Polygenic and clinical risk scores and their impact on age at onset of cardiometabolic diseases and common cancers

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ABSTRACT

Background: Polygenic risk scores (PRS) have shown promise in predicting susceptibility to common diseases. However, the extent to which PRS and clinical risk factors act jointly and identify high-risk individuals for early onset of disease is unknown.

Methods: We used large-scale biobank data (the FinnGen study; n=135,300), with up to 46 years of prospective follow-up, and the FINRISK study with standardized clinical risk factor measurements to build genome-wide PRSs with >6M variants for coronary heart disease (CHD), type 2 diabetes (T2D), atrial fibrillation (AF), and breast and prostate cancer. We evaluated their associations with first disease events, age at disease onset, and impact together with routinely used clinical risk scores for predicting future disease.

Results: Compared to the 20-80th percentiles, a PRS in the top 2.5% translated into hazard ratios (HRs) for incident disease ranging from 2.03 to 4.28 (p-values 1.96×10^{-59} to $<1.00 \times 10^{-100}$) and the bottom 2.5% into HRs ranging from 0.20 to 0.61. The estimated difference in age at disease onset between top and bottom 2.5% of PRSs was 6 to 13 years. Among early-onset cases, 21.3-32.9% had a PRS in the highest decile and in CHD and AF.

Conclusions: The properties of PRS were similar in all five diseases. PRS identified a considerable proportion early-onset cases, and for all ages the performance of PRS was comparable to established clinical risk scores. These findings warrant further clinical studies on application of polygenic risk information for stratified screening or for guiding lifestyle and preventive medical interventions.

INTRODUCTION

Common chronic diseases present a huge burden to societies, with an estimated one billion prevalent cases diagnosed with cardiovascular diseases, diabetes, or neoplasms worldwide.[1] Consequently, the development of strategies to prevent these diseases is critically important. To facilitate prevention, a clear understanding of individual risk is essential to determine whether an individual warrants an intervention as well as to gauge the impact of different interventions. These risk models typically incorporate clinical and laboratory-based risk factors, and can identify individuals at high risk suitable for selective prevention strategies, such as prescribing cholesterol-lowering medications for reducing coronary heart disease (CHD) risk.[2] Although clinical risk scores enable the identification of individuals who may benefit from preventive interventions, these models are imperfect and fail to identify a noticeable proportion of those who develop the diseases, particularly among young individuals.[2,3] Furthermore, in many cancers such as breast and prostate cancer, no widely accepted clinical risk assessment strategy exists.

Large-scale genetic screens comparing disease cases with controls have identified thousands of genetic loci associated with risk of complex diseases,[4] suggesting that genomic information has become a promising candidate for improving clinical risk assessment.[5] While, individually, the associated loci typically modify the disease risks only marginally, for many diseases the cumulative impact of risk across the genome is considerable.[6] Polygenic risk scores (PRS) measure these cumulative genetic effects[7] and have recently been shown to correlate with cases status in many complex diseases including CHD, T2D, and breast cancer.[8-10] However, limited information exists as to both the performance of PRSs in a prospective setting and their value when integrated with the established clinical risk factors and laboratory-based biomarkers.

We set to test the utility of PRSs derived from large-scale genomic information for predicting first disease events in five diseases: CHD, T2D, atrial fibrillation or flutter (AF), and breast and prostate cancer. Specifically, we tested three hypotheses: 1) are the polygenic risk scores associated with first disease events over a long follow-up, 2) can polygenic risk scores help identify early-onset cases, and 3) what is the relative impact of clinical risk scores and the polygenic risk scores? We tested these hypotheses within the FinnGen study cohort comprising of 135,300 individuals with genome-wide genotyping and up to 46 years of follow-up.

METHODS

Individuals

The data comprised of 135,300 Finnish individuals from FinnGen Preparatory Phase Data Freeze 3, which includes prospective epidemiological and disease-based cohorts, and hospital biobank samples (Supplementary Table S1). The data, representing roughly 3% of Finnish adult population, were linked by the unique national personal identification numbers to national hospital discharge (available from 1968), death (1969-), cancer (1953-), and medication reimbursement (1995-) registries.

A subset of FinnGen, the population-based FINRISK study with 21,813 individuals was selected for analyzing the PRSs together with clinical risk factors. The FINRISK surveys, performed in 1992, 1997, 2002, and 2007 comprised random samples of adults within five geographical areas in Finland. The baseline data covered self-reported information assessed by questionnaires, anthropometric measurements, and blood samples. Additional details on the study protocol have been previously described.[11] Information on the genotyping and imputation are provided in the Supplemental Appendix. The study was approved by the Coordinating Ethics Committee of the

Hospital District of Helsinki and Uusimaa (HUS/990/2017). All participants gave written informed consent.

