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Reclassification of coronary artery disease risk using genetic risk score among subjects with borderline or intermediate clinical risk

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Cardiovascular diseases (CVDs), including coronary artery disease (CAD), are the leading cause of death globally. Preventive interventions by lifestyle, lipid and blood pressure management, and pharmacologic therapy have been shown to be effective to reduce the incidence of CVDs [1]. Currently, a risk-based prevention strategy is recommended by leading professional societies [2]. Adults are recommended to undergo 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimation. For subjects with borderline- or intermediate-ASCVD risk (5 % to < 20 %), additional risk-enhancing factors should be considered to guide decisions about preventive interventions. While family history (FH) of premature ASCVD is a risk-enhancing factor [2], other more objective inherited risk measures such as SNP-based polygenic risk scores (PRSs) and monogenic mutations are not included as risk-enhancing factors. This status quo is in contrast to extensive evidence supporting the association between CAD and monogenic/polygenic variants [3]. The objective of this study is to demonstrate that PRS is an informative risk-enhancing factor for subjects with borderline-/intermediate-ASCVD risk.

A CAD incident cohort (N = 366,493) was derived from the UKB, a population-based study [4]. Criteria for defining CAD was described previously [5]. 10-year ASCVD risk at recruitment was estimated for subjects using pooled cohort equations (PCE) [6]. FH information of heart diseases (not limited to premature disease) among first-degree relatives was obtained. Genetic risk score (GRS), a well-established odds ratio (OR)-weighted and population-standardized polygenic risk score was calculated for CAD [7]. Specifically, GRS_{CAD} was calculated based on 205 independent CAD risk-associated SNPs identified from genome-wide association studies (GWAS) of European ancestry (**sTable 1**). The overall reliability of GRS_{CAD} is demonstrated in **sFigure 1**. Because GRS_{CAD} is population-standardized PRS, its value can be considered as an individual's relative risk compared to the general population. As such, subjects were categorized into four risk groups based on their relative risk to the general population: (GRS_{CAD} < 0.5, 0.5–1.49, 1.5–2.99, and ≥3).

As of the last UKB accession date (January 5th, 2022), 23,753 (6.6 %) subjects were diagnosed with incident CAD during an average of 12.6 year of follow-up. Based on multivariable Cox regression analyses adjusting for age and genetic background (top 10 principal components), each of the ASCVD risk factors was associated with CAD (**sTable 2**). In addition, both FH of heart disease and GRS_{CAD} were

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Table 1
Incident CAD rate by by family history and GRS in subjects with borderline-/intermediate-ASCVD risk: UKB, race of white.

	Subjects, No. (%)	CAD, No. (%)	HR (95 % CI)[1]	*P*-value[1]
Total incidence cohort	360,098 (100)	23,753 (6.6)	Ref	
Borderline-/intermediate-ASCVD risk	173,082 (48.07)	15,111 (8.73)	1.35 (1.32–1.37)	1.63E-179
Family history of heart disease				
FH-	92,001 (53.15)	6,776 (7.37)	1.13 (1.10–1.16)	2.00E-18
FH+	81,081 (46.85)	8,335 (10.28)	1.60 (1.56–1.64)	3.71E-295
GRS_{CAD}				
≤ 0.5	31,748 (18.34)	1,883 (5.93)	0.90 (0.86–0.94)	1.26E-05
0.5–1.5	118,963 (68.73)	10,279 (8.64)	1.33 (1.30–1.36)	1.14E-129
1.5–3	20,740 (11.98)	2,657 (12.81)	2.02 (1.94–2.10)	7.53E-259
≥ 3	1,631 (0.94)	292 (17.9)	2.91 (2.59–3.26)	2.26E-73

Abbreviation: CAD, coronary artery disease; ASCVD, atherosclerotic cardiovascular disease; PCE, pooled cohort equations; FH, family history; GRS, genetic risk score; T2D, type 2 diabetes; HR, hazard ratio; 95 % CI, 95 % confidence interval.
[1] HR adjusted for genetic background, time to event (CAD) was year from study recruitment.

significantly associated with incident CAD risk. Per the 10-year ASCVD risk, 158,880 (44.12 %), 51,202 (14.22 %), 121,880 (33.85 %), and 28,136 (7.81 %) subjects were classified as low-, borderline-, intermediate-, and high-ASCVD risk, respectively, with incident CAD rate at 2.18 %, 5.65 %, 10.03 %, and 18.41 %, respectively, $p_{trend} < 0.001$ (the Cochran-Armitage test).

