation increase in polygenic score-corrected for age, sex, and principal components of ancestry-was associated

with a HR of 1.35 (95% CI: 1.07-1.70) for incident CAD. Using regression-based estimation, a HeFH variant carrier with a polygenic score ≥1.4 SDs below the mean would be expected to have a risk comparable to an average noncarrier, corresponding to up to 8% of the HeFH carrier population.

The number of CAD events during follow-up according to a predefined low (lowest quintile), intermediate (second-fourth quintile), and high (highest quintile) polygenic score, were 12 (4.6%), 47 (6.0%), and 25 (9.5%), respectively. This corresponded to 4.2 (95% CI: 2.3-7.1), 5.5 (95% CI: 4.1-7.3), and 9.3 (95% CI: 6.1-13.5) events per 1,000 person-years, respectively. A significant gradient in CAD risk was observed according to polygenic score compared to family noncarriers, ranging from an adjusted HR of 1.24 (95% CI: 0.64-2.34) in those with a low polygenic score to 3.37 (95% CI: 2.11-5.36) for high polygenic scores (**Figure 1A, Central Illustration**).

Consistent with prior studies, traditional risk factors tended to be modestly enriched in those with the highest polygenic scores (Supplemental Table 2).[12,28] Taking LDL-C and hypertension as an example, the mean estimated untreated LDL-C ranged from 204 ± 68 mg/dL to 221 ± 72 mg/dL ($P < 0.01$) and prevalence of hypertension ranged from 8.8% to 17.8% ($P < 0.01$) across quintiles of the score, respectively.

Next, we assessed whether the polygenic score is independently associated with incident CAD after adjustment for traditional risk factors (**Table 2**). In multivariable models that included estimated untreated LDL-C, hypertension, diabetes, and obesity, the polygenic score remained significantly associated with CAD (adjusted HR/SD 1.28, 95% CI 1.01-1.61), with a comparable effect estimate observed for estimated untreated LDL-C (HR/SD 1.33, 95% CI: 1.08-1.65) (**Table 2**).