Disease endpoints

Using the national registries, we studied the incidence of five diseases: CHD, T2D, AF, breast cancer, and prostate cancer (diagnoses based on International Classification of Diseases, ICD-8, ICD-9, and ICD-10 in Supplementary Table S2). Follow-up ended at first-ever diagnosis of the disease of interest, death, or at the end of follow-up on December 31, 2015, whichever came first.

Clinical risk factors

Clinical risk factors were evaluated for CHD, T2D, and AF. The 10-year risk of hard atherosclerotic cardiovascular disease (ASCVD) was evaluated with the pooled cohort equations (PCE) according to guidelines,[12,13] comprising age, sex, self-reported ancestry, total cholesterol (TC), high-density lipoprotein (HDL), systolic blood pressure (SBP), blood pressure-lowering medication, diabetes, and smoking status. The 10-year risk for ASCVD was categorized as intermediate to high risk (≥7.5% which often leads to consideration of preventive medication) or low to borderline risk (<7.5%).[13]

For T2D, individuals who had impaired fasting glucose (≥5.6 mmol/L) or who met the American Diabetes Association (ADA) criteria for testing for diabetes or prediabetes in asymptomatic adults[14] were defined as having high clinical risk for T2D. Family history was the self-reported parental history for any diabetes and early myocardial infarction (MI). Following many previous studies, the definition for early-onset cases was age 55 for CHD, 45 for T2D, 60 for AF, 40 for breast cancer, and 55 for prostate cancer.

For AF, the clinical assessment of the 5-year absolute risk for individuals above age 45 was carried out with the CHARGE-AF score, comprising age, height, weight, systolic and diastolic blood pressure, smoking status, blood pressure-lowering treatment, prevalent diabetes, heart failure, and history of myocardial infarction.[15] CHARGE-AF was revised and the risk was categorized as ≤5% or >5%.[15] Additional information on the clinical risk factors are provided in the Supplemental Appendix.

Polygenic risk scores

The summary association statistics came from recent genome-wide association studies (GWAS) (Supplementary Table S3, Supplementary Figure 1).[16-20] LDpred was used to account for linkage disequilibrium among loci,[21] with whole-genome sequencing data on 2,690 Finns serving as the LD reference panel. After performing quality control, the final scores were generated with PLINK2[24] by calculating the weighted sum of risk allele dosages for each single nucleotide polymorphism (SNP). The final PRSs comprised 6,412,950 variants for CHD PRS, 6,437,380 for T2D PRS, 6,171,733 for

AF PRS, 6,390,808 for breast cancer PRS, and 6,606,785 for prostate cancer PRS (candidate LDpred scores with respect to the tuning parameter in Supplementary Table S4).

Statistical analysis

The PRS distributions were divided into bins of <2.5, 2.5-20, 20-80, 80-97.5, >97.5, using 20-80 as the reference, to display the risk in the tails with respect to a large group of individuals defined to have average risk. When comparing clinical and polygenic risk, we defined elevated PRS as a polygenic risk score above the 90th percentile. Cox proportional hazards model was used to estimate survival curves and hazard ratios (HRs) and 95% confidence intervals (CI). Schoenfeld residuals and log-log inspection showed that proportional assumption criteria applied in our models. Unless otherwise stated, we used age as the time scale, stratified regression models by sex and adjusted for FINRISK survey collection year, genotyping array, and the first ten principal components of ancestry. Breast cancer was studied only in women and prostate cancer only in men. The relative contributions of PRS and clinical scores were estimated using logistic regression and discrimination was evaluated by the area under the receiver operating characteristic curve (AUC), and for the survival models by C-index.

In FINRISK analyses, the association of PRSs was tested for incident disease cases only. Participants with prevalent diabetes were excluded from all prospective CHD analyses performed in FINRISK. The FINRISK had 1805 individuals overlapping with the AF GWAS, and we excluded these individuals from the AF analyses. Age at disease onset and the differences between PRS categories were estimated with restricted mean survival time (RMST).[22] For statistical analyses, we used R 3.5.2, and Stata 14.2 (College Station, TX, USA).

RESULTS

Polygenic risk score associations

We first derived PRSs for five diseases, CHD, T2D, AF, breast cancer, and prostate cancer by weighting the individual SNPs by their effect sizes from published GWASs and by accounting for linkage disequilibrium between markers. We tested the association between these newly derived PRSs and disease events within the independent FinnGen study cohort (n = 135,300), which comprised 20,179 individuals with CHD, 17,519 with T2D, 12,809 with AF, 3,904 with breast cancer, and 3,263 with prostate cancer. FinnGen was comprised of 56.3% women, with mean age 59.2 (standard deviation, SD 16.6) at the end of follow-up.

