

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

4
5 Isabella C. Schoepf^{1*}, Christian W. Thorball^{2,3*}, Bruno Ledergerber⁴, Tanja Engel¹, Marieke
6 Raffenberg¹, Neeltje A. Kootstra⁶, Peter Reiss⁷, Barbara Hasse⁴, Catia Marzolini⁸, Christine Thurnheer⁹,
7 Marco Seneghini¹⁰, Enos Bernasconi¹¹, Matthias Cavassini¹², H el ene Buvelot¹³, Roger Kouyos^{4,5},
8 Huldrych F. G unthard^{4,5}, Jacques Fellay^{2,3}, and Philip E. Tarr¹, for the Swiss HIV Cohort Study

9
10 ** these authors contributed equally to the manuscript*

11
12 ¹ University Department of Medicine and Infectious Diseases Service, Kantonsspital Baselland, University of Basel, 4101
13 Bruderholz, Switzerland

14 ² Precision Medicine Unit, Lausanne University Hospital and University of Lausanne, 1011 Lausanne, Switzerland

15 ³ School of Life Sciences, Ecole Polytechnique F ed erale de Lausanne, 1015 Lausanne, Switzerland

16 ⁴ Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, 8091 Zurich,
17 Switzerland

18 ⁵ Institute of Medical Virology, University of Zurich, Zurich, 8091 Zurich, Switzerland

19 ⁶ Department of Experimental Immunology, Amsterdam University Medical Centers, University of Amsterdam, Netherlands

20 ⁷ Department of Global Health and Division of Infectious Disease, Amsterdam University Medical Centers, University of
21 Amsterdam, and Amsterdam Institute for Global Health and Development, Amsterdam, The Netherlands

22 ⁸ Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, 4031 Basel, Switzerland

23 ⁹ Department of Infectious Diseases, Bern University Hospital, University of Bern, 3010 Bern, Switzerland

24 ¹⁰ Division of Infectious Diseases, Kantonsspital St Gallen, 9007 St. Gallen, Switzerland

25 ¹¹ Division of Infectious Diseases, Ospedale Regionale Lugano, University of Geneva and Universit a della Svizzera italiana,
26 6900 Lugano, Switzerland

27 ¹² Infectious Diseases Service, Lausanne University Hospital, University of Lausanne, 1011 Lausanne, Switzerland

28 ¹³ Division of Infectious Disease, Geneva University Hospital, 1205 Geneva, Switzerland

29
30 **Corresponding author:** Philip E. Tarr, MD, University Dept. of Medicine and Infectious Diseases
31 Service, Kantonsspital Baselland, University of Basel, 4101 Bruderholz, Switzerland; Phone +41 (61)
32 436 2212, Fax +41 (61) 436 3670, philip.tarr@unibas.ch

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

36 **Running head:** Schoepf Polygenic Risk Score CAD HIV

37 **Word counts:** Abstract 248, Main text 2989

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

42

43 **Abstract**

44

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

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

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

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

65

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

67 **Introduction**

68 Current meta-analyses and guidelines suggest an approximately two-fold elevated rate of coronary
69 artery disease (CAD) events in people living with HIV (PLWH), including in those with suppressed
70 viremia on antiretroviral therapy (ART), compared to the general population.[1-2] Individual
71 susceptibility to CAD in PLWH is influenced by traditional CAD risk factors as well as HIV-associated
72 factors including adverse antiretroviral exposures.[3-4] CAD also has a strong hereditary
73 component.[5-8] Genome-wide association studies (GWAS) [9-13] have identified common genetic
74 variants that contribute to CAD risk in the general population, with CAD lifetime risk trajectories
75 robustly established based on a polygenic risk score (PRS) consisting of 1.7 million single nucleotide
76 polymorphisms (SNPs) in >480,000 individuals.[13]
77 We have previously reported a 1.47-fold increased CAD risk in PLWH with unfavorable genetic
78 background, based on 23 common SNPs.[14] This genetic CAD risk increase was similar to the risk
79 increase attributable to traditional risk factors (e.g. dyslipidemia) or adverse antiretroviral exposures
80 (e.g. abacavir, lopinavir).[14] Since there is concern that aging in PLWH may be accelerated and/or
81 accentuated, there is interest in the potential for improved genetic CAD risk prediction by including
82 SNPs that have been reliably associated with successful aging and longevity in the general
83 population.[15-16] Here we evaluate CAD event prediction in Swiss PLWH based on traditional, HIV-
84 related and genetic risk factors, including different PRS built from validated, CAD-associated and
85 longevity-associated SNPs.

