Accepted author's manuscript. Published in final edited form as:
Clinical Infectious Diseases 2021; 73(9): 1597-1604. Publisher DOI: 10.1093/cid/ciab521

Coronary Artery Disease-associated and Longevity-associated Polygenic Risk Scores for Prediction of Coronary Artery Disease Events in Persons Living with HIV: The Swiss HIV Cohort Study

Isabella C. Schoepf[1]*, Christian W. Thorball[2,3]*, Bruno Ledergerber[4], Tanja Engel[1], Marieke Raffenberg[1], Neeltje A. Kootstra[6], Peter Reiss[7], Barbara Hasse[4], Catia Marzolini[8], Christine Thurnheer[9], Marco Seneghini[10], Enos Bernasconi[11], Matthias Cavassini[12], Hélène Buvelot[13], Roger Kouyos[4,5], Huldrych F. Günthard[4,5], Jacques Fellay[2,3], and Philip E. Tarr[1], for the Swiss HIV Cohort Study

* *these authors contributed equally to the manuscript*

[1] University Department of Medicine and Infectious Diseases Service, Kantonsspital Baselland, University of Basel, 4101 Bruderholz, Switzerland
[2] Precision Medicine Unit, Lausanne University Hospital and University of Lausanne, 1011 Lausanne, Switzerland
[3] School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne, 1015 Lausanne, Switzerland
[4] Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, 8091 Zurich, Switzerland
[5] Institute of Medical Virology, University of Zurich, Zurich, 8091 Zurich, Switzerland
[6] Department of Experimental Immunology, Amsterdam University Medical Centers, University of Amsterdam, Netherlands
[7] Department of Global Health an Division of Infectious Disease, Amsterdam University Medical Centers, University of Amsterdam, and Amsterdam Institute for Global Health and Development, Amsterdam, The Netherlands
[8] Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, 4031 Basel, Switzerland
[9] Department of Infectious Diseases, Bern University Hospital, University of Bern, 3010 Bern, Switzerland
[10] Division of Infectious Diseases, Kantonsspital St Gallen, 9007 St. Gallen, Switzerland
[11] Division of Infectious Diseases, Ospedale Regionale Lugano, University of Geneva and Università della Svizzera italiana, 6900 Lugano, Switzerland
[12] Infectious Diseases Service, Lausanne University Hospital, University of Lausanne, 1011 Lausanne, Switzerland
[13] Division of Infectious Disease, Geneva University Hospital, 1205 Geneva, Switzerland

Corresponding author: Philip E. Tarr, MD, University Dept. of Medicine and Infectious Diseases Service, Kantonsspital Baselland, University of Basel, 4101 Bruderholz, Switzerland; Phone +41 (61) 436 2212, Fax +41 (61) 436 3670, philip.tarr@unibas.ch

Alternative corresponding author: Isabella C. Schoepf, MD, University Dept. of Medicine and Infectious Diseases Service, Kantonsspital Baselland, University of Basel, 4101 Bruderholz, Switzerland; Phone +41 (76) 432 1535, isabella.schoepf@unibas.ch

Running head: Schoepf Polygenic Risk Score CAD HIV

Word counts: Abstract 248, Main text 2989

Brief, 40-word-or-less summary of the article's main point. Genetic background is associated with coronary artery disease (CAD) events. People living with HIV (PLWH) have accentuated aging. Adding longevity-associated genetic variants to an individual polygenic risk score based on CAD-associated variants improves CAD event prediction.

Abstract

Background. Coronary artery disease (CAD) is in part genetically determined. Aging is accentuated in people with HIV (PLWH). It is unknown whether genetic CAD event prediction in PLWH is improved by applying individual polygenic risk scores (PRS) and by considering genetic variants associated with successful aging and longevity.

Methods. In Swiss HIV Cohort Study participants of self-reported European descent, we determined univariable and multivariable odds ratios (OR) for CAD events, based on traditional CAD risk factors, adverse antiretroviral exposures, and different validated genome-wide PRS. PRS were built from CAD-associated single nucleotide polymorphisms (SNPs), longevity-associated SNPs, or both.

Results. We included 269 cases with CAD events between 2000-2017 (Median age 54 years, 87% male, 82% with suppressed HIV RNA) and 567 event-free controls. Clinical (i.e. traditional and HIV-related) risk factors, and PRS built from CAD-associated SNPs, longevity-associated SNPs, or both, each contributed independently to CAD events ($p \leq 0.001$). Participants with the most unfavorable clinical risk factor profile (top quintile) had adjusted CAD-OR=17.82 (8.19-38.76), compared to participants in the bottom quintile. Participants with the most unfavorable CAD-PRS (top quintile) had adjusted CAD-OR=3.17 (1.74-5.79), compared to the bottom quintile. After adding longevity-associated SNPs to the CAD-PRS, participants with the most unfavorable genetic background (top quintile) had adjusted CAD-OR=3.67 (2.00-6.73), compared to the bottom quintile.

Conclusions. In Swiss PLWH, CAD prediction based on traditional and HIV-related risk factors was superior to genetic CAD prediction based on longevity- and CAD-associated PRS. Combining traditional, HIV-related and genetic risk factors provided the most powerful CAD prediction.

Keywords. HIV infection, coronary artery disease, polygenic risk score, aging, multivariable analysis.

Introduction

Current meta-analyses and guidelines suggest an approximately two-fold elevated rate of coronary artery disease (CAD) events in people living with HIV (PLWH), including in those with suppressed viremia on antiretroviral therapy (ART), compared to the general population.[1-2] Individual susceptibility to CAD in PLWH is influenced by traditional CAD risk factors as well as HIV-associated factors including adverse antiretroviral exposures.[3-4] CAD also has a strong hereditary component.[5-8] Genome-wide association studies (GWAS) [9-13] have identified common genetic variants that contribute to CAD risk in the general population, with CAD lifetime risk trajectories robustly established based on a polygenic risk score (PRS) consisting of 1.7 million single nucleotide polymorphisms (SNPs) in >480,000 individuals.[13]

We have previously reported a 1.47-fold increased CAD risk in PLWH with unfavorable genetic background, based on 23 common SNPs.[14] This genetic CAD risk increase was similar to the risk increase attributable to traditional risk factors (e.g. dyslipidemia) or adverse antiretroviral exposures (e.g. abacavir, lopinavir).[14] Since there is concern that aging in PLWH may be accelerated and/or accentuated, there is interest in the potential for improved genetic CAD risk prediction by including SNPs that have been reliably associated with successful aging and longevity in the general population.[15-16] Here we evaluate CAD event prediction in Swiss PLWH based on traditional, HIV-related and genetic risk factors, including different PRS built from validated, CAD-associated and longevity-associated SNPs.