For all five diseases, a higher PRS was strongly associated with a higher incidence rate (Figure 1, Table 1). The HR per SD increment (all p-values $<1.00 \times 10^{-100}$) was 1.31 for CHD (95% CI 1.29-1.33), for

T2D 1.74 (1.72-1.77), for AF 1.62 (1.59-1.65), for breast cancer 1.67 (1.62-1.72), and for prostate cancer 1.86 (1.80-1.93). Compared to individuals with average PRS (20-80th percentile of the PRS distribution), being in the top 2.5% of the distribution translated into HRs ranging from 2.03 to 4.28 (p-values 1.96×10^{-59} to $<1.00 \times 10^{-100}$; Table 1). Similarly, in the lowest 2.5% of the PRS, the HRs when comparing to the average PRS were 0.20-0.61 (p-values 4.35×10^{-10} to 7.11×10^{-64}).

In addition, we built estrogen receptor-negative (ER-negative) and estrogen receptor-positive (ER-positive) breast cancer PRSs (Supplementary Figure 2). With any breast cancer as the outcome, for ER-negative PRS the HR for average PRS vs top 2.5% of the PRS distribution was 1.77 (95% CI 1.51-2.07, p = 9.00×10^{-13}) and for ER-positive PRS, 2.75 (95% CI 2.41-3.13, p = 1.26×10^{-50}).

The higher the PRS, the earlier was the disease onset for all five diseases (Figure 2, sex-specific results in Supplementary Figure 3). Compared to individuals with average PRS, those in the top 2.5% of the distribution had a disease onset 4 to 9 years earlier. The largest difference in age at onset between the top and bottom 2.5%, 13.4 years, was seen for T2D.

Relative contribution of polygenic and clinical risk for CHD, T2D, and AF

In CHD and T2D, clinical risk factors are routinely used for risk evaluation. Therefore, we assessed the relative and combined effect of PRSs and clinical risk calculators, using the FINRISK study (n = 21,813, mean age at baseline 48.0, 52.7% women) with major cardiometabolic risk factors measured (Supplementary Table S5). Overall, the correlation between polygenic and clinical risk scores was weak, and family history of CHD or T2D had only a minor effect on the association between polygenic risk and disease (Supplementary Figure 4; Supplementary Table S6).

To guide decision-making, prevention guidelines report thresholds for clinical risk calculators. These thresholds were used for identifying individuals at clinical high risk, and to assess the extent to which PRS and clinical risk assessment individually and jointly identify high-risk individuals. PRS helped identify individuals at very high risk: in those with both high clinical risk and high PRS, the risk was elevated compared to those with only high clinical risk or only high PRS (Figure 3). Combining both scores provided only a minor increment to the PRS accuracy (Supplementary Figure 5).

After dividing the individuals into early- and late-onset cases, we compared how often either the PRS or clinical risk was elevated among cases. In all five diseases, around one-quarter of the early-onset cases also had an elevated PRS, whereas around one-fifth of the late-onset cases had an elevated PRS (Figure 4). Compared to early-onset cases, a larger proportion of late-onset cases had high clinical risk. In early-onset CHD, the proportion of either elevated PRS or ASCVD ≥7.5% was 39.7% and 6.7% had both risk scores elevated. In early-onset T2D, high clinical risk was over twice more common than an elevated PRS, with 73.2% having one risk score elevated and 14.4% having

both scores elevated. In early-onset AF, 25.0% had an elevated PRS, whereas hardly anyone had CHARGE-AF >5%.

Effect of polygenic risk on breast and prostate cancer prevalence

Breast cancer screening starts from age 50 in Finland, when its cumulative incidence reaches 2.0%. Using the population-based FINRISK study, we estimated the age when the cumulative incidence reached 2.0% in the different PRS groups: 44.5 years in PRS category >97.5%, 45.4 years in 80-97.5%, 50.0 years in 20-80%, and 58.5 years in PRS <20%. Similarly, a 2% cumulative incidence for prostate cancer in men was reached at age 62. When estimated separately for the PRS groups, a 2% cumulative incidence was reached at age 55.6 in PRS category >97.5%, at 59.4 in 80-97.5%, at 62.4 in 20-80%, and at 69.9 in <20%.

DISCUSSION

For all five common diseases, we detected similar patterns for the impact of polygenic risk. Over the long follow-up, high polygenic risk correlated with a substantial elevation in disease risk, replicating the results from earlier cross-sectional investigations applying highly polygenic scores,[8] now in a population-based setting with population-level disease prevalence and decades-long follow-up. This risk elevation also translated into large shifts in ages at disease onset. Compared to individuals with an average PRS, those in the top 2.5% of the PRS distribution had a disease onset 4 to 9 years earlier. Of early-onset cases, approximately one-quarter had an elevated PRS.

The relative contribution of polygenic and clinical risk was assessed for CHD, T2D, and AF. The PRS complemented routinely used clinical risk calculators and identified high-risk individuals missed by established clinical risk calculators. As most cardiovascular risk calculators have been trained with data on middle-aged individuals, their ability to identify individuals at risk for early-onset CHD is limited.[2,12] In early-onset CHD and AF, the PRS identified more high-risk individuals than did the routinely used clinical risk calculators, but in all the diseases, the PRS influenced disease risk also in late-onset cases, and improved identification of those at very high disease risk. Hence, polygenic and clinical risk scores complement each other and provide most benefit for prediction when utilized together. As early disease onset may also implicate more aggressive forms of disease,[23,24] preventing or postponing the disease onset in individuals with high polygenic risk could translate into considerable health benefits. How to integrate PRS into clinical practice and how to communicate this information to patients should carefully be assessed for each disease.