86

87

88

89

90

91

92 **Methods**

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

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

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

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

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

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

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

132 The longevity-PRS was calculated using the p-values and effect sizes from a large recent longevity
133 GWAS study by Deelen,[16] using the 90th survival percentile as phenotype. Following matching
134 between the genotype data and summary statistics, the variants were clumped using windows of
135 250kb and an $r^2=0.1$. The best-fit model with 4 independent genome-wide significant SNPs ($P<5e-8$)
136 from Deelen *et al*[16] was found by P-value thresholding with PRSice. Of note, a *favorable* longevity-
137 PRS associates with longevity in the reference study; an *unfavorable* longevity-PRS associates with
138 CAD events in the present study. We also applied a combined “meta-PRS” (i.e. CAD-PRS plus
139 longevity-PRS), which we calculated following the same principles described previously by Inouye
140 [13] (**Supplemental Methods**).

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

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

158

159 **Results**

160

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

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

172 **Probability of CAD Events: Univariable Analysis.** Cases had higher clinical CAD risk and higher
173 genetic CAD risk than controls, as indicated by the asymmetric distribution of cases among the
174 quintiles, i.e. distribution of cases was skewed towards the 5th (most unfavorable) vs. the other
175 quintiles of clinical risk (**Figure 1A**), CAD-PRS (**Figure 1B**), longevity-PRS (**Figure 1C**), and meta-PRS
176 (**Figure 1D**). CAD event probability was significantly associated with clinical risk (test for trend,
177 $p<0.001$), CAD-PRS ($p<0.001$), longevity-PRS ($p=0.001$), and meta-PRS ($p<0.001$) (**Figure 2**).

178 **Probability of CAD Events According to Clinical Risk Factors: Univariable Analysis.** Regarding
179 traditional risk factors, CAD was associated with age, family history of CAD, current smoking, diabetes
180 mellitus, dyslipidemia, CMV seropositivity, and HCV seropositivity. Compared to participants in the
181 first (most favorable) quintile of *traditional* risk, participants in the second, third, fourth, and fifth
182 (most unfavorable) quintiles had univariable CAD-OR=2.63 (1.36-5.09), 3.96 (2.09-7.52), 3.68 (1.95-
183 6.95) and 8.70 (4.82-15.68), respectively.

184 Regarding HIV-associated risk factors, CAD was associated with current use of ABC, cumulative
185 exposure to LPV, IDV, DRV, d4T, and CD4 nadir, but not with HIV viral load or CD4 count at the
186 matching date, or with cocaine use (**Supplementary Table 2**). Compared to participants in the first
187 quintile of *HIV-associated* risk, participants in the second, third, fourth, and fifth quintiles had
188 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),
189 respectively. Compared to participants in the first quintile of *clinical* risk (i.e. traditional and HIV-
190 related risk factors combined), participants in the second, third, fourth, and fifth quintiles had
191 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),
192 respectively.

193 **Probability of CAD Events According to Polygenic Risk Scores: Univariable Analysis.** Compared to
194 the first (most favorable) CAD-PRS quintile, participants in the second, third, fourth, and fifth (most
195 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
196 (1.78-4.82), respectively. Compared to the first longevity-PRS quintile, participants in the second,
197 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
198 2.28 (1.39-3.76), respectively. Compared to the first meta-PRS quintile, participants in the second,
199 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
200 4.02 (2.43-6.66), respectively.

201 **CAD Probability According to Clinical Risk Factors: Multivariable Analysis.** CAD events remained
202 associated with age, dyslipidemia, diabetes, CMV seropositivity, current use of ABC, cumulative
203 exposure to IDV, DRV/r, and d4T (**Supplementary Table 2**). The effect size of clinical risk factors was
204 similar when *unadjusted* for genetic background and when we *adjusted* for either CAD-PRS,
205 longevity-PRS, or meta-PRS (**Figure 2, left column**). For example, participants in the fifth vs. the first
206 clinical risk quintile had adjusted CAD-OR=19.31 (8.74-42.66), 17.57 (8.04-38.41), and 17.41 (7.91-
207 38.31), when adjusted for CAD-PRS, longevity-PRS, or meta-PRS, respectively. There was no evidence
208 for interactions when formally testing with likelihood-ratio tests (all $p>0.4$).

209 **CAD Probability According to Different Polygenic Risk Scores: Multivariable Analysis.** When
210 adjusting for clinical risk, and compared to the first (most favorable) *CAD-PRS* quintile, participants in
211 the second, third, fourth, and fifth (most unfavorable) quintiles of *CAD-PRS* had multivariable CAD-
212 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,**
213 **right column**). When adjusting for clinical risk, and compared to the first *longevity-PRS* quintile,
214 participants in the second, third, fourth, and fifth *longevity-PRS* quintiles had multivariable ORs=1.41
215 (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
216 clinical risk, and compared to the first *meta-PRS* quintile, participants in the second, third, fourth, and
217 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)
218 and 3.67 (2.00-6.73), respectively.