Methods

Study population. We included PLWH enrolled in the Swiss HIV Cohort Study (SHCS, www.shcs.ch)[17] who were participants of our previous CAD event prediction study.[18] The study was approved by the respective local ethics committees. Participants provided written informed consent for genetic testing. Cases had a first CAD event and controls were CAD event-free during the study period (01.01.2000-31.12.2017). Because previous CAD-GWAS in the general population were conducted in populations of mostly European descent,[19] the study was restricted to participants of self-reported European descent.

CAD events. CAD events were defined according to the Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) study and the MONICA Project of the World Health Organization,[20] as previously reported.[18]

Case-control matching. As previously reported,[18] we aimed to select 3 controls who were CAD event-free at the CAD event date of the corresponding case (matching date) using risk-set sampling.[21] We used incidence density sampling for matching,[22] i.e. we matched controls on similar observation *duration*, and their observation *period* was during similar calendar periods, in order to account for differences in ART (with different potential CAD risk associations[23-24]) in use at different times and other differences during the observation period. As previously reported,[18] we used as matching criteria sex, age +/- 4 years, and date of SHCS enrolment +/- 4 years. Cases were observed until the matching date and controls were observed until the first regular SHCS follow-up examination after the CAD event date of the corresponding case, respectively. We allowed re-use of controls for up to 3 cases.[21]

Non-genetic clinical CAD risk factors. As previously reported,[18] co-variables included smoking (current, past, never), age (per 1 year older), family history of CAD, diabetes mellitus, hypertension, and dyslipidemia (defined as previously published).[27] HIV-related co-variables included HIV viremia at the matching date (HIV RNA < or ≥50 copies/mL), CD4 nadir, and ART exposures, defined *a priori*, based on their CAD-association in the D:A:D study, i.e. current (last 6 months) exposure to abacavir

(ABC),[23] and cumulative exposure (≥1 year) to lopinavir (LPV), indinavir (IDV), darunavir (DRV)[24], and stavudine (d4T) [25-26] until the matching date, cytomegalovirus (CMV) seropositivity,[28] hepatitis C (HCV) seropositivity,[29-30] and intravenous drug use (IDU).

Genotyping. DNA samples were obtained from peripheral blood mononuclear cells (PBMC) and genotyped with the Global Screening Array v2.0+MD (Illumina, San Diego, CA), or in the setting of previous SHCS genetic studies. All quality control, filtering and imputation steps prior to the merging of batches were performed separately for each batch of samples as described (**Supplementary Methods).** For the final merged dataset used to calculate the PRS, only variants with a minor allele frequency >5% and missingness <10% were kept.

Genome-wide Polygenic Risk Scores. PRS were calculated using PRSice (v2.3.3). The CAD-PRS was calculated by directly applying the variant information from the CAD-PRS previously validated by Inouye.[13] Information on included variants in this score and their weights were downloaded from the PGS Catalog.[31] In total, 607,895 variants from the Inouye PRS[13] were successfully matched and included in the CAD-PRS.

The longevity-PRS was calculated using the p-values and effect sizes from a large recent longevity GWAS study by Deelen,[16] using the 90th survival percentile as phenotype. Following matching between the genotype data and summary statistics, the variants were clumped using windows of 250kb and an r2=0.1. The best-fit model with 4 independent genome-wide significant SNPs (P<5e-8) from Deelen *et al*[16] was found by P-value thresholding with PRSice. Of note, a *favorable* longevity-PRS associates with longevity in the reference study; an *unfavorable* longevity-PRS associates with CAD events in the present study. We also applied a combined "meta-PRS" (i.e. CAD-PRS plus longevity-PRS), which we calculated following the same principles described previously by Inouye [13] (**Supplemental Methods**).

Power calculation. In order to detect CAD event odds ratios of ≥1.6, 255 cases and 2 controls per case would be required.[32] As recommended, the calculations assume a correlation of exposure between pairs in the case-control set of 0.2.[32]

Statistical analyses. Univariable and multivariable conditional logistic regression analyses were used to estimate associations of the different clinical and genetic risk factors. We decided a priori to stratify the genetic risk factors into quintiles for better visualization of their potentially non-linear associations with CAD events. Clinical variables were entered into the multivariable model if their association in the univariable model had $p<0.2$. We combined all traditional and HIV-related risk factors into a single measure of "clinical" CAD event risk by creating quintiles of the individually predicted CAD event probabilities from the multivariable model with the clinical risk factors as described above. These clinical risk quintiles were then used to check for and visualize interactions with genetic risk factors. Model fit and interactions were analyzed using Akaike and Bayesian information criteria and likelihood ratio tests. CAD event variation explained by the different models with combinations of clinical and genetic risk factors were documented with Pseudo R^2 values (as in our 2013 CAD-genetic study [14]) and receiver operating characteristic (ROC) values. To assess for an association between TL, longevity-PRS, and CAD prediction, we added TL to the multivariable models. We used Stata/SE 16.1 (StataCorp, College Station, TX, USA).

Results

Participants. After excluding 46 cases and 31 controls (because of excessive missingness in the genotyping data), and 98 participants (because of incomplete case-control pairs), the study population consisted of 269 cases and 567 controls, based on 357 individual control participants who were used for one (n=212), two (n=80), or three cases (n=65). CAD events included myocardial infarction (n=143), coronary angioplasty/stenting (n=102), coronary artery bypass grafting (n=17), and fatal CAD with evidence of CAD before death (n=7).[18] The participants' baseline characteristics are shown in **Table 1**. Cases were older, more likely to be IDU, current smokers, diabetic, dyslipidemic, or have a CAD family history, and their ART exposure was longer.

Polygenic Risk Scores. Following p-value thresholding, the CAD-PRS included 607,895 SNPs, and the longevity-PRS included 4 independent SNPs after clumping (**Supplementary Table 1**). There was no evidence of a correlation between CAD-PRS and longevity-PRS (Pearson correlation r=0.06).