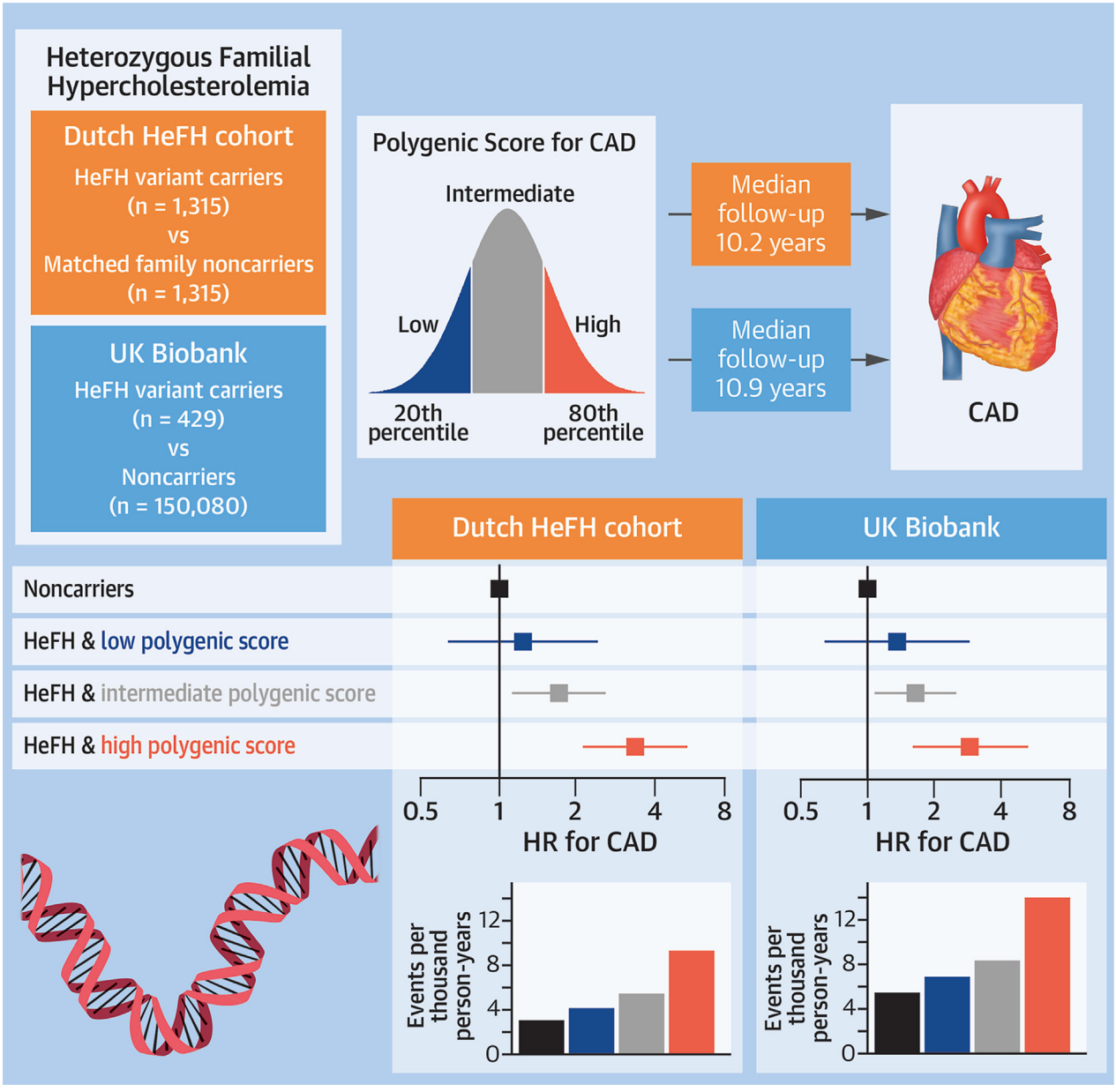
To explore the interplay between polygenic score and estimated untreated LDL-C we estimated 10-year CAD risk according to polygenic score and estimated untreated LDL-C groups (<130, ≥130-190, and ≥190 mg/dL). The highest 10-year risk (6.0%, 95% CI: 2.4-9.5) was observed in HeFH variant carriers with estimated untreated LDL-C ≥190 mg/dL and a high polygenic score (**Figure 1B**, Supplemental Table 3). Lower polygenic score in those with estimated untreated LDL-C ≥190 mg/dL appeared to offset CAD risk to a comparable risk (2.8%, 95% CI: 0.9-4.7) as observed in HeFH variant carriers with a high polygenic score but low estimated untreated LDL-C (3.1%, 95% CI: 0.9-5.4) (Supplemental Table 3). No significant interaction between polygenic score and LDL-C was observed in a model adjusted for age, sex and principal components of ancestry, suggesting that this risk factor contributes to risk in a largely additive and independent fashion (P interaction = 0.84).

To understand the extent to which polygenic scores and traditional risk factors improve risk discrimination for CAD, change in C-statistic was computed after adding each variable to a base model consisting of age, sex and first 5 principal components of ancestry (Supplemental Table 4). None of the risk factors, including polygenic score, significantly increased model performance when individually assessed. The addition of the polygenic score to the base model, increased the c-statistic by 0.020 (95% CI: −0.023 to 0.043) from 0.693 to 0.713. The model with the highest discriminatory capacity was a full clinical model including all risk factors including polygenic score (c-statistic 0.748, 95% CI: 0.699-0.798), although this model did not perform significantly better than the full clinical model without polygenic score (c-statistic 0.743, 95% CI: 0.698-0.788, difference 0.005, 95% CI: −0.013 to 0.020, $P = 0.65$).

ANALYSIS OF THE UK BIOBANK. In the UK Biobank, 429 HeFH variant carriers and 150,580 noncarriers free of atherosclerotic cardiovascular disease at baseline were included (Supplemental Table 1). 259 (60.4%) of HeFH variant carriers and 85,104 (56.5%) of noncarriers were female, with a mean age of 56.2 ± 8.3 years and 56.6 ± 8.1 years, respectively (**Table 3**). Measured and estimated untreated LDL-C were significantly higher in HeFH variant carriers compared to noncarriers (170 ± 47 mg/dL vs 139 ± 33 mg/dL and 198 ± 51 mg/dL vs 145 ± 33 mg/dL, respectively. Both $P < 0.01$) (**Table 3**, Supplemental Figure 3). 40 (9.3%) HeFH variant carriers and 8,724 (5.8%) noncarriers had incident CAD over a median follow-up time of 10.9 years, respectively, corresponding to 8.9 (95% CI: 6.5-12.1) and 5.4 (95% CI: 5.3-5.5) events per 1,000 person-years and an adjusted HR of 1.78 (95% CI: 1.31-2.43) (**Figure 2A**).