219 **CAD Variability Explained by Clinical Risk Factors and Different Polygenic Risk Scores, Final**
220 **multivariable model.** CAD variability explained by traditional and HIV-related risk factors is shown in
221 the **Supplementary Results**. The area under the ROC curve (ROC AUC) for clinical risk factors was
222 0.851. The ROC AUC for *CAD-PRS*, *longevity-PRS*, and *meta-PRS* was 0.688, 0.645, 0.688, respectively.
223 The ROC AUC was improved when clinical and genetic risk factors were combined, i.e. ROC AUC for
224 full clinical model plus *CAD-PRS*, full model plus *longevity-PRS*, and full model plus *meta-PRS* was
225 0.870, 0.855, and 0.868, respectively (**Figure 3**). Results were similar when we applied pseudo-R²
226 values rather than ROC AUC, e.g. 0.309 (full clinical model), 0.060 (*CAD-PRS*), and 0.353 (full model
227 plus *CAD-PRS*), respectively (**Figure 3**).

228 **Addition of Telomere Length (TL) to the multivariable models.** ROC AUC and pseudo-R² values were
229 further improved when we added TL, i.e. for full clinical model plus *CAD-PRS* + TL, full model plus
230 *longevity-PRS* + TL, and full model + *meta-PRS* + TL, ROC AUC was 0.876, 0.864, and 0.876,
231 respectively, and pseudo-R² was 0.371, 0.338, 0.366, respectively. We found no evidence of a
232 correlation between *longevity-PRS* and TL (Spearman rank correlation $\rho=0.7$).

233

234 **Discussion**

235

236 Our study investigating clinical and genetic CAD prediction in Swiss PLWH of European descent has
237 two main findings: First, an unfavorable genetic background independently increases CAD event risk
238 3.17-fold, when applying an individual PRS based on CAD-associated SNPs, and CAD event risk was
239 increased 3.67-fold when adding longevity-associated SNP to this CAD-PRS in a combined meta-PRS.
240 Second, we provide a combined estimate of the impact of traditional and HIV-related risk factors
241 (clinical risk) and show that the highest clinical risk category was associated with a 17.4 to 19.3-fold
242 increased CAD risk. Thus, while clinical risk factors clearly explained a larger proportion of CAD
243 variability than genetic background, clinical and genetic models independently predicted CAD events,
244 and a combined clinical plus genetic model afforded the best CAD prediction.

245 Our results confirm our previous CAD-genetic report from 2013 that was based on a multinational
246 (MAGNIFICENT) consortium of PLWH cohorts.[14] Importantly, we extend the MAGNIFICENT results
247 by showing improved CAD prediction when applying an individual PRS in this study, as compared to a
248 validated panel of 23 common SNPs (associated with CAD in the general population) that we applied
249 in the MAGNIFICENT study.[14] The inclusion of common variants of smaller effect sizes in PRS, in
250 addition to only the genome-wide significant variants, is now a well-established method to improve
251 the predictive power of genetic risk scores.[13][33-34] The CAD effect of genetic background was not
252 subtle, i.e. an unfavorable PRS increased CAD odds ratio 3.17-fold to 3.67-fold, depending on which
253 PRS we applied. In contrast, an unfavorable genetic background based on 23 SNPs in MAGNIFICENT
254 [14] was associated with a 1.47-fold increased CAD odds ratio. Similarly, CAD event variability
255 explained was 6% (pseudo-R2 test) for CAD-PRS and meta-PRS, compared to 2% for longevity PRS,
256 and only 0.9% in MAGNIFICENT.[14] CAD variability explained by traditional and HIV-related risk
257 factors was higher (14% and 18%, respectively, and 31% in combination), emphasizing the
258 importance of clinical risk factors for CAD event prediction. However, the best CAD prediction model
259 overall was the combination of clinical risk factors plus meta-PRS (35% CAD event variability

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

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

273 Our genetic results appear robust because we only considered SNPs that have been validated in large
274 reference GWAS in the general population.[13][16] We applied rigorous quality control to the genetic
275 data, corrected for residual population stratification, and excluded population outliers. Additional
276 strengths include that we exploited prospectively recorded information in participants of the well-
277 established Swiss HIV Cohort Study, which allowed us to quantify and compare the CAD effects of all
278 relevant, i.e. clinical, HIV-related, and genetic risk factors. Of note, genetic background predicted
279 individual CAD risk independently of family history of CAD, consistent with the MAGNIFICENT study
280 [14] and findings in the general population.[35-36]

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

285 findings suggest how an individual PRS might be applied in clinical HIV practice. The knowledge that
286 an unfavorable genetic background independently increases the CAD event risk 3.67-fold in those
287 20% PLWH in 5th meta-PRS quintile may suggest paying even greater attention to the optimization of
288 clinical risk factors, and, perhaps, instituting primary CAD prevention with statins in such individuals.
289 In addition, applying different PRS can inform the selection of PLWH at increased risk for attaining
290 relevant endpoints in clinical trials.