In many countries including Finland, breast cancer screening is initiated at around age 50 by which approximately 2% of women have been diagnosed with breast cancer.[25,26] In our data, this 2%

prevalence was reached at age 50 in those with an average PRS, with the difference between the tails of the PRS distribution amounting to 14 years. Our results suggest that PRS could provide new tools for risk stratification even in situations where only few robust clinical risk factors exist, as in the case of the common cancers assessed in this study.

As the data comprised of individuals of European ancestry, PRSs need to be tested also in non-European samples.[27] It is of utmost importance to conduct GWASs in non-Europeans to provide input for polygenic risk scores in populations of non-European origin.[28] Although our analyses were performed in Finns, our results are in line with earlier reports from other samples of European origin.[8,9,29] A fraction of individuals in FinnGen were ascertained through hospital biobanks or disease-based cohorts, which may lead to overestimation of risks. However, the effects of the PRSs in FinnGen were highly similar to those in the population-based FINRISK (Supplementary Tables S7-S8, Supplementary Figure 6). Reasons for selecting this range of diseases were twofold. First, we aimed to explore patterns for polygenic risk across a variety of common diseases. Second, each have large existing GWAS with openly accessible summary-level data for generating these highly polygenic scores. Similar patterns are expected to be present in other common and heritable diseases.[30]

In conclusion, when predicting first disease events, polygenic risk scores identified individuals missed by established clinical risk prediction models, particularly those at high risk for early-onset disease. The opportunities to apply polygenic risk information for stratified screening or for guiding lifestyle and medical interventions in the clinical setting remain to be defined in further studies.

Conflicts of interests A.P. is a member of the Pfizer Genetics Scientific Advisory Panel. V.S. has participated in a conference trip sponsored by Novo Nordisk and received an honorarium for participating in an advisory board meeting (unrelated to the present study). V.S. also has research collaboration with Bayer Ltd (unrelated to the present study).

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Table 1. Hazard ratios (HR) and 95% confidence intervals (CI) for polygenic risk score (PRS) bins in FinnGen.