For subjects with borderline-/intermediate-ASCVD risk (48 % in the cohort), their CAD risk was further stratified by FH and GRS_{CAD} (Table 1). Using FH, subjects were stratified into two risk groups: with (47 %) and without FH (53 %). The incident CAD rate was moderately higher in those with FH (10.28 %) than without FH (7.37 %), $p < 0.001$. In contrast, GRS_{CAD} was able to stratify subjects into four groups, <0.5 ('low', 18 %), 0.5–1.49 ('average', 69 %), 1.5–2.99 ('high', 12 %) and $\geq$ 3 ('very high', 1 %). Incident CAD rate differed substantially among the four GRS_{CAD} groups: 5.93 %, 8.64 %, 12.81 %, and 17.9 %, respectively, $p_{trend} < 0.001$. Subjects with 'very high' GRS_{CAD} had a CAD rate that was similar to that of high-ASCVD risk. It is also noted that 18 % of subjects with 'low' GRS_{CAD} had significantly lower CAD risk compared to the entire cohort, hazard ratio (HR) was 0.90, 95 % confidence interval: 0.86–0.94.

Similar results were found from time to incident CAD analysis (Kaplan-Meier log-rank test) for four ASCVD risk groups in the entire cohort (Fig. 1a) as well as for subjects with borderline/intermediate-ASCVD risk by FH (Fig. 1b), GRS_{CAD} (Fig. 1c), and combination of FH and GRS_{CAD} (Fig. 1d). A similar result was found using different GRS_{CAD} cutoff values (<0.5, 0.5–1.99, 2–3 and $\geq$ 3) (**sFigure 2**).

A novel finding of this study is the demonstration of better performance of GRS_{CAD} than FH for stratifying CAD risk among subjects with borderline-/intermediate-ASCVD risk. Approximately 13 % and 18 % of these subjects can be further reclassified into higher ($GRS_{CAD} \geq 1.5$) or lower risk groups ($GRS_{CAD} < 0.5$), respectively. These results, derived from a large population-based prospective cohort, provide a high level of evidence (Level II) to support GRS_{CAD} as another risk-enhancing factor.

Results from our study are generally consistent with previous studies on PRS of CAD [3,8], including those utilizing the UKB data [9–12]. However, our study differs from published studies in the objective, design, and methodology. Instead of developing a model that combines GRS with clinical variables in the entire cohort, we assessed added value of GRS in a key clinically defined group (borderline-/intermediate-ASCVD risk) where additional risk stratification tools are needed. Furthermore, because this is not a model development study, we did not use statistics commonly used for assessing the model performance such as C-statistic and net reclassification improvement (NRI). Rather, we used a simple and clinical meaningful statistic (incident CAD rate) to measure its performance. Finally, we used GRS as a PRS method of choice for several considerations, including 1) simple interpretation to facilitate clinical use (the value of GRS can be interpreted as relative risk to the general population regardless number of SNPs), 2) risk-associated SNPs are well established in prior studies, and 3) fewer number of SNPs for simplifying clinical laboratory regulation (compared with millions of SNPs in other PRSs). It is noted that the performance of various PRSs are similar for CAD and other diseases [8,13]. Our results, together with a newly published study demonstrating improved quality-adjusted life-years by implementing PRS [14], suggest PRS is a cost-effective risk-enhancing factor.

A major limitation of the study is that only subjects of White ancestry were analyzed. It is critical to validate our finding in other ancestry groups. Another limitation is incomplete FH of heart disease in the UKB. More detailed FH information, especially about premature CVDs in first- and second-degree relatives, may improve the discriminative performance of FH [15].

In conclusion, our study provides evidence for GRS_{CAD} to be considered as a risk-enhancing factor among subjects of European ancestry with borderline-/intermediate-ASCVD risk. This result should be validated in other ancestry-specific populations.