291 Addition of TL to the model further improved CAD prediction, consistent with our previous report
292 [18]. Although aging correlates with shorter TL, we found no evidence of a link between longevity-
293 PRS and TL in our dataset. Detailed pathway analyses based on genetic information, using the
294 principle of Mendelian randomization, can reveal causal relationships and provide pathogenic
295 insights into CAD, and help avoid the risk of unknown confounding factors and reverse causation.[39-
296 40] Based on limited study population size, our study was not powered for this type of genetic
297 analysis.

298 Our study has additional limitations. We included only participants of European descent, because
299 most GWAS of CAD have been conducted in populations of European descent. Our population was
300 87% male and relatively young; thus, results should only cautiously be extrapolated to females and
301 elderly PLWH.

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

310 **Notes**

311

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

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

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

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

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

336 Kahlert CR, Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Ledergerber B, Martinetti G, Martinez
337 de Tejada B, Marzolini C, Metzner KJ, Muller N, Nicca D, Paioni P, Pantaleo G, Perreau M, Rauch A
338 (Chairman of the Scientific Board), Rudin C (Chairman of the Mother & Child Substudy), Scherrer AU
339 (Head of Data Centre), Schmid P, Speck R, Stockle M, Tarr P, Trkola A, Vernazza P, Wandeler G,
340 Weber R, Yerly S.
341

342 **References**

- 343
344 1. Shah ASV, Stelzle D, Lee KK, et al. Global Burden of Atherosclerotic Cardiovascular Disease in People
345 Living With HIV. *Circulation*. **2018**; 138(11):1100-1112.
- 346 2. Feinstein MJ, Hsue PY, Benjamin LA, et al. Characteristics, Prevention, and Management of
347 Cardiovascular Disease in People Living with HIV: A Scientific Statement from the American Heart
348 Association. *Circulation*. **2019**; 140(2):e98-e124.
- 349 3. Friis-Moller N, Reiss P, Sabin CA et al. Class of Antiretroviral Drugs and the Risk of Myocardial
350 Infarction. *N Engl J Med*. **2007**; 356:1723-1735.
- 351 4. Sabin CA, Worm SW, Weber R, et al. Use of nucleoside reverse transcriptase inhibitors and risk of
352 myocardial infarction in HIV-infected patients enrolled in the D:A:D study: A multi-cohort collaboration.
353 *Lancet*. **2008**; 371(9622):1417-1426.
- 354 5. Lohmueller KE, Pearce CL, Pike M, Lander ES, Hirschhorn JN. Meta-analysis of genetic association
355 studies supports a contribution of common variants to susceptibility to common disease. *Nat Genet*.
356 **2003**; 33(2):177-182.
- 357 6. Lloyd-Jones D, Nam B, D'Agostino R, et al. Parental Cardiovascular Disease as a Risk Factor for
358 Cardiovascular Disease in Middle-aged Adults A Prospective Study of Parents and Offspring. *J Am Med*
359 *Assoc*. **2004**; 291:2204–2211.
- 360 7. Murabito JM, Pencina MJ, Nam BH, et al. Sibling cardiovascular disease as a risk factor for
361 cardiovascular disease in middle-aged adults. *J Am Med Assoc*. **2005**; 294(24):3117-3123.
- 362 8. Mangino M, Spector T. Understanding coronary artery disease using twin studies. *Heart*. **2013**;
363 99(6):373-375.
- 364 9. Samani N, Erdmann J, Mangino M, et al. Genomewide Association Analysis of Coronary Artery Disease
365 Nilesh. *N Engl J Med*. Published online 2007; 443-453.
- 366 10. CARDIoGRAMplusC4D C. Large-scale association analysis identifies new risk loci for coronary artery
367 disease. *Nat Genet*. **2013**; 45(1):25-33.
- 368 11. Nikpay M, Goel A, Won HH, et al. A comprehensive 1000 Genomes-based genome-wide association
369 meta-analysis of coronary artery disease. *Nat Genet*. **2015**; 47(10):1121-1130.
- 370 12. Van Der Harst P, Verweij N. Identification of 64 novel genetic loci provides an expanded view on the

