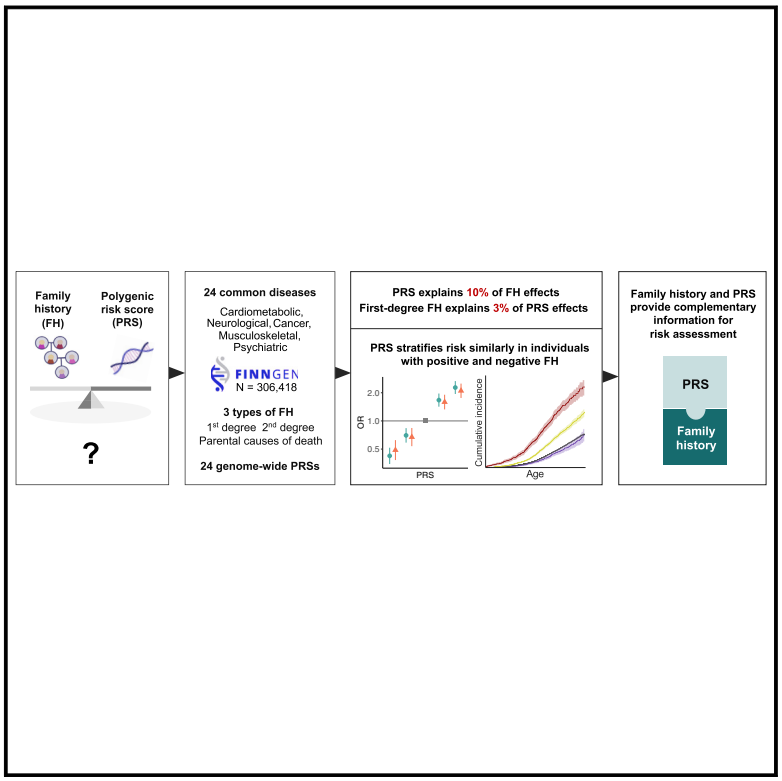
Systematic comparison of family history and polygenic risk across 24 common diseases

Graphical abstract



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Leveraging family relationships, nationwide registries, and genome-wide genotyping, Mars et al. systematically compared two measures of inherited disease risk across 24 diseases: family history and polygenic risk scores. The measures provided complementary information for risk assessment, demonstrating opportunities for a more comprehensive way of assessing inherited risk in clinical care.

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ARTICLE

Systematic comparison of family history and polygenic risk across 24 common diseases

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Summary

Family history is the standard indirect measure of inherited susceptibility in clinical care, whereas polygenic risk scores (PRSs) have more recently demonstrated potential for more directly capturing genetic risk in many diseases. Few studies have systematically compared how these overlap and complement each other across common diseases. Within FinnGen (N = 306,418), we leverage family relationships, up to 50 years of nationwide registries, and genome-wide genotyping to examine the interplay of family history and genome-wide PRSs. We explore the dynamic for three types of family history across 24 common diseases: first- and second-degree family history and parental causes of death. Covering a large proportion of the burden of non-communicable diseases in adults, we show that family history and PRS are independent and not interchangeable measures, but instead provide complementary information on inherited disease susceptibility. The PRSs explained on average 10% of the effect of first-degree family history, and first-degree family history 3% of PRSs, and PRS effects were independent of both early- and late-onset family history. The PRS stratified the risk similarly in individuals with and without family history. In most diseases, including coronary artery disease, glaucoma, and type 2 diabetes, a positive family history with a high PRS was associated with a considerably elevated risk, whereas a low PRS compensated completely for the risk implied by positive family history. This study provides a catalogue of risk estimates for both family history of disease and PRSs and highlights opportunities for a more comprehensive way of assessing inherited disease risk across common diseases.

Introduction

Family history (FH) is a risk factor in most common, non-communicable diseases.[1] With multiple advantages, including low cost and non-invasiveness, it captures both genetic and non-genetic familial risk and is therefore widely applied for risk stratification and health promotion. Common clinical applications include assessment of FH of breast cancer for targeted screening, earlier initiation of cardiovascular disease prevention, and evaluating the likelihood of rheumatic disease in individuals with inflammatory arthritis.[2–4] Despite the advantages, assessment of FH also has important limitations in capturing inherited disease risk. Many individuals with common diseases have no FH, or may not know the diseases their relatives have, and the same level of familial risk is assigned to all relatives of similar degree. The accuracy of FH is fairly low owing to factors such as recall bias, and sensitivity to wording in queries may lead to misinterpretation of risk.[5,6] With average family sizes declining in many developed countries,[7] FH will also provide increasingly less information for a comprehensive assessment of familial risk.