Ethical approval and consent to participate

The UK Biobank was approved by North West – Haydock Research Ethics Committee (REC reference: 16/NW/0274; IRAS project ID: 200778). Data from the UK Biobank was accessed through a Material Transfer Agreement under Application Reference Number: 50295. This study was performed in accordance with the Declaration of Helsinki.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

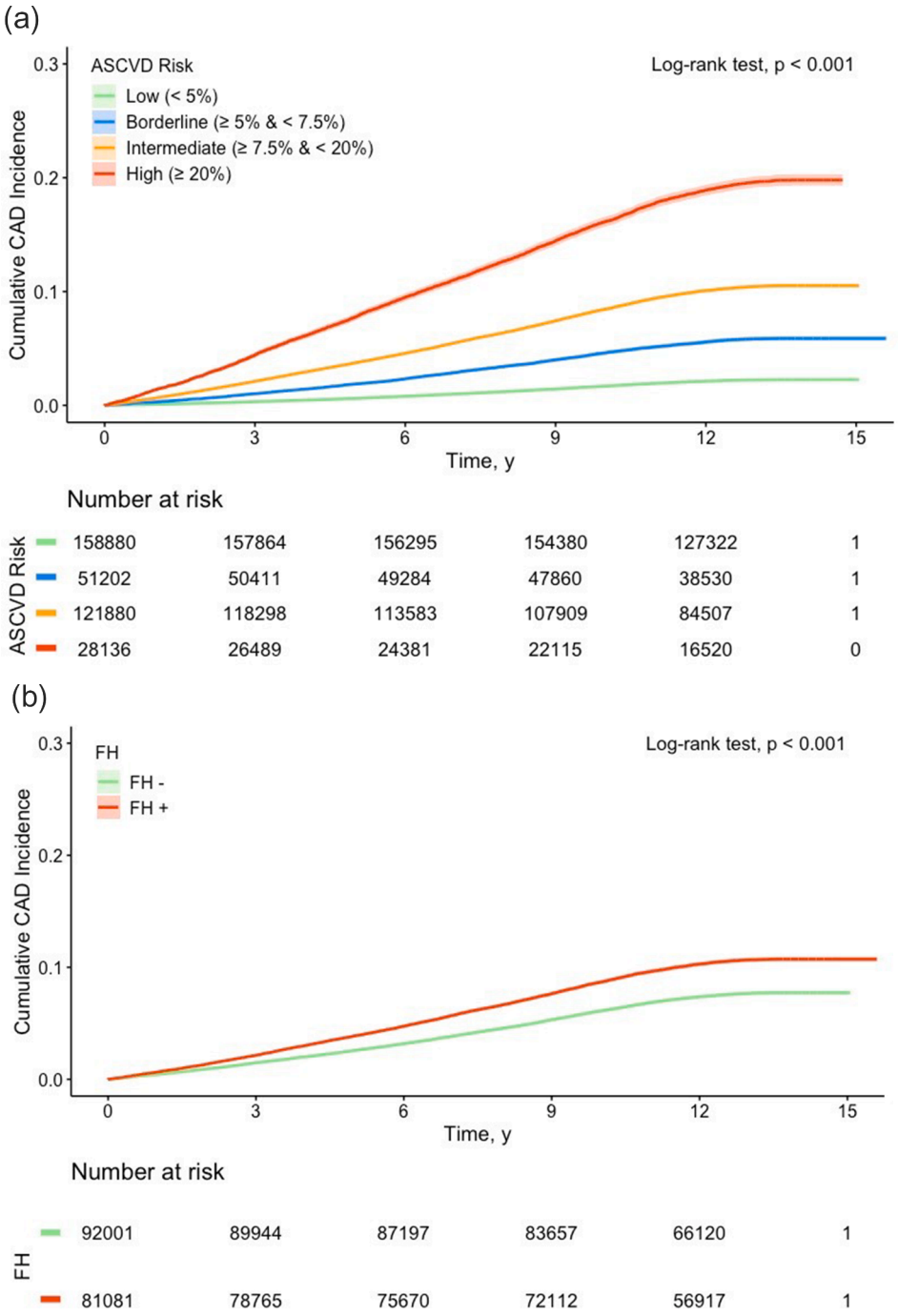

Fig. 1. Kaplan-Meier analysis for time to incident CAD from study recruitment in the UKB (White): a) four ASCVD risk groups in the entire cohort, b) with or without a family history (FH) of heart disease among subjects with borderline/intermediate-ASCVD risk, c) four GRS_{CAD} risk groups (<0.5, 0.5–1.49, 1.5–3 and ≥ 3) among subjects with borderline/intermediate-ASCVD risk, and d) combination of FH status and GRS_{CAD} risk groups.