- 371 genetic architecture of coronary artery disease. *Circ Res.* **2018**; 122(3):433-443.
- 372 13. Inouye M, Abraham G, Nelson CP, et al. Genomic Risk Prediction of Coronary Artery Disease in 480,000
373 Adults: Implications for Primary Prevention. *J Am Coll Cardiol.* **2018**; 72(16):1883-1893.
- 374 14. Rotger M, Glass TR, Junier T, et al. Contribution of genetic background, traditional risk factors, and HIV-
375 related factors to coronary artery disease events in HIV-positive persons. *Clin Infect Dis.* **2013**;
376 57(1):112-121.
- 377 15. Pilling LC, Kuo CL, Sicinski K, et al. Human longevity: 25 genetic loci associated in 389,166 UK biobank
378 participants. *Aging (Albany NY).* **2017**; 9(12):2504-2520.
- 379 16. Deelen J, Evans DS, Arking DE, et al. A meta-analysis of genome-wide association studies identifies
380 multiple longevity genes. *Nat Commun.* **2019**; 10(1).
- 381 17. Schoeni-Affolter F, Ledergerber B, Rickenbach M, et al. Cohort profile: The Swiss HIV cohort study. *Int J*
382 *Epidemiol.* **2010**; 39(5):1179-1189.
- 383 18. Engel T, Raffenberg M, Schoepf IC, et al. Telomere Length, Traditional Risk Factors, HIV- related Factors
384 and Coronary Artery Disease Events in Swiss Persons Living with HIV. *Clin Infect Dis.* **2020**; ciaa1034.
- 385 19. Schunkert H, König IR, Kathiresan S, et al. Large-scale association analysis identifies 13 new
386 susceptibility loci for coronary artery disease. *Nat Genet.* **2011**; 43(4):333-340.
- 387 20. World Health Organisation WHO. Monica Manual, Part IV: Event Registration, Section 1: Coronary
388 Event Registration Data Component. 199. Available at:
389 <https://www.thl.fi/publications/monica/manual/part4/iv-1.htm>. Accessed 08 September 2020.
- 390 21. Essebag V, Genest J, Suissa S, Pilote L. The nested case-control study in cardiology. *Am Heart J.* **2003**;
391 146(4):581-590.
- 392 22. Greenland S, Thomas DC. On the need for the rare disease assumption in cases-control studies.
393 *Epidemiology.* **1982**; 116(3):547-553.
- 394 23. D:A:D study, Sabin CA, Worm SW, et al. Use of nucleoside reverse transcriptase inhibitors and risk of
395 myocardial infarction in HIV-infected patients enrolled in the D:A:D study: A multi-cohort collaboration.
396 *Lancet.* **2008**; 371(9622):1417-1426.
- 397 24. Ryom L, Lundgren JD, El-Sadr W, et al. Cardiovascular disease and use of contemporary protease
398 inhibitors: the D:A:D international prospective multicohort study. *Lancet HIV.* **2018**; 5(6):e291-e300.
- 399 25. Van Zoest R, Wit FW, Kooij KW et al. Higher Prevalence of Hypertension in HIV-1-Infected