Traditional risk factors were also associated with incident CAD among HeFH variant carriers. The adjusted HR per increment in standard deviation for estimated untreated LDL-C was 1.57 (95% CI: 1.29-1.90), for hypertension 4.86 (95% CI: 2.34-10.1), diabetes 6.10 (95% CI: 2.88-12.90), and obesity 3.00 (95% CI: 1.58-5.71). A 1 SD increase in polygenic score was associated with an adjusted HR/SD for incident CAD of 1.31 (95% CI: 0.97-1.77) in HeFH variant carriers

CENTRAL ILLUSTRATION **Polygenic Background Modifies Risk of Coronary Artery Disease Among Individuals With Heterozygous Familial Hypercholesterolemia**



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HeFH variant carriers in the Dutch HeFH cohort and UK Biobank were genotyped and a genome wide polygenic score for CAD was calculated. Its association with incident CAD was assessed over a median follow-up time of 10.2 and 10.9 years in the Dutch HeFH Cohort and UK Biobank, respectively. Polygenic background of HeFH carriers modified CAD risk compared to family noncarrier (Dutch HeFH cohort) and noncarriers (UK Biobank). CAD = coronary artery disease; HeFH = heterozygous familial hypercholesterolemia.

TABLE 2 Multivariable Model for CAD in HeFH Variant Carriers in the Dutch HeFH Cohort

	Adjusted HR (95% CI)		
	Model 1[a]	Model 2[b]	Model 3[c]
Polygenic score (per SD increment)	1.35 (1.07-1.70)	1.30 (1.03-1.65)	1.28 (1.01-1.62)
Estimated untreated LDL-C (per SD increment)	-	1.38 (1.14-1.67)	1.33 (1.08-1.65)

[a]Model 1: Sex, age, and ancestry principal components as covariates (n = 1,315). [b]Model 2: Sex, age, ancestry principal components as covariates plus estimated untreated LDL-C (n = 1,248, complete data only). [c]Model 3: Sex, age, ancestry principal components, estimated untreated LDL-C as covariates plus hypertension, diabetes, and obesity (n = 1,212, complete data only).

HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol.

only and an adjusted HR/SD of 1.48 (95% CI: 1.45-1.51) when carriers and noncarriers were analyzed as a whole (*P* interaction = 0.39). Using regression-based estimation, a HeFH variant carrier with a polygenic score ≥1.2 SDs below the mean would be expected to have a risk comparable to an average noncarrier, corresponding to up to 12% of the HeFH carrier population. HeFH variant carriers with a high polygenic score were at the highest risk for CAD during follow-up with event rates of 7.1%, 8.7%, and 14.1% in HeFH variant carriers with a low, intermediate, and high polygenic score, respectively. This corresponded to 6.8 (95% CI: 3-13.4), 8.3 (95% CI: 5.3-12.3), and 14.0 (95% CI: 7.4-24.3) events per 1,000 person-years. Compared to noncarriers, HeFH variant carriers with a high polygenic score were at increased risk for CAD (HR: 2.88, 95% CI: 1.59-5.20) while those with a low polygenic score were at similar risk (HR: 1.36, 95% CI: 0.65-2.85) as noncarriers (**Figure 2A**). Sensitivity analyses that restricted analysis to carriers to those with "loss-of-function" mutations in *LDLR* or whose variant was annotated as pathogenic or likely pathogenic based on manual geneticist curation yielded similar results (Supplemental Tables 5 to 7).

Modest differences in traditional risk factors according to polygenic score were observed (Supplemental Table 8). For example, among HeFH variant carriers mean estimated untreated LDL-C was 192 ± 42 mg/dL in those with a low polygenic score and 213 ± 46 mg/dL in those with a high polygenic score (*P* = 0.02).