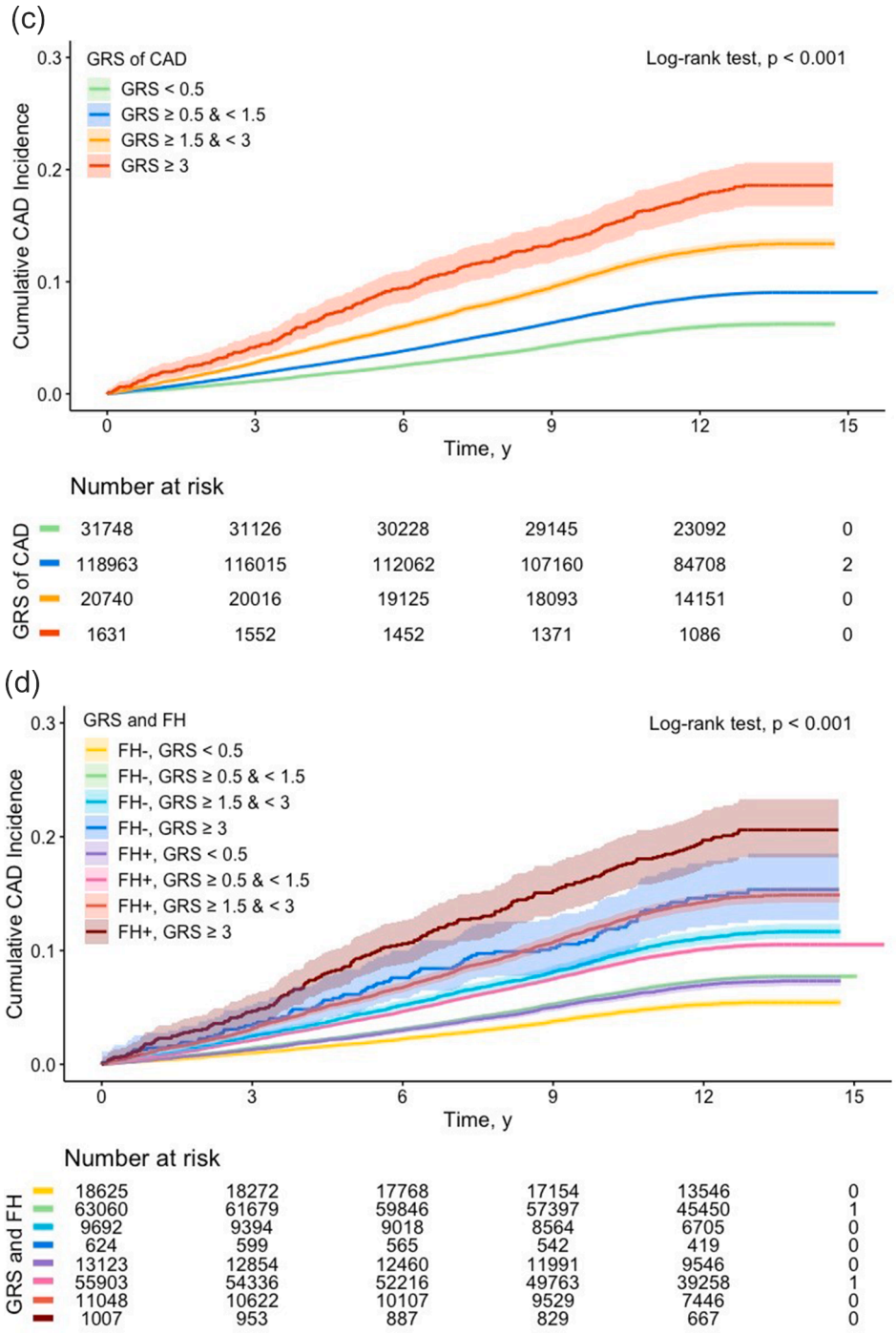

Fig. 1. (*continued*).