Probability of CAD Events: Univariable Analysis. Cases had higher clinical CAD risk and higher genetic CAD risk than controls, as indicated by the asymmetric distribution of cases among the quintiles, i.e. distribution of cases was skewed towards the 5th (most unfavorable) vs. the other quintiles of clinical risk (**Figure 1A**), CAD-PRS (**Figure 1B**), longevity-PRS (**Figure 1C**), and meta-PRS (**Figure 1D**). CAD event probability was significantly associated with clinical risk (test for trend, $p<0.001$), CAD-PRS ($p<0.001$), longevity-PRS ($p=0.001$), and meta-PRS ($p<0.001$) (**Figure 2**).

Probability of CAD Events According to Clinical Risk Factors: Univariable Analysis. Regarding traditional risk factors, CAD was associated with age, family history of CAD, current smoking, diabetes mellitus, dyslipidemia, CMV seropositivity, and HCV seropositivity. Compared to participants in the first (most favorable) quintile of *traditional* risk, participants in the second, third, fourth, and fifth (most unfavorable) quintiles had univariable CAD-OR=2.63 (1.36-5.09), 3.96 (2.09-7.52), 3.68 (1.95-6.95) and 8.70 (4.82-15.68), respectively.

Regarding HIV-associated risk factors, CAD was associated with current use of ABC, cumulative exposure to LPV, IDV, DRV, d4T, and CD4 nadir, but not with HIV viral load or CD4 count at the matching date, or with cocaine use (**Supplementary Table 2**). Compared to participants in the first quintile of *HIV-associated* risk, participants in the second, third, fourth, and fifth quintiles had univariable CAD-OR=1.63 (0.80-3.31), 3.65 (1.80-7.42), 4.04 (2.09-7.82) and 8.71 (4.93-15.39), respectively. Compared to participants in the first quintile of *clinical* risk (i.e. traditional and HIV-related risk factors combined), participants in the second, third, fourth, and fifth quintiles had univariable CAD-OR=2.31 (0.91-5.89), 6.50 (2.73-15.49), 17.18 (6.94-42.56) and 17.82 (8.19-38.76), respectively.

Probability of CAD Events According to Polygenic Risk Scores: Univariable Analysis. Compared to the first (most favorable) CAD-PRS quintile, participants in the second, third, fourth, and fifth (most unfavorable) quintiles had CAD-OR=0.99 (0.59-1.63), 0.79 (0.48-1.31), 1.79 (1.11-2.89) and 2.93 (1.78-4.82), respectively. Compared to the first longevity-PRS quintile, participants in the second, third, fourth, and fifth quintiles had CAD-OR=1.31 (0.76-2.27), 1.17 (0.69-1.99), 1.43 (0.91-2.25) and 2.28 (1.39-3.76), respectively. Compared to the first meta-PRS quintile, participants in the second, third, fourth, and fifth quintiles had CAD-OR=1.49 (0.88-2.51), 1.63 (1.00-2.69), 1.91 (1.16-3.15) and 4.02 (2.43-6.66), respectively.

CAD Probability According to Clinical Risk Factors: Multivariable Analysis. CAD events remained associated with age, dyslipidemia, diabetes, CMV seropositivity, current use of ABC, cumulative exposure to IDV, DRV/r, and d4T (**Supplementary Table 2**). The effect size of clinical risk factors was similar when *unadjusted* for genetic background and when we *adjusted* for either CAD-PRS, longevity-PRS, or meta-PRS (**Figure 2, left column**). For example, participants in the fifth vs. the first clinical risk quintile had adjusted CAD-OR=19.31 (8.74-42.66), 17.57 (8.04-38.41), and 17.41 (7.91-38.31), when adjusted for CAD-PRS, longevity-PRS, or meta-PRS, respectively. There was no evidence for interactions when formally testing with likelihood-ratio tests (all p>0.4).

CAD Probability According to Different Polygenic Risk Scores: Multivariable Analysis. When adjusting for clinical risk, and compared to the first (most favorable) *CAD-PRS* quintile, participants in the second, third, fourth, and fifth (most unfavorable) quintiles of CAD-PRS had multivariable CAD-OR=1.24 (0.67-2.30), 0.76 (0.40-1.42), 1.82 (1.00-3.00) and 3.17 (1.74-5.79), respectively (**Figure 2, right column**). When adjusting for clinical risk, and compared to the first *longevity-PRS* quintile, participants in the second, third, fourth, and fifth longevity-PRS quintiles had multivariable ORs=1.41 (0.74-2.71), 0.97 (0.51-1.85), 1.13 (0.66-1.93) and 1.61 (0.89-2.91), respectively). When adjusting for clinical risk, and compared to the first *meta-PRS* quintile, participants in the second, third, fourth, and fifth meta-PRS quintiles had multivariable ORs=1.31 (0.71-2.42), 1.40 (0.77-2.56), 1.62 (0.89-2.96) and 3.67 (2.00-6.73), respectively.

CAD Variability Explained by Clinical Risk Factors and Different Polygenic Risk Scores, Final multivariable model. CAD variability explained by traditional and HIV-related risk factors is shown in the **Supplementary Results**. The area under the ROC curve (ROC AUC) for clinical risk factors was 0.851. The ROC AUC for CAD-PRS, longevity-PRS, and meta-PRS was 0.688, 0.645, 0.688, respectively. The ROC AUC was improved when clinical and genetic risk factors were combined, i.e. ROC AUC for full clinical model plus CAD-PRS, full model plus longevity-PRS, and full model plus meta-PRS was 0.870, 0.855, and 0.868, respectively (**Figure 3**). Results were similar when we applied pseudo-R^2 values rather than ROC AUC, e.g. 0.309 (full clinical model), 0.060 (CAD-PRS), and 0.353 (full model plus CAD-PRS), respectively (**Figure 3**).

Addition of Telomere Length (TL) to the multivariable models. ROC AUC and pseudo-R^2 values were further improved when we added TL, i.e. for full clinical model plus CAD-PRS + TL, full model plus longevity-PRS + TL, and full model + meta-PRS + TL, ROC AUC was 0.876, 0.864, and 0.876, respectively, and pseudo-R^2 was 0.371, 0.338, 0.366, respectively. We found no evidence of a correlation between longevity-PRS and TL (Spearman rank correlation p=0.7).