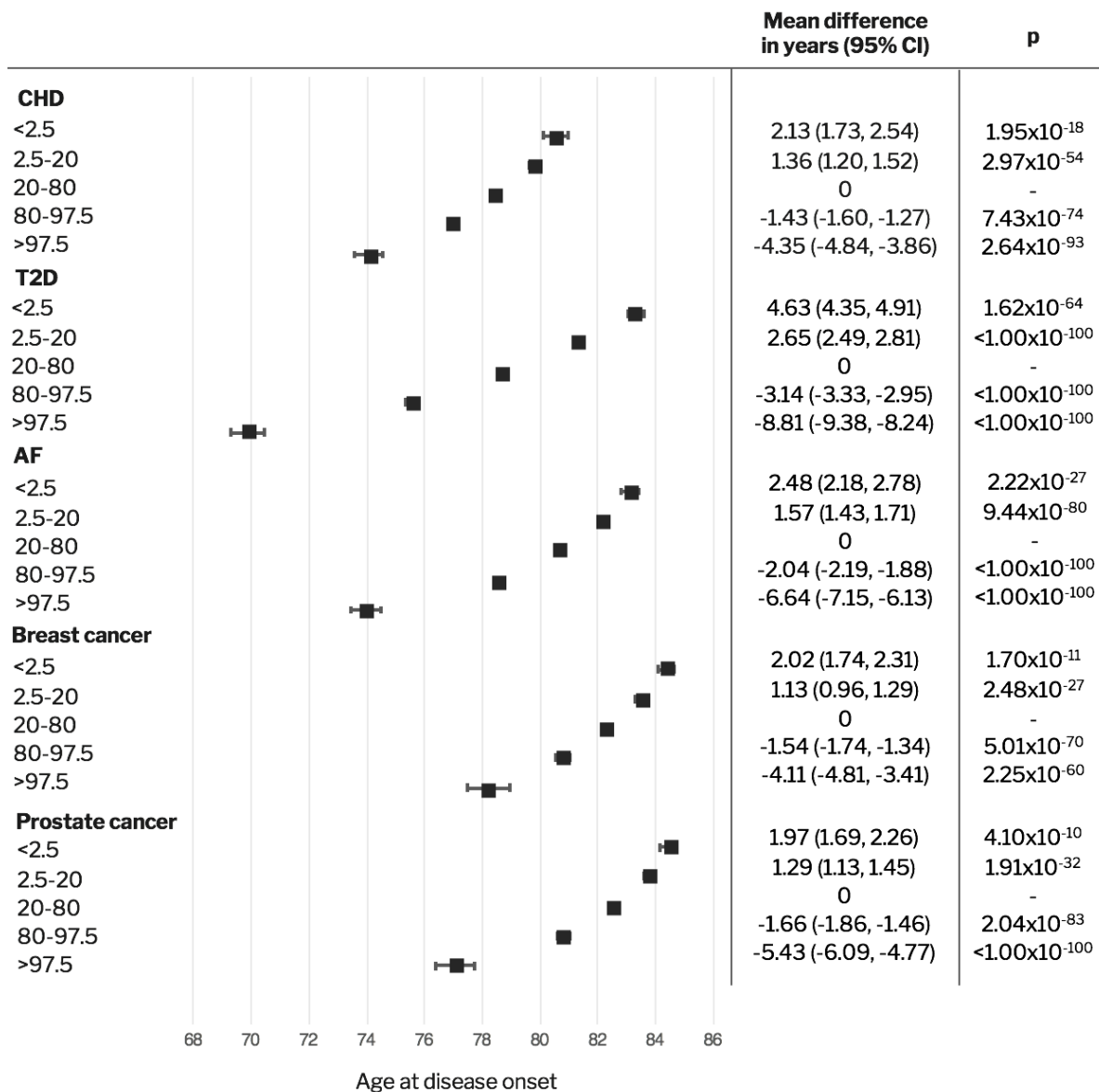|	HR (95% CI)	p	Cases / Controls
CHD PRS			
<2.5	0.61 (0.55-0.69)	3.04×10^{-18}	329 / 3,054
2.5-20	0.72 (0.69-0.75)	2.41×10^{-53}	2,580 / 21,097
20-80	1 (reference)	-	11,832 / 69,348
80-97.5	1.38 (1.34-1.43)	1.30×10^{-76}	4,532 / 19,145
>97.5	2.03 (1.90-2.18)	2.87×10^{-93}	906 / 2,477
T2D PRS			
<2.5	0.22 (0.19-0.27)	7.11×10^{-64}	131 / 3,195
2.5-20	0.48 (0.46-0.51)	$<1.00 \times 10^{-100}$	1,653 / 21,548
20-80	1 (reference)	-	9,869 / 68,998
80-97.5	1.92 (1.85-1.99)	$<1.00 \times 10^{-100}$	4,776 / 17,970
>97.5	3.45 (3.24-3.67)	$<1.00 \times 10^{-100}$	1,090 / 2,072
AF PRS			
<2.5	0.39 (0.33-0.46)	1.34×10^{-27}	136 / 3,247
2.5-20	0.56 (0.53-0.59)	3.92×10^{-81}	1,281 / 22,396
20-80	1 (reference)	-	7,159 / 74,021
80-97.5	1.81 (1.73-1.88)	$<1.00 \times 10^{-100}$	3,417 / 20,260
>97.5	3.50 (3.26-3.77)	$<1.00 \times 10^{-100}$	816 / 2,567
Breast cancer PRS			
<2.5	0.23 (0.15-0.35)	1.27×10^{-11}	21 / 1,885
2.5-20	0.52 (0.46-0.59)	1.45×10^{-27}	320 / 13,020
20-80	1 (reference)	-	2,126 / 43,606
80-97.5	1.90 (1.77-2.04)	1.33×10^{-69}	1,179 / 12,160
>97.5	2.93 (2.58-3.34)	1.96×10^{-59}	258 / 1,648
Prostate cancer PRS			
<2.5	0.20 (0.12-0.33)	4.35×10^{-10}	15 / 1,462
2.5-20	0.43 (0.37-0.49)	3.63×10^{-32}	215 / 10,123
20-80	1 (reference)	-	1,725 / 33,716
80-97.5	2.12 (1.96-2.29)	1.08×10^{-79}	1,020 / 9,317
>97.5	4.28 (3.77-4.85)	$<1.00 \times 10^{-100}$	288 / 1,188

CHD = coronary heart disease, AF = atrial fibrillation or flutter, T2D = type 2 diabetes