A stepwise increase in estimated 10-year CAD event rates was observed for increasing estimated untreated LDL-C levels and increasing polygenic scores. HeFH variant carriers with a low polygenic score are expected to have lower 10-year event rates at high (≥190 mg/dL) estimated untreated LDL-C levels as compared to carriers with a high polygenic score (3.9% [95% CI: 2.7%-5.1%] vs 10.9% [95% CI: 7.6%-14.2%]) (**Figure 2B**, Supplemental Table 9). Conversely, lower estimated untreated LDL-C (<130 mg/dL) was associated with lower event rates in all polygenic score groups. For example, among HeFH variant carriers with a high polygenic score, the 10-year estimated event rate is 7.5% (95% CI: 5.1-9.9) for those with low LDL-C levels (<130 mg/dL) compared to 10.9% (95% CI: 7.6-14.6) in those with estimated untreated LDL-C of ≥190 mg/dL (**Figure 2B**, Supplemental Table 9). Again, no significant interaction between polygenic

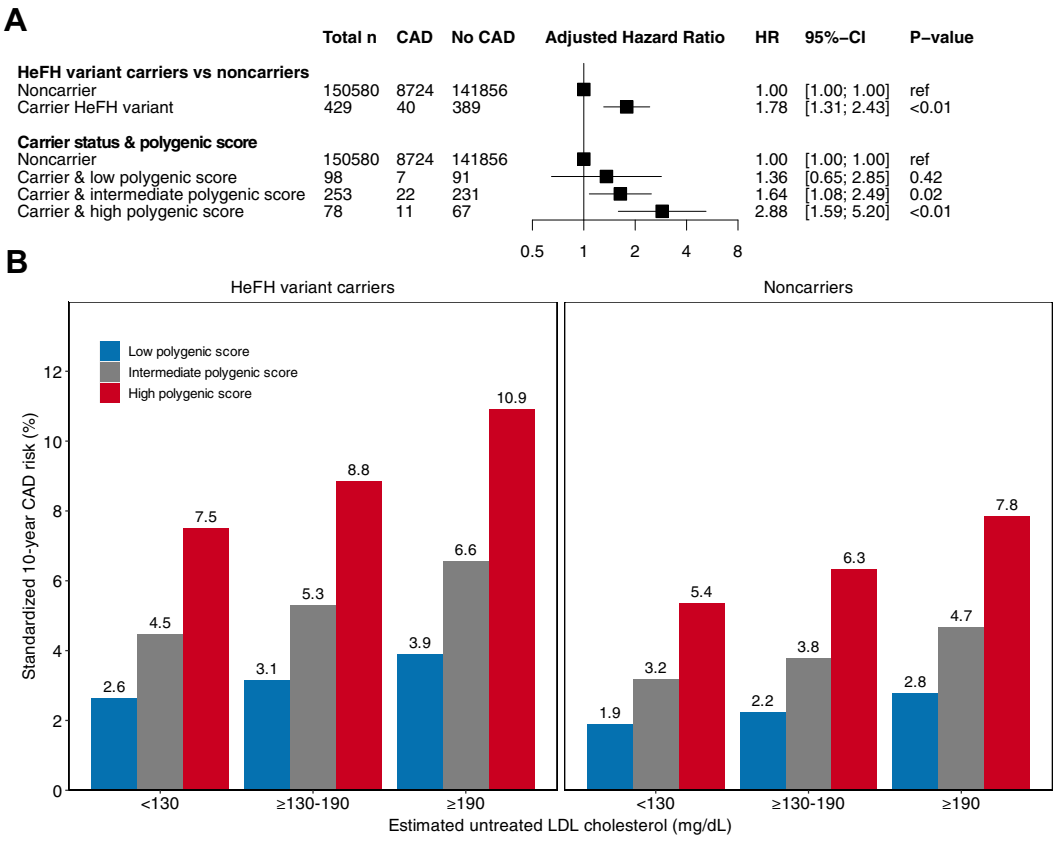
TABLE 3 Characteristics of HeFH Variant Carriers and Noncarriers in the UK Biobank

	HeFH Variant Carrier (n = 429)	Noncarriers (n = 150,580)	*P* Value
Females	259 (60.4)	85,104 (56.5)	0.12
Age at start follow-up, y	56.2 ± 8.3	56.6 ± 8.1	0.34
Self-reported race			<0.01
White	383 (89.3)	138,904 (92.2)	
Asian	27 (6.3)	4,543 (3.0)	
Black	9 (2.1)	3,099 (2.1)	
Other/not reported	10 (2.3)	4,034 (2.7)	
BMI, kg/m^2	27.2 ± 4.6	27.3 ± 4.7	0.73
Smoker	38 (8.9)	14,375 (9.6)	0.69
Alcohol use	165 (38.6)	64,863 (43.2)	0.07
Hypertension	127 (29.6)	45,608 (30.3)	0.80
Diabetes	29 (6.8)	9,200 (6.8)	0.65
Affected gene			-
LDLR	320 (74.6)	0 (0)	-
APOB	97 (22.6)	0 (0)	-
PCSK9	12 (2.8)	0 (0)	-
Total cholesterol, mg/dL	256 ± 59	222 ± 43	<0.01
Estimated untreated LDL-C, mg/dL	198 ± 51	145 ± 33	<0.01
Measured LDL-C, mg/dL	170 ± 47	139 ± 33	<0.01
HDL-C, mg/dL	55 ± 13	57 ± 15	0.05
Triglycerides, mg/dL	119 (88-172)	130 (92-188)	<0.01
Statin use	175 (40.8)	19,141 (12.7)	<0.01
Ezetimibe use	21 (4.9)	518 (0.3)	<0.01