Discussion

Our study investigating clinical and genetic CAD prediction in Swiss PLWH of European descent has two main findings: First, an unfavorable genetic background independently increases CAD event risk 3.17-fold, when applying an individual PRS based on CAD-associated SNPs, and CAD event risk was increased 3.67-fold when adding longevity-associated SNP to this CAD-PRS in a combined meta-PRS. Second, we provide a combined estimate of the impact of traditional and HIV-related risk factors (clinical risk) and show that the highest clinical risk category was associated with a 17.4 to 19.3-fold increased CAD risk. Thus, while clinical risk factors clearly explained a larger proportion of CAD variability than genetic background, clinical and genetic models independently predicted CAD events, and a combined clinical plus genetic model afforded the best CAD prediction.

Our results confirm our previous CAD-genetic report from 2013 that was based on a multinational (MAGNIFICENT) consortium of PLWH cohorts.[14] Importantly, we extend the MAGNIFICENT results by showing improved CAD prediction when applying an individual PRS in this study, as compared to a validated panel of 23 common SNPs (associated with CAD in the general population) that we applied in the MAGNIFICENT study.[14] The inclusion of common variants of smaller effect sizes in PRS, in addition to only the genome-wide significant variants, is now a well-established method to improve the predictive power of genetic risk scores.[13][33-34] The CAD effect of genetic background was not subtle, i.e. an unfavorable PRS increased CAD odds ratio 3.17-fold to 3.67-fold, depending on which PRS we applied. In contrast, an unfavorable genetic background based on 23 SNPs in MAGNIFICENT [14] was associated with a 1.47-fold increased CAD odds ratio. Similarly, CAD event variability explained was 6% (pseudo-R2 test) for CAD-PRS and meta-PRS, compared to 2% for longevity PRS, and only 0.9% in MAGNIFICENT.[14] CAD variability explained by traditional and HIV-related risk factors was higher (14% and 18%, respectively, and 31% in combination), emphasizing the importance of clinical risk factors for CAD event prediction. However, the best CAD prediction model overall was the combination of clinical risk factors plus meta-PRS (35% CAD event variability

explained). Adding telomere length to the models increased CAD prediction further (37% CAD event variability explained).

We investigated the hypothesis of improved CAD prediction by applying a PRS based not only on SNPs associated with CAD, but also on SNPs linked to longevity in large meta-analyses in the general population.[15-16] There is some overlap of SNPs associated with longevity and SNPs associated with CAD and other aging traits such as Alzheimer disease, diabetes, and cancer. This is supported by the longevity-PRS being dominated by the effect of rs429358 located within the *APOE* gene, a SNP that is also part of the CAD-PRS. The T allele of rs429358 has previously been associated with decreased triglycerides, decreased low-density lipoprotein levels and increased high-density lipoprotein levels,[37] while the C allele has been associated with an increased risk of Alzheimer disease.[38] However, we found no evidence of a correlation between CAD-PRS and longevity-PRS, providing the rationale for combining the CAD-PRS and the longevity-PRS into the meta-PRS, which modestly improved CAD prediction when compared to the CAD-PRS.

Our genetic results appear robust because we only considered SNPs that have been validated in large reference GWAS in the general population.[13][16] We applied rigorous quality control to the genetic data, corrected for residual population stratification, and excluded population outliers. Additional strengths include that we exploited prospectively recorded information in participants of the well-established Swiss HIV Cohort Study, which allowed us to quantify and compare the CAD effects of all relevant, i.e. clinical, HIV-related, and genetic risk factors. Of note, genetic background predicted individual CAD risk independently of family history of CAD, consistent with the MAGNIFICENT study [14] and findings in the general population.[35-36]

The contribution of genetic variation to common diseases such as CAD has been well studied in the general population, demonstrating a clinical value of genetic testing. Knowledge on how genetic risk factors contribute to HIV-related comorbidities remains limited. It was beyond the scope of our study to assess the clinical value of genetic testing (this will require prospective trials). Nonetheless, our

findings suggest how an individual PRS might be applied in clinical HIV practice. The knowledge that an unfavorable genetic background independently increases the CAD event risk 3.67-fold in those 20% PLWH in 5th meta-PRS quintile may suggest paying even greater attention to the optimization of clinical risk factors, and, perhaps, instituting primary CAD prevention with statins in such individuals. In addition, applying different PRS can inform the selection of PLWH at increased risk for attaining relevant endpoints in clinical trials.

Addition of TL to the model further improved CAD prediction, consistent with our previous report [18]. Although aging correlates with shorter TL, we found no evidence of a link between longevity-PRS and TL in our dataset. Detailed pathway analyses based on genetic information, using the principle of Mendelian randomization, can reveal causal relationships and provide pathogenic insights into CAD, and help avoid the risk of unknown confounding factors and reverse causation.[39-40] Based on limited study population size, our study was not powered for this type of genetic analysis.

Our study has additional limitations. We included only participants of European descent, because most GWAS of CAD have been conducted in populations of European descent. Our population was 87% male and relatively young; thus, results should only cautiously be extrapolated to females and elderly PLWH.

In conclusion, PLWH may have a significantly increased CAD risk because of clinical risk factors, an unfavorable genetic background, or the combination of both. Our results suggest that an unfavorable genetic background may explain why certain PLWH with low clinical CAD risk have coronary events, even in the absence of established traditional or HIV-related CAD risk factors, and vice versa. Our analyses demonstrate an independent contribution of individual PRS to explaining interindividual variation in CAD risk, when analyzed in the context of multiple traditional, HIV-related, and antiretroviral CAD risk factors. A combination of CAD-PRS and longevity-PRS modestly improved CAD prediction.

Notes

Author Contributions. Study design: ICS, CWT, BL, NAK, PR, RDK, HFG, JF, PET. Data management, participant selection, case-control matching: BL. Data acquisition: CWT, BL, BH, CM, CT, MS, EB, MC, HB, JF, PET. Data analysis: ICS, CWT, BL, JF, PET. Drafting of the manuscript: IS, CWT, BL, PET. Critical review and revision of the manuscript: All authors.

