Joint consideration of LDL-C and polygenic risk for incident coronary heart disease in a multi-ethnic cohort of 48,881 individuals

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Background and Study Aim

Elevated LDL-cholesterol (LDL-C) is a major independent modifiable risk factor for coronary heart disease (CHD).

However, the degree to which background polygenic risk can modulate the effect of high LDL-C remains unclear.

The aim of this study was to examine whether the risk imparted by high LDL-C levels is modified by background polygenic risk.

Methods

The analytical sample consisted of 48,881 Genetic Epidemiology Resource in Adult Health and Aging (GERA) cohort members who were non-diabetic and not taking cholesterol lowering medication at baseline. All completed a self-administered questionnaire in 2007-08 and donated a saliva sample.

Genotyping was conducted at the Institute for Human Genetics, University of California San Francisco, using custom designed arrays. The CARDIO inCode-Score® CHD PRS was computed as the sum of the number of risk alleles across 12 genetic variants after weighting each one by its estimated effect size in the CARDIoGRAMplusC4D Consortium.

Incident CHD through 12/31/2022 (mean ± SD follow-up=13.8 ± 3.8 years) included non-fatal AMI, angina and coronary revascularization procedures (coronary by-pass or percutaneous intervention) or CHD death.

Age-adjusted CHD rates per 10,000 person-years were estimated using Poisson regression according to polygenic risk and LDL-C level.

Hazard ratios and 95% confidence intervals for 1 standard deviation (SD) increment of LDL-C in each PRS group were obtain using Cox regression adjusting for 10 principal components of ancestry plus traditional risk factors.

We tested for formal interaction LDL-C*PRS as continuous variables in the fully adjusted model. As a complimentary approach we tested interaction between high PRS (Q5 vs lower) and LDL ≥190 mg/dL.

Finally, we calculated number needed treat (NNT) to prevent 1 CHD event in each PRS group.

Results

Characteristics of the Study Cohort (n=48,881; 1,725 events).

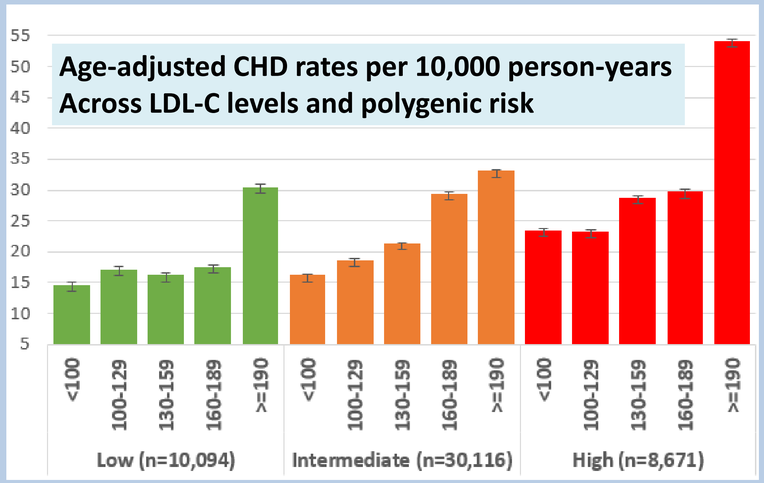
Age, years (mean ± SD)	58 ± 10
Male Sex, n (%)	18,214 (37%)
European, n (%)	39,998 (82%)
African American, n (%)	1,468 (3%)
Hispanic/Latino, n (%)	3,287 (7%)
Asian, n (%)	3,794 (8%)
Less than college education, n (%)	5,893 (12%)
Current smoking, n (%)	2,283 (5%)
Body mass index ≥30 kg/m², n (%)	14,380 (24%)
Hypertension, n (%)	17,606 (36%)
LDL Cholesterol, mg/dL (mean ± SD)	121 ± 28
HDL Cholesterol, mg/dL (mean ± SD)	58 ± 16

Independent Main Effects Model*

	HR (95% CI)	p
Age, per 1 SD	1.84 (1.74 - 1.95)	<0.001
Male gender	2.08 (1.86 - 2.32)	<0.001
Less than a College Education	1.23 (1.08 - 1.40)	<0.01
Current Smoking	1.56 (1.29 - 1.90)	<0.001
BMI ≥ 30 kg/m²	1.15 (1.01 - 1.30)	<0.05
Hypertension	1.55 (1.40 - 1.72)	<0.001
LDL-C, per 1 SD	1.19 (1.14 - 1.25)	<0.001
HDL-C, per 1 SD	0.58 (0.52 - 0.65)	<0.001
PRS Quintiles 2, 3 and 4 vs. 1	1.22 (1.07 - 1.39)	<0.01
PRS Quintile 5 vs. 1	1.60 (1.38 - 1.87)	<0.001

* adjusting for 10 principal components of genetic ancestry

NNT to prevent 1 CHD event by polygenic risk.	
Low	565
Intermediate	460
High	273



LDL-C – CHD association by polygenic risk.			
	Low	Intermediate	High
HR (95% CI) per 1 SD	1.07 (0.95-1.71)	1.22 (1.15-1.29)	1.14 (1.03-1.26)
p-value	0.24	< 0.0001	0.009
HR (95% CI) ≥ 190 vs < 190	1.94 (0.86-4.36)	1.78 (1.18-2.67)	1.98 (1.08-3.63)
p-value	0.10	0.005	0.02
p-interaction PRS*LDL	0.34		
p-interaction PRS_Q5*LDL≥ 190	0.74		

Conclusions

- **LDL-C and polygenic risk are independently associated with incident CHD.**
- **While all patients with elevated LDL-C ought to be treated, our data suggest that lipid lowering therapy interventions may be more effective among those with high polygenic risk, as the NNT was much lower in the high polygenic risk group.**
- **In line with recent publications (Bolli 2021; Boccanelli and Bottà 2021), our data also suggest that subjects with high polygenic risk should not have LDL-C levels above 130 mg/dL, as their CHD risk is similar to those with LDL-C levels ≥190 mg/dL and a low polygenic risk.**

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