Values are n (%), mean ± SD, or median (IQR).

APOB = apolipoprotein B gene; BMI = body mass index; CAD = coronary artery disease; HDL-C = high density lipoprotein cholesterol; IQR = interquartile range; LDL-C = low density lipoprotein cholesterol; *LDLR* = low-density receptor gene; LLT = lipid lowering therapy; N = number; *PCSK9* = proprotein convertase subtilisin/kexin type 9 gene.

FIGURE 2 Polygenic Risk and Incident CAD in the UK Biobank



HeFH variant carriers in the UK Biobank are at higher risk for CAD during follow-up compared to noncarriers (A, upper part). Moreover, a marked increase in risk is observed according to polygenic score compared to noncarriers (A, lower part). HeFH variant carriers with a high polygenic score and high estimated untreated LDL-C are at higher 10-year CAD risk compared to other combinations of polygenic score and LDL-C among participants with available LDL-C measurements (n = 143,486) (B). CAD = coronary artery disease; HeFH = heterozygous familial hypercholesterolemia.

score and LDL-C was observed suggesting that these factors contributed to risk in an additive fashion (*P* interaction = 0.14).

In a multivariable model adjusted for traditional risk factors, the polygenic score was associated with incident CAD (adjusted HR/SD: 1.46, 95% CI: 1.08-1.65) in HeFH variant carriers, with a similar associated risk as estimated untreated LDL-C (adjusted HR/SD: 1.55, 95% CI: 1.24-1.93). Evaluating all UK Biobank participants, including noncarriers, the polygenic score was associated with a HR/SD of 1.42 (95% CI: 1.38-1.45), but the effect per standard deviation increment in estimated untreated LDL-C was less pronounced (HR: 1.15, 95% CI: 1.13-1.18) (Supplemental Table 10).

Addition of the polygenic score to a full clinical model led to modest but statistically significant improvement in CAD discriminatory capacity as assessed by the c-statistic metric (Supplemental Table 4). Addition of the polygenic score to a base model with covariates for sex, age, and principal components of ancestry, increased c-statistic from 0.716 (95% CI: 0.711-0.722) to 0.740 (95% CI: 0.734-0.745), well within the range or exceeding that of other traditional risk factors. As observed in the Dutch HeFH cohort, the highest discriminatory capacity was achieved in a full clinical model that included the polygenic score (c-statistic: 0.772, 95% CI: 0.767-0.777) corresponding to a 0.024 (95% CI: 0.018-0.029) increase.

DISCUSSION

In this study, we investigated the extent to which a polygenic score for CAD was associated with risk of incident disease in 1,744 participants with genetically confirmed HeFH across 2 studies (Dutch HeFH cohort and the UK Biobank). A polygenic score of CAD was associated with risk of incident CAD with a similar magnitude as LDL-C. Moreover, a clear gradient in CAD risk across quintiles of polygenic score was observed-ranging from 1.24- and 1.36-fold increase in the lowest quintile to 3.37- and 2.88-fold increase in the highest quintile compared to noncarriers in the Dutch HeFH cohort and UK Biobank, respectively. Lastly, we evaluated the effect of estimated untreated LDL-C levels on 10-year CAD risk and observed that both lower polygenic score and lower LDL-C attenuated the risk of CAD among HeFH variant carriers.

The gradient in CAD risk associated with the polygenic score observed in our HeFH cohort is in line with previous reports.[15] The HeFH variant carriers in the Dutch HeFH cohort were identified in a cascade-screening program and treated with statins and other lipid lowering therapies in the majority of cases but were still at increased CAD risk. It is, however, known that CAD risk in HeFH is heterogeneous and not every HeFH variant carrier develops CAD, partly depending on the presence of other CAD risk factors.[1,5,29,30] Our study provides important confirmation of this concept, whereby polygenic background impacts the penetrance of rare monogenic HeFH variants on CAD risk.