Acknowledgments. The authors acknowledge the effort and commitment of investigators, study nurses, laboratory personnel, and participants.

Funding statement. This work was supported by the SHCS [project 836]; the Swiss National Science Foundation (grant number 177499); and the SHCS Research Foundation. SHCS data are gathered by the 5 Swiss university hospitals, 2 cantonal hospitals, 15 affiliated hospitals, and 36 private physicians (listed in http://www.shcs.ch/180-health-care-providers).

Potential conflicts of interest statement: P. E. T.'s institution reports grants from Gilead and ViiV, outside the submitted work. B. L. received personal fees from Kantonsspital Baselland, Liestal, Switzerland, during the conduct of the study, and reports personal fees from Gilead, and ViiV, outside the submitted work. HFG, outside of this study, reports grants from Swiss HIV Cohort Study, grants from Swiss National Science Foundation, during the conduct of the study; grants from Swiss HIV Cohort Study, grants from Swiss National Science Foundation, grants from NIH, grants from Gilead unrestricted research grant, personal fees from Advisor/consultant for Merck, ViiV healthcare and Gilead Sciences and member of DSMB for Merck, grants from Yvonne Jacob Foundation. All other authors report no potential conflicts of interest. All authors have prepared ICMJE forms for disclosure of potential conflicts of interest.

Swiss HIV Cohort Study (SHCS) members. Anagnostopoulos A, Battegay M, Bernasconi E, Boni J, Braun DL, Bucher HC, Calmy A, Cavassini M, Ciuffi A, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Gunthard HF (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hoffmann M, Hosli I, Huber M,

Kahlert CR, Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Marzolini C, Metzner KJ, Muller N, Nicca D, Paioni P, Pantaleo G, Perreau M, Rauch A (Chairman of the Scientific Board), Rudin C (Chairman of the Mother & Child Substudy), Scherrer AU (Head of Data Centre), Schmid P, Speck R, Stockle M, Tarr P, Trkola A, Vernazza P, Wandeler G, Weber R, Yerly S.

References

1. Shah ASV, Stelzle D, Lee KK, et al. Global Burden of Atherosclerotic Cardiovascular Disease in People Living With HIV. *Circulation*. **2018**; 138(11):1100-1112.
2. Feinstein MJ, Hsue PY, Benjamin LA, et al. Characteristics, Prevention, and Management of Cardiovascular Disease in People Living with HIV: A Scientific Statement from the American Heart Association. *Circulation*. **2019**; 140(2):e98-e124.
3. Friis-Moller N, Reiss P, Sabin CA et al. Class of Antiretroviral Drugs and the Risk of Myocardial Infarction. *N Engl J Med*. **2007**; 356:1723-1735.
4. Sabin CA, Worm SW, Weber R, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: A multi-cohort collaboration. *Lancet*. **2008**; 371(9622):1417-1426.
5. Lohmueller KE, Pearce CL, Pike M, Lander ES, Hirschhorn JN. Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. *Nat Genet*. **2003**; 33(2):177-182.
6. Lloyd-Jones D, Nam B, D'Agostino R, et al. Parental Cardiovascular Disease as a Risk Factor for Cardiovascular Disease in Middle-aged Adults A Prospective Study of Parents and Offspring. *J Am Med Assoc*. **2004**; 291:2204–2211.
7. Murabito JM, Pencina MJ, Nam BH, et al. Sibling cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults. *J Am Med Assoc*. **2005**; 294(24):3117-3123.
8. Mangino M, Spector T. Understanding coronary artery disease using twin studies. *Heart*. **2013**; 99(6):373-375.
9. Samani N, Erdmann J, Mangino M, et al. Genomewide Association Analysis of Coronary Artery Disease Nilesh. *N Engl J Med*. Published online 2007; 443-453.
10. CARDIoGRAMplusC4D C. Large-scale association analysis identifies new risk loci for coronary artery disease. *Nat Genet*. **2013**; 45(1):25-33.
11. Nikpay M, Goel A, Won HH, et al. A comprehensive 1000 Genomes-based genome-wide association meta-analysis of coronary artery disease. *Nat Genet*. **2015**; 47(10):1121-1130.
12. Van Der Harst P, Verweij N. Identification of 64 novel genetic loci provides an expanded view on the

genetic architecture of coronary artery disease. *Circ Res*. **2018**; 122(3):433-443.

13. Inouye M, Abraham G, Nelson CP, et al. Genomic Risk Prediction of Coronary Artery Disease in 480,000 Adults: Implications for Primary Prevention. *J Am Coll Cardiol*. **2018**; 72(16):1883-1893.

14. Rotger M, Glass TR, Junier T, et al. Contribution of genetic background, traditional risk factors, and HIV-related factors to coronary artery disease events in HIV-positive persons. *Clin Infect Dis*. **2013**; 57(1):112-121.

15. Pilling LC, Kuo CL, Sicinski K, et al. Human longevity: 25 genetic loci associated in 389,166 UK biobank participants. *Aging (Albany NY)*. **2017**; 9(12):2504-2520.

16. Deelen J, Evans DS, Arking DE, et al. A meta-analysis of genome-wide association studies identifies multiple longevity genes. *Nat Commun*. **2019**; 10(1).

17. Schoeni-Affolter F, Ledergerber B, Rickenbach M, et al. Cohort profile: The Swiss HIV cohort study. *Int J Epidemiol*. **2010**; 39(5):1179-1189.

18. Engel T, Raffenberg M, Schoepf IC, et al. Telomere Length, Traditional Risk Factors, HIV- related Factors and Coronary Artery Disease Events in Swiss Persons Living with HIV. *Clin Infect Dis*. **2020**; ciaa1034.

19. Schunkert H, König IR, Kathiresan S, et al. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. *Nat Genet*. **2011**; 43(4):333-340.

20. World Health Organisation WHO. Monica Manual, Part IV: Event Registration, Section 1: Coronary Event Registration Data Component. 199. Available at: https://www.thl.fi/publications/monica/manual/part4/iv-1.htm. Accessed 08 September 2020.

21. Essebag V, Genest J, Suissa S, Pilote L. The nested case-control study in cardiology. *Am Heart J*. **2003**; 146(4):581-590.

22. Greenland S, Thomas DC. On the need for the rare disease assumption in cases-control studies. *Epidemiology*. **1982**; 116(3):547-553.