Figure 1. Adjusted survival curves in FinnGen, showing the cumulative risk of disease by polygenic risk score (PRS) categories (p-value for trend <1.00x10^{-100} for each).
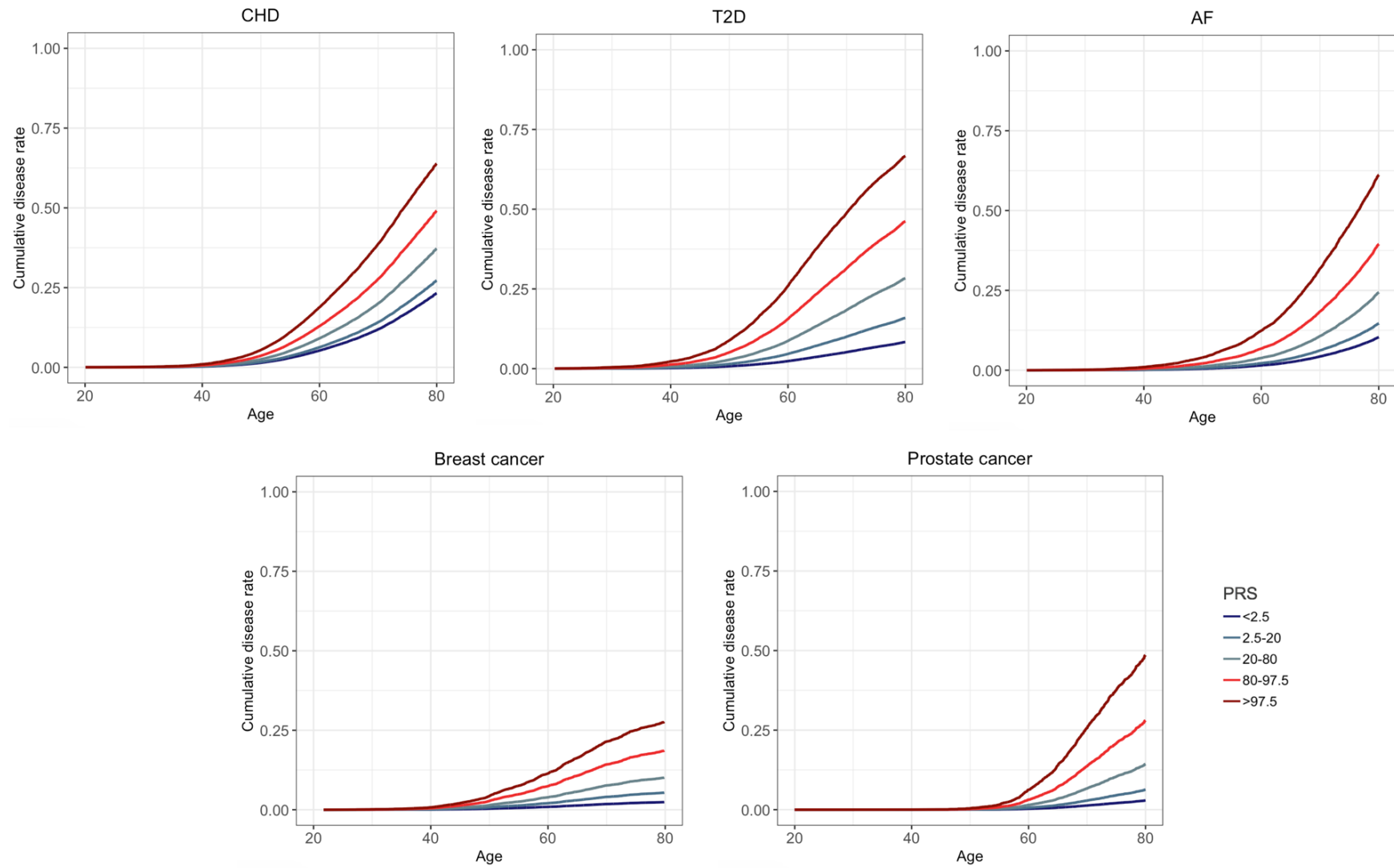

CHD = coronary heart disease, AF = atrial fibrillation or flutter, T2D = type 2 diabetes

Figure 2. Difference in ages at disease onset across polygenic risk score categories in FinnGen.

|	Mean difference in years (95% CI)	p
CHD		
<2.5	2.13 (1.73, 2.54)	1.95×10^{-18}
2.5-20	1.36 (1.20, 1.52)	2.97×10^{-54}
20-80	0	-
80-97.5	-1.43 (-1.60, -1.27)	7.43×10^{-74}
>97.5	-4.35 (-4.84, -3.86)	2.64×10^{-93}
T2D		
<2.5	4.63 (4.35, 4.91)	1.62×10^{-64}
2.5-20	2.65 (2.49, 2.81)	$<1.00 \times 10^{-100}$
20-80	0	-
80-97.5	-3.14 (-3.33, -2.95)	$<1.00 \times 10^{-100}$
>97.5	-8.81 (-9.38, -8.24)	$<1.00 \times 10^{-100}$
AF		
<2.5	2.48 (2.18, 2.78)	2.22×10^{-27}
2.5-20	1.57 (1.43, 1.71)	9.44×10^{-80}
20-80	0	-
80-97.5	-2.04 (-2.19, -1.88)	$<1.00 \times 10^{-100}$
>97.5	-6.64 (-7.15, -6.13)	$<1.00 \times 10^{-100}$
Breast cancer		
<2.5	2.02 (1.74, 2.31)	1.70×10^{-11}
2.5-20	1.13 (0.96, 1.29)	2.48×10^{-27}
20-80	0	-
80-97.5	-1.54 (-1.74, -1.34)	5.01×10^{-70}
>97.5	-4.11 (-4.81, -3.41)	2.25×10^{-60}
Prostate cancer		
<2.5	1.97 (1.69, 2.26)	4.10×10^{-10}
2.5-20	1.29 (1.13, 1.45)	1.91×10^{-32}
20-80	0	-
80-97.5	-1.66 (-1.86, -1.46)	2.04×10^{-83}
>97.5	-5.43 (-6.09, -4.77)	$<1.00 \times 10^{-100}$

Age at disease onset

CHD = coronary heart disease, AF = atrial fibrillation or flutter, T2D = type 2 diabetes. The estimands for age at onset are restricted mean survival times (RMST).