- 400 Patients on Combination Antiretroviral Therapy Is Associated With Changes in Body Composition and
401 Prior Stavudine Exposure. *Clin Infect Dis.* **2016**; 63(2):205-213.
- 402 26. Gelpi M, Afzal S, Lundgren J, et al. Higher Risk of Abdominal Obesity, Elevated Low-Density Lipoprotein
403 Cholesterol, and Hypertriglyceridemia, but not of Hypertension, in People Living With Human
404 Immunodeficiency Virus (HIV): Results From the Copenhagen Comorbidity in HIV Infection Study.
405 *Clin Infect Dis.* **2018**; 67(4):579-586.
- 406 27. Tarr PE, Ledergerber B, Calmy A, et al. Subclinical coronary artery disease in Swiss HIV-positive and HIV-
407 negative persons. *Eur Heart J.* **2018**; 39(23):2147-2154.
- 408 28. Combs JA, Norton EB, Saifudeen ZR, et al. Human Cytomegalovirus Alters Host Cell Mitochondrial
409 Function during Acute Infection. *J Virol.* **2019**; 94(2):1-19.
- 410 29. Wong RJ, Kanwal F, Younossi ZM AA. Hepatitis C virus infection and coronary artery disease risk: a
411 systematic review of the literature. *Dig Dis Sci.* **2014**; 59:1586-1593.
- 412 30. Kovari H, Rauch A, Kouyos R, et al. Hepatitis C infection and the risk of non-liver-related morbidity and
413 mortality in HIV-infected persons in the swiss HIV cohort study. *Clin Infect Dis.* **2017**; 64(4):490-497.
- 414 31. Lambert SA, Gil L, Jupp S, et al. The Polygenic Score Catalog: an open database for reproducibility and
415 systematic evaluation. *medRxiv*. Published online January 1, 2020; 2020.05.20.20108217.
- 416 32. Dupont WD. Power Calculations for Matched Case-Control Studies. *Biometrics.* **1988**; 44(4):1157.
- 417 33. International Schizophrenia Consortium, Purcell S, Wray N et al. Common polygenic variation
418 contributes to risk of schizophrenia that overlaps with bipolar disorder International. *Nature.* **2009**;
419 460:748– 752.
- 420 34. Chatterjee N, Wheeler B, Sampson J, Hartge P, Chanock SJ, Park J-H. Polygenic Analyses of Genome-
421 Wide Association Studies. *Nat Genet.* **2013**; 45(4):400-405.
- 422 35. Chow C, Bautista L, Rumboldt Z, et al. Parental History and Myocardial Infarction Risk Across the World.
423 *J Am Coll Cardiol.* **2011**; 57:619-627.
- 424 36. Tada H, Melander O, Louie JZ, et al. Risk prediction by genetic risk scores for coronary heart disease is
425 independent of self-reported family history. *Eur Heart J.* **2016**; 37(6):561-567.
- 426 37. Hoffmann TJ, Theusch E, Haldar T, et al. A large electronic-health-record-based genome-wide study of
427 serum lipids. *Nat Genet.* **2018**; 50(3):401-413.
- 428 38. Kamboh M, Demirci F, Wang X, et al. Genome-wide association study of Alzheimer's disease. *Transl*

429 Psychiatry 2. **2012** e117.

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

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

434

435

436

437

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 \geq 1 year, n (%)		79 (29.4)	100 (17.6)
Indinavir, exposure \geq 1 year, n (%)		65 (24.2)	53 (9.4)

Darunavir, exposure \geq 1 year, n (%)		45 (16.7)	60 (10.6)
Stavudine, exposure \geq 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/ μ L), median (IQR)		169 (71-257)	205 (126-318)
CD4 nadir <50 cells/ μ L, 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)

439

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

441 indicated.

442 * in 6 months prior to matching date

443 ** From registration in the SHCS until the matching date, and, for controls, until first regular, twice-yearly

444 follow-up visit after the matching date

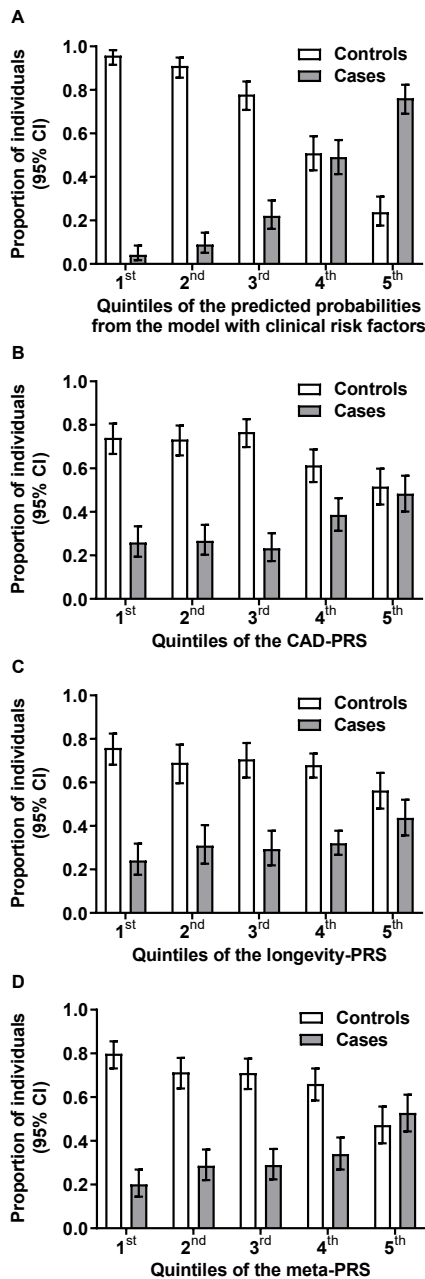
445 **Abbreviations.** ART, antiretroviral therapy; CAD, coronary artery disease; CMV, cytomegalovirus; IDU,

446 intravenous drug use; IQR, interquartile range; MSM, men who have sex with men.