23. D:A:D study, Sabin CA, Worm SW, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: A multi-cohort collaboration. *Lancet*. **2008**; 371(9622):1417-1426.

24. Ryom L, Lundgren JD, El-Sadr W, et al. Cardiovascular disease and use of contemporary protease inhibitors: the D:A:D international prospective multicohort study. *Lancet HIV*. **2018**; 5(6):e291-e300.

25. Van Zoest R, Wit FW, Kooij KW et al. Higher Prevalence of Hypertension in HIV-1-Infected

Patients on Combination Antiretroviral Therapy Is Associated With Changes in Body Composition and Prior Stavudine Exposure. *Clin Infect Dis*. **2016**; 63(2):205-213.

26. Gelpi M, Afzal S, Lundgren J, et al. Higher Risk of Abdominal Obesity, Elevated Low-Density Lipoprotein Cholesterol, and Hypertriglyceridemia, but not of Hypertension, in People Living With Human Immunodeficiency Virus (HIV): Results From the Copenhagen Comorbidity in HIV Infection Study. *Clin Infect Dis*. **2018**; 67(4):579-586.

27. Tarr PE, Ledergerber B, Calmy A, et al. Subclinical coronary artery disease in Swiss HIV-positive and HIV-negative persons. *Eur Heart J*. **2018**; 39(23):2147-2154.

28. Combs JA, Norton EB, Saifudeen ZR, et al. Human Cytomegalovirus Alters Host Cell Mitochondrial Function during Acute Infection. *J Virol*. **2019**; 94(2):1-19.

29. Wong RJ, Kanwal F, Younossi ZM AA. Hepatitis C virus infection and coronary artery disease risk: a systematic 28 review of the literature. *Dig Dis Sci*. **2014**; 59:1586-1593.

30. Kovari H, Rauch A, Kouyos R, et al. Hepatitis C infection and the risk of non-liver-related morbidity and mortality in HIV-infected persons in the swiss HIV cohort study. *Clin Infect Dis*. **2017**; 64(4):490-497.

31. Lambert SA, Gil L, Jupp S, et al. The Polygenic Score Catalog: an open database for reproducibility and systematic evaluation. *medRxiv*. Published online January 1, 2020; 2020.05.20.20108217.

32. Dupont WD. Power Calculations for Matched Case-Control Studies. *Biometrics*. **1988**; 44(4):1157.

33. International Schizophrenia Consortium, Purcell S, Wray N et al. Common polygenic variation contributes to risk of schizophrenia that overlaps with bipolar disorder International. *Nature*. **2009**; 460:748– 752.

34. Chatterjee N, Wheeler B, Sampson J, Hartge P, Chanock SJ, Park J-H. Polygenic Analyses of Genome-Wide Association Studies. *Nat Genet*. **2013**; 45(4):400-405.

35. Chow C, Bautista L, Rumboldt Z, et al. Parental History and Myocardial Infarction Risk Across the World. *J Am Coll Cardiol*. **2011**; 57:619-627.

36. Tada H, Melander O, Louie JZ, et al. Risk prediction by genetic risk scores for coronary heart disease is independent of self-reported family history. *Eur Heart J*. **2016**; 37(6):561-567.

37. Hoffmann TJ, Theusch E, Haldar T, et al. A large electronic-health-record-based genome-wide study of serum lipids. Nat Genet. **2018**; 50(3):401-413.

38. Kamboh M, Demirci F, Wang X, et al. Genome-wide association study of Alzheimer's disease. Transl

Psychiatry 2. **2012** e117.

39. Nordestgaard BG, Palmer TM, Benn M, et al. The effect of elevated body mass index on ischemic heart disease risk: Causal estimates from a mendelian randomisation approach. *PLoS Med*. **2012**; 9(5).

40. Erdmann J, Kessler T, Munoz Venegas L, Schunkert H. A decade of genome-wide association studies for coronary artery disease: The challenges ahead. *Cardiovasc Res*. **2018**; 114(9):1241-1257.

438 **Table 1: Characteristics of Cases and Controls at the Matching Date**

		Cases (n=269)	**Controls** (n=567)
Male sex, n (%)		235 (87.4)	500 (88.2)
Age (years), median (IQR)		54 (48-62)	53 (47-62)
HIV acquisition mode, n (%)			
	heterosexual	70 (26.0)	162 (28.6)
	MSM	132 (49.1)	295 (52.0)
	IDU	57 (21.2)	96 (16.9)
	other	10 (3.7)	14 (2.5)
Smoking, n (%)			
	current	135 (50.2)	246 (43.4)
	past	81 (30.1)	173 (30.5)
	never	53 (19.7)	148 (26.1)
Cocaine use, n (%)	Recent*	10 (3.7)	22 (3.9)
	Ever	22 (8.2)	50 (8.8)
Family History of CAD, n (%)		44 (16.4)	61 (10.8)
Diabetes mellitus, n (%)		47 (17.5)	37 (6.5)
Hypertension, n (%)		83 (30.9)	163 (28.8)
Dyslipidemia, n (%)		177 (65.8)	264 (46.6)
On ART, n (%)		247 (91.8)	481 (84.8)
On ART, HIV RNA <50 copies/mL (undetectable), n (%)		221 (82.2)	453 (79.9)
Total years on ART, median (IQR)		10.9 (6.6-15.8)	6.0 (2.5-10.9)
Duration of observation** (years), median (IQR)		11.8 (8.1-17.4)	11.2 (7.6-17.2)
Currently on Abacavir, n (%)		84 (31.2)	113 (20.0)
Lopinavir, exposure ≥1 year, n (%)		79 (29.4)	100 (17.6)
Indinavir, exposure ≥1 year, n (%)		65 (24.2)	53 (9.4)

Darunavir, exposure ≥1 year, n (%)		45 (16.7)	60 (10.6)
Stavudine, exposure ≥1 year, n (%)		117 (43.5)	87 (15.3)
CD4 at matching date, median (IQR)		490 (353-722)	526 (376-688)
CD4 during observation time, median (IQR)		459 (323-618)	470 (356-585)
CD4 nadir (cells/µL), median (IQR)		169 (71-257)	205 (126-318)
CD4 nadir <50 cells/µL, n (%)		50 (18.6)	58 (10.2)
Previous AIDS, n (%)		69 (25.6)	121 (21.3)
Hepatitis C Seropositivity, n (%)		121 (21.3)	75 (27.9)
CMV Seropositivity, n (%)		234 (87.0)	458 (80.8)