Figure 3. Adjusted survival curves with respective hazard ratios (95% confidence interval) in FINRISK for high clinical risk, high PRS, and both.
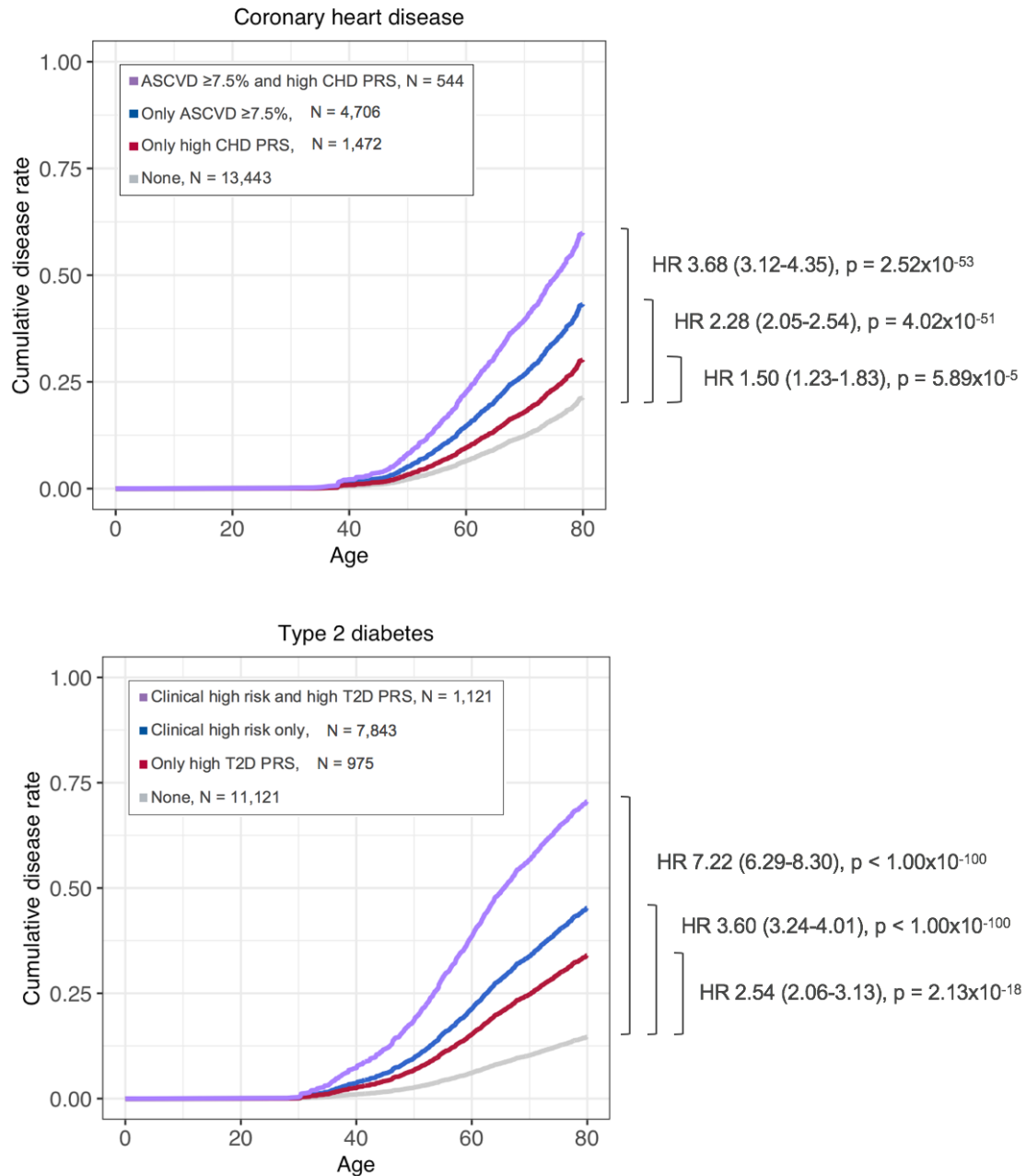
CHD = coronary heart disease, T2D = type 2 diabetes. High PRS = in top decile of the distribution. ASCVD = the 10-year risk calculator for hard atherosclerotic cardiovascular disease (ASCVD), according to the Pooled Cohort Equations by ACC/AHA (2013). The model with CHD not adjusted for sex, as sex is included in ASCVD. Clinical high risk for T2D defined as BMI ≥25kg/m2 and one of more additional clinical risk factors.[14]