447

448

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



452

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

456 **A: Distribution of cases and controls according to quintiles of clinical risk.** There were 7 (4.2%) cases
457 vs. 160 (95.8%) controls in the 1st (most favorable) quintile, 15 (9%) vs. 152 (91%) in the 2nd quintile,
458 37 (22.2%) vs. 130 (77.8%) in the 3rd quintile, 82 (49.1%) vs. 85 (50.9%) in the 4th quintile, and 128
459 (76.2%) vs. 40 (23.8%) in the 5th (most unfavorable) quintile.

460 **B: Distribution of cases and controls according to quintiles of CAD-PRS.** There were 42 (25.9%) cases
461 vs. 120 (74.1%) controls in the 1st quintile, 46 (26.7%) vs. 126 (73.3%) in the 2nd quintile, 42 (23.3%)
462 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
463 (51.7%) in the 5th quintile.

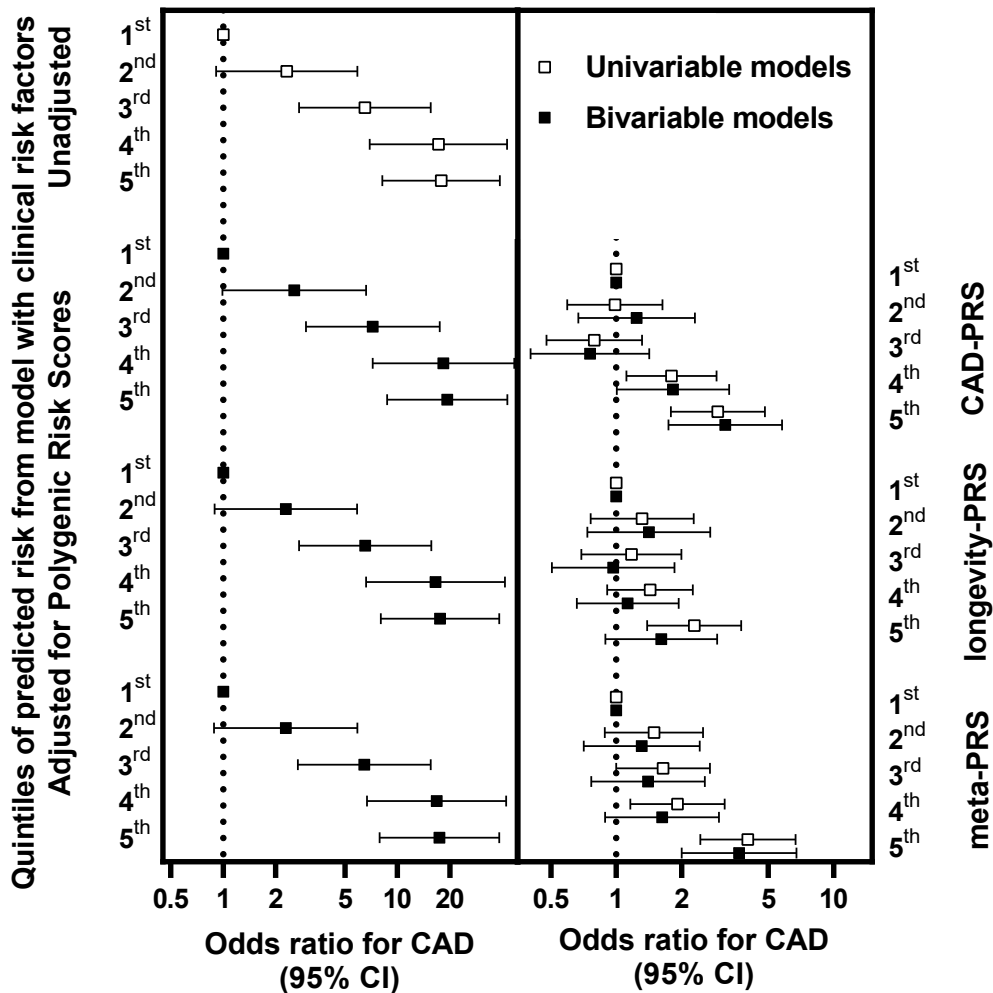
464 **C: Distribution of cases and controls according to quintiles of longevity-PRS.** There were 36 (24.2%)
465 cases vs. 113 (75.8%) controls in the 1st quintile, 35 (31%) vs. 78 (69%) in the 2nd quintile, 40 (29.4%)
466 vs. 96 (70.6%) in the 3rd quintile, 92 (32.1%) vs. 195 (67.9%) in the 4th quintile, and 66 (43.7%) vs. 85
467 (56.3%) in the 5th quintile.