For HeFH participants with a polygenic score in the lowest quintile, risk of CAD approached that of noncarriers in both the Dutch HeFH cohort and the UK Biobank studies. Using a regression-based framework, we estimate that approximately 10% of individuals with HeFH have risk equivalent to or lower than noncarriers based on polygenic background. This concept is likely to be generalizable across a range of complex disease, with evidence that polygenic background is similarly predictive among participants with hereditary breast cancer and Lynch syndrome variants.[16] These results suggest that, moving forward, genomic risk interpretation should optimally include assessment of both a polygenic score and the presence of a monogenic HeFH mutation in order to be able to tailor LDL-C lowering therapies in FH patients according to their individually-assessed CAD risk. We recently reported initial implementation of such an approach within a Preventive Genomics Clinic at Massachusetts General Hospital, and look forward to results of additional ongoing similar studies.[31]

The interplay of LDL-C and polygenic CAD becomes apparent in our study when untreated LDL-C and CAD risk are investigated: Dutch HeFH variant carriers with untreated LDL-C ≥190 mg/dL and a high polygenic risk have a 10-year risk of 6.0% compared to 3.1% in carriers with LDL-C levels of <130 mg/dL and a high polygenic risk. In contrast, in HeFH variant carriers with a low polygenic score the difference in 10-year estimated risk between LDL-C <130 mg/dL and ≥190 mg/dL is 1.3%. This interplay underscores the role of lifelong LDL-C exposure in atherogenesis in HeFH, especially in those with an unfavorable polygenic background.

To mitigate CAD risk associated with polygenic score and cumulative LDL-C exposure, lipid-lowering therapies are essential. Several studies have retrospectively investigated the effect of statins and Proprotein convertase subtilisin/kexin 9 inhibitors on incident CAD according to polygenic scores in participants of randomized controlled trials and revealed a greater risk reduction in participants with a high polygenic risk.[24,25,32,33] Additional efforts are warranted to determine if this general concept holds true in patients with HeFH.

STUDY LIMITATIONS. First, cause-specific mortality is not available within the Dutch HeFH cohort, and it was not possible to study the relationship between the polygenic scores and these outcomes. Second, family noncarriers in the Dutch HeFH cohort were not genotyped, preventing a direct comparison in polygenic scores between carriers and noncarriers in this cohort. Third, additional data are needed to understand the extent to which the observations from this study hold true in the context of secondary prevention. Fourth, variant annotation was performed by a geneticist in the Dutch HeFH cohort and a combination of manual curation and bioinformatic assessment in the UK Biobank. It is, therefore, possible that both HeFH populations are less comparable than could be expected from a single variant annotation approach and the bioinformatic approach might be less precise compared to stringent variant selection by trained geneticists. Furthermore, variant pathogenicity assessment recommendations are and will continue to evolve over time and contain at least some element of subjective assessments. To that end, we note recent FH-specific annotation guidelines published after this research was conducted, but do not believe differences, if any, would meaningfully affect the primary results.[34] Last, currently available polygenic scores tend to have greater effect size in European

ancestral populations vs other groups.[35,36] Although we believe it is likely that polygenic background modifies the risk conferred by FH variants regardless of ancestral background, this topic warrants confirmation in future studies that ideally include a ancestry-specific polygenic score and a large number of FH carriers from diverse backgrounds. To that end, recent publications on familial hypercholesterolemia and polygenic risk scores within the US Million Veterans Program, inclusive of up to 17,202 CAD cases in Black individuals and 6,378 CAD cases in Hispanic individuals, are of considerable interest.[37,38]

CONCLUSIONS

In the largest study of polygenic scores in HeFH variant carriers to date, we observe a significant gradient in risk for incident CAD according to polygenic score. In HeFH variant carriers with a high polygenic score CAD risk is 3-fold higher compared to noncarriers, while comparable in those with low polygenic scores.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Polygenic scores for CAD capture the effects of common genetic variants with small effects on risk. In patients with familial hypercholesterolemia, CAD risk varies substantially according to polygenic background.

TRANSLATIONAL OUTLOOK: Assessment of a CAD polygenic score in patients with familial hypercholesterolemia variants may prove useful in refining risk estimate or guiding intensity of therapy.

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APPENDIX For supplemental methods, tables, and figures, please see the online version of this paper.