Figure 4. The proportion early- and late-onset cases with high clinical risk, high polygenic risk, or neither.
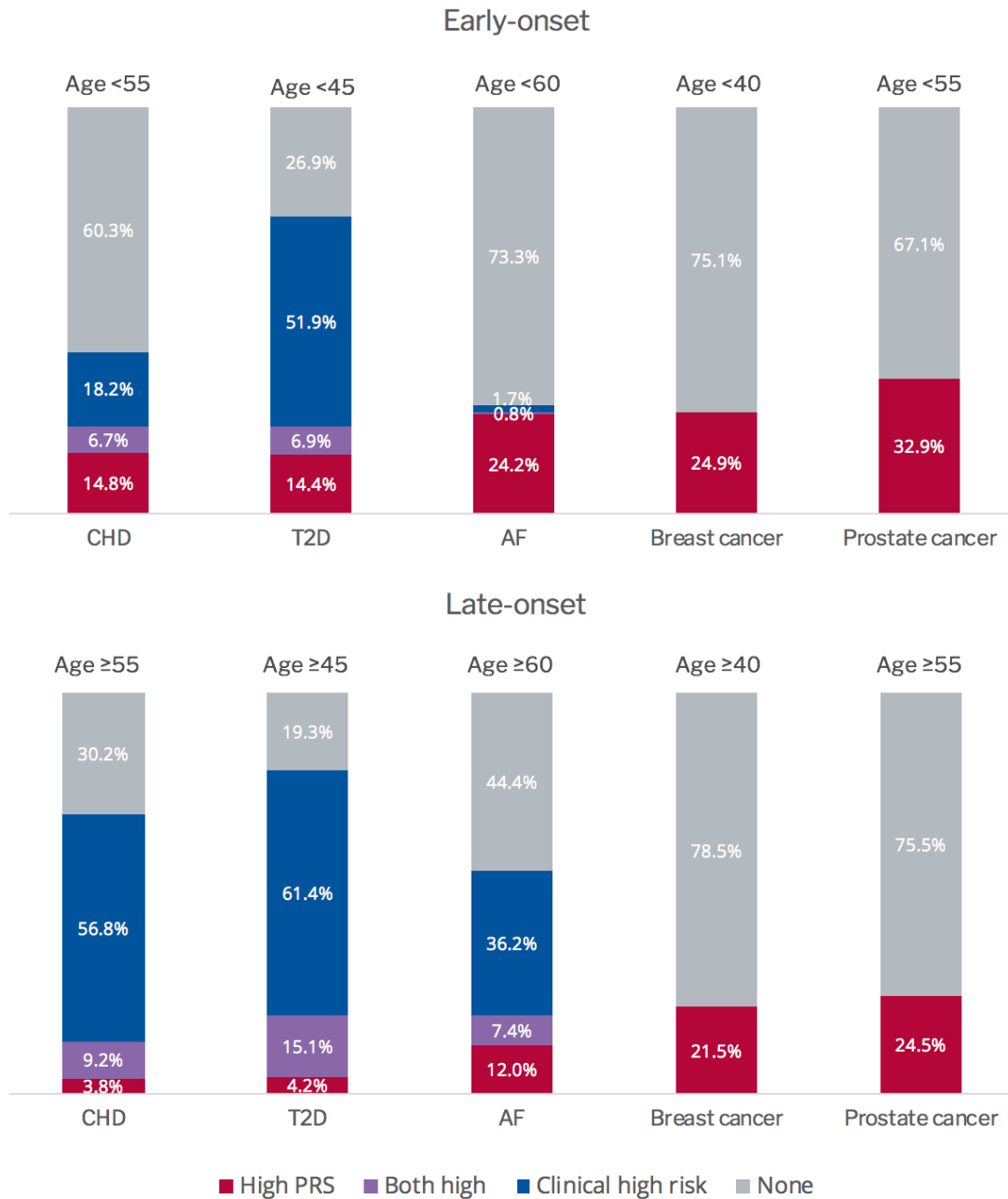
CHD = coronary heart disease, AF = atrial fibrillation or flutter, T2D = type 2 diabetes. High PRS = in top decile of the distribution. The number of early- and late-onset cases for CHD was 297 and 1,818, for T2D 160 and 2,342, for AF 160 and 1,099, for breast cancer 177 and 3,727, and for prostate cancer 155 and 3,108. CHD, T2D, and AF cases from FINRISK, and breast and prostate cancer from FinnGen. Clinical high risk definitions were following: For CHD, the 10-year risk calculator for hard atherosclerotic cardiovascular disease (ASCVD) ≥7.5%, according to the Pooled Cohort Equations by ACC/AHA (2013). For T2D, BMI ≥25kg/m^2 and one of more additional clinical risk factors.[16] For AF, the 5-year risk of AF >5%, by a revised version of the CHARGE-AF.