468 **D: Distribution of cases and controls according to quintiles of combined CAD-PRS and longevity-PRS**
469 **(meta-PRS).** There were 35 (20.1%) cases vs. 139 (79.9%) controls in the 1st quintile, 49 (28.7%) vs.
470 122 (71.4%) in the 2nd quintile, 51 (29%) vs. 125 (71%) in the 3rd quintile, 58 (33.9%) vs. 113 (66.1%) in
471 the 4th quintile, and 76 (52.8%) vs. 68 (47.2%) in the 5th quintile.

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

473

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

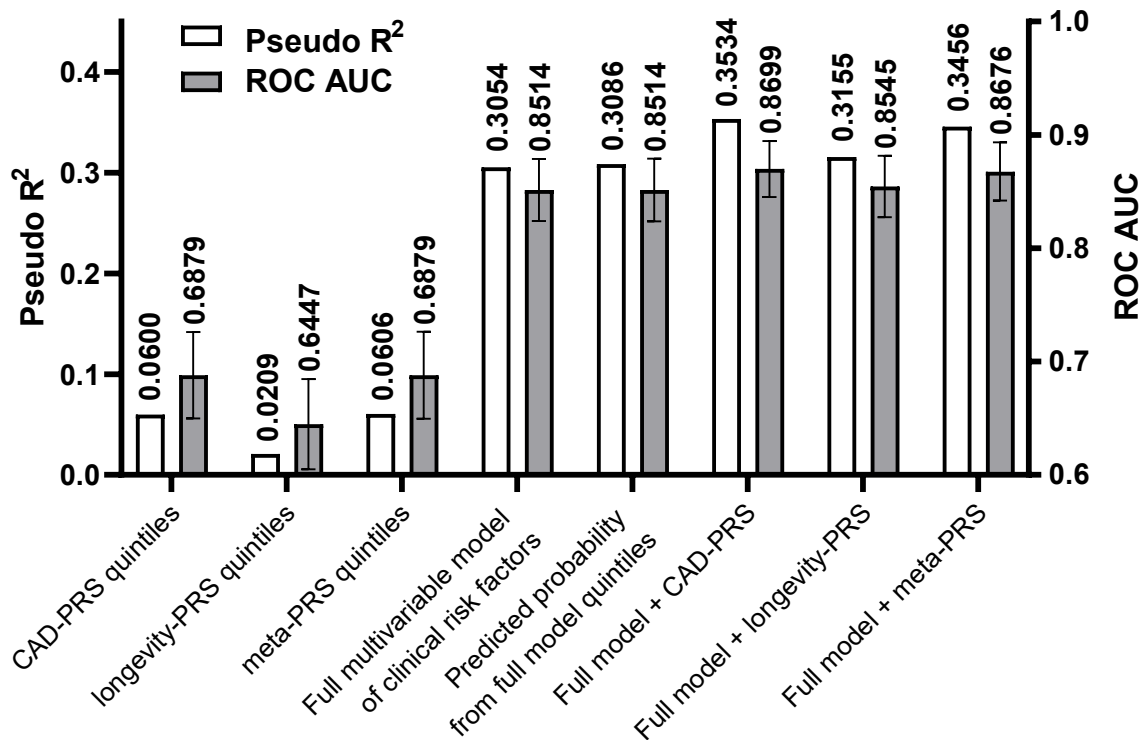


476

477 Uni- and multivariable conditional logistic regression of associations with CAD events. Results involve
 478 269 cases and 567 controls. Compared to the first (most favorable) quintile of clinical risk,
 479 participants in the second, third, fourth, and fifth (most unfavorable) quintile had multivariable ORs
 480 that remained similar, irrespective for which PRS we adjusted (**left column**). After adjustment for
 481 clinical risk factors, the CAD-PRS and meta-PRS remained significantly associated with CAD events,
 482 but not the longevity-PRS (**right column**). **Abbreviations:** CAD, coronary artery disease; CI,
 483 confidence interval; PRS, polygenic risk score

484

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



487
 488 CAD event variability (white bars; based on pseudoR2 test) that is explained by CAD-PRS, longevity-
 489 PRS, meta-PRS, full model of clinical risk factors without considering any PRS (continuous model and
 490 model that included quintiles of clinical risk), and CAD event variability explained by full model plus
 491 CAD-PRS, longevity-PRS, and meta-PRS. CAD event variability (gray bars; based on ROC AUC values)
 492 that is explained by CAD-PRS, longevity-PRS, meta-PRS, full model of clinical risk factors without
 493 considering any PRS (continuous model and model that included quintiles of clinical risk), and CAD
 494 event variability explained by full model plus CAD-PRS, longevity-PRS, and meta-PRS.

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

497