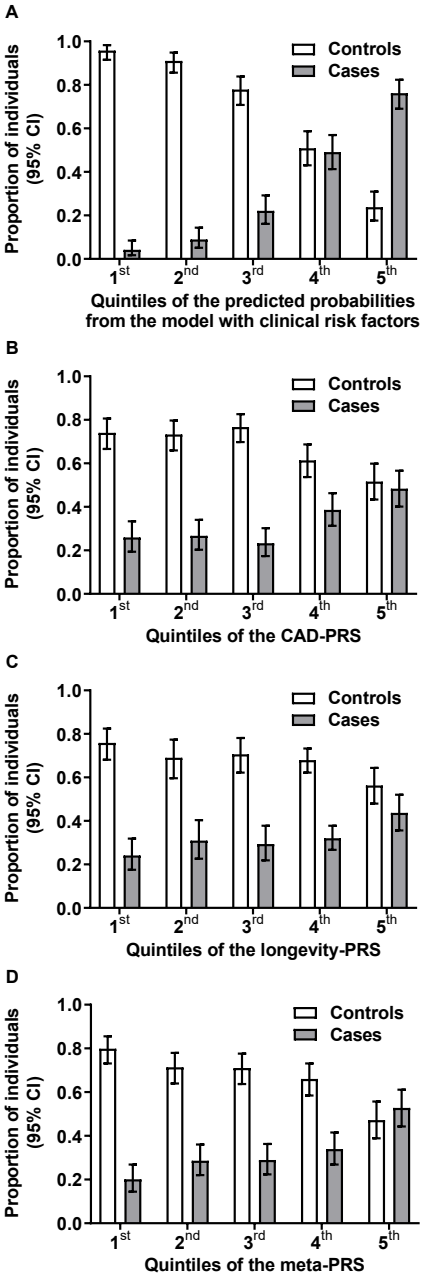
Note. All data shown apply to the matching date and are number (%) of participants, unless otherwise indicated.

* in 6 months prior to matching date

** From registration in the SHCS until the matching date, and, for controls, until first regular, twice-yearly follow-up visit after the matching date

Abbreviations. ART, antiretroviral therapy; CAD, coronary artery disease; CMV, cytomegalovirus; IDU, intravenous drug use; IQR, interquartile range; MSM, men who have sex with men.

Figure 1, A-D: Distribution of clinical risk factors and polygenic risk scores in 567 controls without coronary artery events (white bars) and in 269 cases with coronary artery events (gray bars).



We divided study participants into 5 quintiles according to their individual clinical and polygenic risk scores and show here the number, percentage and 95% confidence intervals of participants in each quintile.

A: Distribution of cases and controls according to quintiles of clinical risk. There were 7 (4.2%) cases vs. 160 (95.8%) controls in the 1st (most favorable) quintile, 15 (9%) vs. 152 (91%) in the 2nd quintile, 37 (22.2%) vs. 130 (77.8%) in the 3rd quintile, 82 (49.1%) vs. 85 (50.9%) in the 4th quintile, and 128 (76.2%) vs. 40 (23.8%) in the 5th (most unfavorable) quintile.

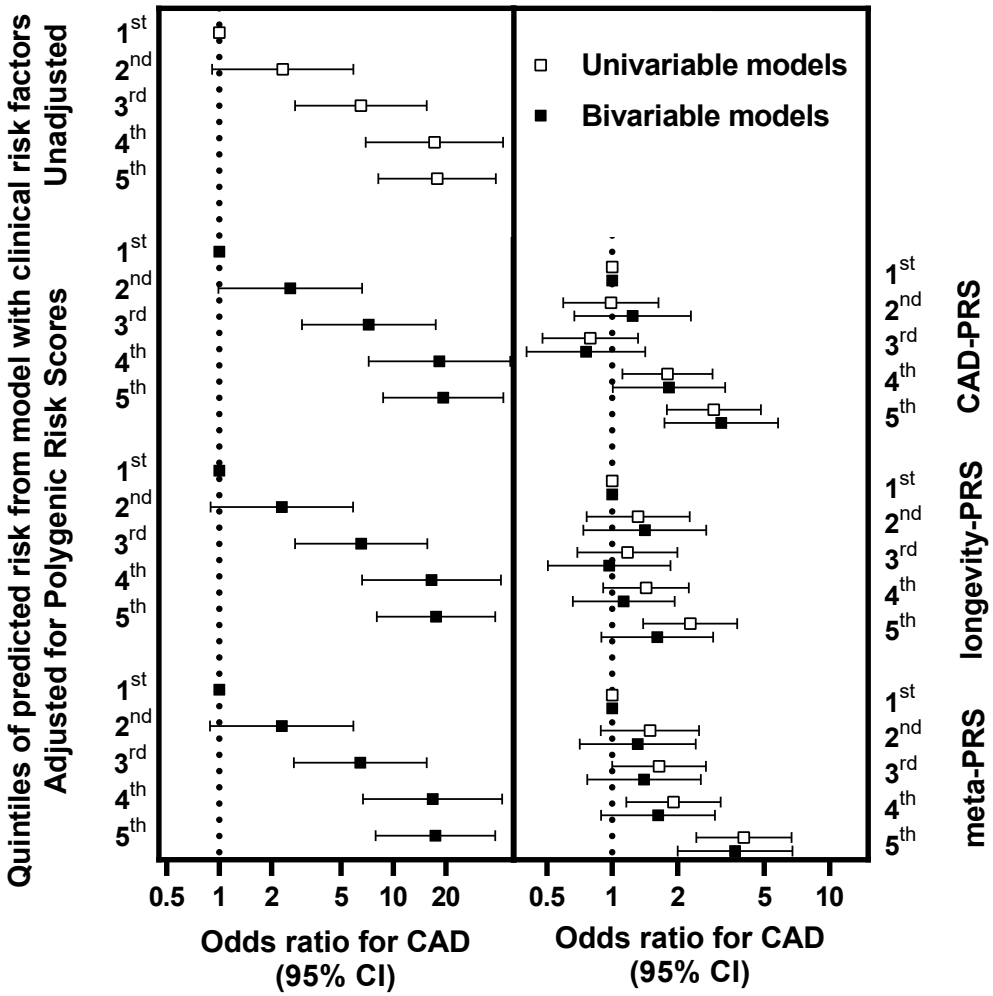
B: Distribution of cases and controls according to quintiles of CAD-PRS. There were 42 (25.9%) cases vs. 120 (74.1%) controls in the 1st quintile, 46 (26.7%) vs. 126 (73.3%) in the 2nd quintile, 42 (23.3%) vs. 138 (76.7%) in the 3rd quintile, 66 (38.6%) vs. 105 (61.4%) in the 4th quintile, and 73 (48.3%) vs. 78 (51.7%) in the 5th quintile.