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2022.101136.

References

[1] N.D. Wong, M.J. Budoff, K. Ferdinand, I.M. Graham, E.D. Michos, T. Reddy, et al., Atherosclerotic cardiovascular disease risk assessment: An American Society for Preventive Cardiology clinical practice statement, Am J Prev Cardiol 10) (2022), 100335.

[2] D.K. Arnett, R.S. Blumenthal, M.A. Albert, A.B. Buroker, Z.D. Goldberger, E. J. Hahn, et al., 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American college of cardiology/American heart association task force on clinical practice guidelines, Circulation 140 (11) (2019) e596–e646.

[3] J.W. O'Sullivan, S. Raghavan, C. Marquez-Luna, J.A. Luzum, S.M. Damrauer, E. A. Ashley, et al., Polygenic risk scores for cardiovascular disease: A scientific statement from the american heart association, Circulation 146 (8) (2022) e93–e118.

[4] C. Bycroft, C. Freeman, D. Petkova, G. Band, L.T. Elliott, K. Sharp, et al., The UK Biobank resource with deep phenotyping and genomic data, Nature 562 (7726) (2018) 203–209.
[5] P. van der Harst, N. Verweij, Identification of 64 novel genetic loci provides an expanded view on the genetic architecture of coronary artery disease, Circ Res 122 (3) (2018) 433–443.
[6] American College of Cardiology, American Heart Association. ASCVD Risk Estimator 2022 [Available from: https://tools.acc.org/ldl/ascvd_risk_estimator/index.html#!/calulate/estimator/estimator.
[7] H. Yu, Z. Shi, Y. Wu, C.H. Wang, X. Lin, C. Perschon, et al., Concept and benchmarks for assessing narrow-sense validity of genetic risk score values, Prostate 79 (10) (2019) 1099–1105.
[8] K.G. Aragam, A. Dobbyn, R. Judy, M. Chaffin, K. Chaudhary, G. Hindy, et al., Limitations of contemporary guidelines for managing patients at high genetic risk of coronary artery disease, J Am Coll Cardiol 75 (22) (2020) 2769–2780.
[9] J. Elliott, B. Bodinier, T.A. Bond, M. Chadeau-Hyam, E. Evangelou, K.G.M. Moons, et al., Predictive accuracy of a polygenic risk score-enhanced prediction model vs a clinical risk score for coronary artery disease, JAMA 323 (7) (2020) 636–645.
[10] G. Hindy, K.G. Aragam, K. Ng, M. Chaffin, L.A. Lotta, A. Baras, et al., Genome-wide polygenic score, clinical risk factors, and long-term trajectories of coronary artery disease, Arterioscler Thromb Vasc Biol 40 (11) (2020) 2738–2746.
[11] C. Yang, F. Starnecker, S. Pang, Z. Chen, U. Guldener, L. Li, et al., Polygenic risk for coronary artery disease in the Scottish and English population, BMC Cardiovasc Disord 21 (1) (2021) 586.
[12] F. Riveros-Mckay, M.E. Weale, R. Moore, S. Selzam, E. Krapohl, R.M. Sivley, et al., Integrated polygenic tool substantially enhances coronary artery disease prediction, Circ Genom Precis Med 14 (2) (2021) e003304.
[13] Y. Ma, X. Zhou, Genetic prediction of complex traits with polygenic scores: a statistical review, Trends Genet 37 (11) (2021) 995–1011.
[14] D. Mujwara, G. Henno, S.T. Vernon, S. Peng, P. Di Domenico, B. Schroeder, et al., Integrating a polygenic risk score for coronary artery disease as a risk-enhancing factor in the pooled cohort equation: a cost-effectiveness analysis study, J Am Heart Assoc 11 (12) (2022) e025236.
[15] D.M. Lloyd-Jones, B.H. Nam, R.B. D'Agostino Sr., D. Levy, J.M. Murabito, T. J. Wang, et al., Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring, JAMA 291 (18) (2004) 2204–2211.