C: Distribution of cases and controls according to quintiles of longevity-PRS. There were 36 (24.2%) cases vs. 113 (75.8%) controls in the 1st quintile, 35 (31%) vs. 78 (69%) in the 2nd quintile, 40 (29.4%) vs. 96 (70.6%) in the 3rd quintile, 92 (32.1%) vs. 195 (67.9%) in the 4th quintile, and 66 (43.7%) vs. 85 (56.3%) in the 5th quintile.

D: Distribution of cases and controls according to quintiles of combined CAD-PRS and longevity-PRS (meta-PRS). There were 35 (20.1%) cases vs. 139 (79.9%) controls in the 1st quintile, 49 (28.7%) vs. 122 (71.4%) in the 2nd quintile, 51 (29%) vs. 125 (71%) in the 3rd quintile, 58 (33.9%) vs. 113 (66.1%) in the 4th quintile, and 76 (52.8%) vs. 68 (47.2%) in the 5th quintile.

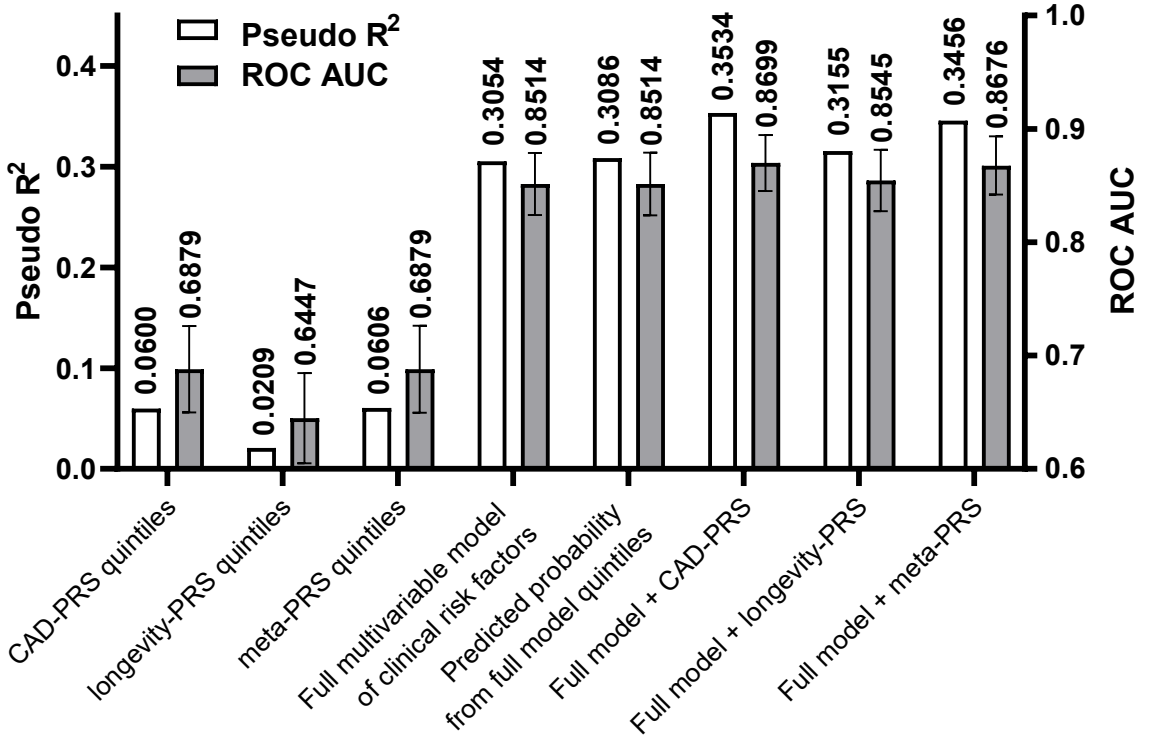
Abbreviations: CAD, coronary artery disease; CI, confidence interval; PRS, polygenic risk score.

Figure 2: CAD Event Odds Ratios (OR) according to Clinical Risk Factors and Different Polygenic Risk Scores (PRS).



Uni- and multivariable conditional logistic regression of associations with CAD events. Results involve 269 cases and 567 controls. Compared to the first (most favorable) quintile of clinical risk, participants in the second, third, fourth, and fifth (most unfavorable) quintile had multivariable ORs that remained similar, irrespective for which PRS we adjusted (**left column**). After adjustment for clinical risk factors, the CAD-PRS and meta-PRS remained significantly associated with CAD events, but not the longevity-PRS (**right column**). **Abbreviations**: CAD, coronary artery disease; CI, confidence interval; PRS, polygenic risk score

Figure 3: Coronary Artery Disease Event Variability Explained by Clinical Risk Factors and Different Polygenic Risk Scores.



CAD event variability (white bars; based on pseudoR2 test) that is explained by CAD-PRS, longevity-PRS, meta-PRS, full model of clinical risk factors without considering any PRS (continuous model and model that included quintiles of clinical risk), and CAD event variability explained by full model plus CAD-PRS, longevity-PRS, and meta-PRS. CAD event variability (gray bars; based on ROC AUC values) that is explained by CAD-PRS, longevity-PRS, meta-PRS, full model of clinical risk factors without considering any PRS (continuous model and model that included quintiles of clinical risk), and CAD event variability explained by full model plus CAD-PRS, longevity-PRS, and meta-PRS.

Abbreviations: CAD, coronary artery disease; PRS, polygenic risk score; ROC AUC, area under the receiver operating characteristic curve.