The algorithmic developments and rapid growth in genome-wide genetic testing provide a more personalized approach for measuring genetic susceptibility through polygenic risk scores (PRSs).[8,9] PRSs employ information from large-scale genetic screens comparing allele frequencies in thousands of individuals with a disease to healthy controls and have identified numerous genetic loci for virtually all common diseases.[10] To estimate polygenic risks, the common genetic variation and the effects on the disease risks are integrated into a single metric, the PRS. The effectiveness of PRSs in risk stratification has been demonstrated for many diseases, with predictive value demonstrated alongside established clinical risk assessment tools.[11] Similarly, PRSs modify risk among individuals with high-risk variants and identify high-risk individuals for whom existing prediction tools are suboptimal.[11–16]

Given the initial expense of implementing PRS estimation in a clinical setting relative to the seemingly simple questions pertaining to family history, systematic evaluation of the independent added benefit of PRS across common diseases is essential. Studies on individual diseases have observed fairly independent effects of PRS and first-degree FH,[11,15,17–27] but few studies have systematically compared the relative contributions and overlap of PRS and FH across different types of familial risk, across varying genetic architectures, and across a wide range of diseases. Moreover, only a few studies have used genome-wide PRSs, although these contemporary PRSs containing a large number of variants have demonstrated improved

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performance beyond PRSs with less variants due to high polygenicity in common diseases.[13,28–30] Here we study the interplay of first- and second-degree FH, parental causes of death, and genome-wide PRSs for 24 diseases using FinnGen (N = 306,418), showing that FH and PRSs are largely independent and provide complementary information in risk assessment.

Material and methods

Participants and diseases

This observational study uses FinnGen study Data Freeze 7, a collection of 306,418 adults (age ≥18) from epidemiological cohorts, disease-based cohorts, and hospital biobanks (Table S1). We used three binary definitions for FH: (1) any type of first-degree FH (FH_{1st} morbidity or mortality), (2) any type of second-degree FH (FH_{2nd}), and (3) parental cause of death (FH_P). Both for the index individual and their relatives (i.e., how FH was obtained), cases were identified through nationwide healthcare registries. The first two definitions were mapped using the genetic information to identify pairs of related FinnGen participants, whereas information on parental causes of death was available for all FinnGen participants. The 24 diseases were chosen based on availability of large published genome-wide association studies (GWASs) with full summary statistics available for genome-wide PRSs (Table S2). Disease definitions are in Table S3. Registry follow-up ended on December 31, 2019, with parental causes of death available until December 31, 2018. For FH_P, we studied 15 out of the 24 diseases, identifying causes of death (immediate, contributing, and underlying causes of death). The study was conducted in accordance with the ethical standards of the institutional and national research committees, with participants providing informed consent. Ethics statement and details on genotypes, PRS generation, and inference of relatedness are in the supplemental material and methods.

Polygenic risk scores

For each of the 24 diseases, we constructed disease-specific PRSs in a systematic manner. PRS-CS[31] was used for inferring posterior effect sizes from the GWASs listed in Table S2, with the number of cases in the GWASs ranging from 3,769 (epilepsy) to 567,460 (eGFR used for chronic kidney disease). The 1000 Genomes Project European sample (N = 503) served as the external linkage disequilibrium (LD) reference panel.[32] The posterior effect sizes were then used for calculating the PRSs.

The PRS was analyzed primarily as a continuous variable, with selected analyses applying either a (1) binary definition of FH, with high PRS defined as a PRS in the top decile of the distribution, with the rest as the reference group, or (2) PRS categories 0%–10%, 10%–20%, 20%–40%, 40%–60%, 60%–80%, 80%–90%, and 90%–100%, with the reference group being 40%–60%. To assess the impact of high versus low PRS, the reference category was 33rd to 90th percentiles, and low PRS was defined as the lowest tertile of the distribution, to allow for a sufficient number of cases with low PRSs.

Statistical analysis

Associations between FH, PRS, and risk of disease were assessed with logistic regression, with models adjusted for sex, birth year, genotyping array, cohort, and the first ten genetic principal components of ancestry. Interactions between FH and the continuous PRS (scaled to zero mean and unit variance) were assessed by introducing their interaction term to the regression model, assessing statistical significance set at a p value threshold of 0.0013 (Bonferroni correction for 24 + 15 tests). Cumulative incidences by age 80 were estimated with Kaplan-Meier survival curves (R package survminer). Statistical analyses were performed using R, version 4.1.0.

Results

FinnGen comprises 306,418 individuals (56.3% women; mean age 59.8 at the end of follow-up in 2019, SD 17.3). For the 24 diseases, FH was defined as (1) first-degree family history, FH_{1st} (morbidity or mortality), (2) second-degree family history, FH_{2nd}, and (3) parental cause of death, FH_P. Each identifies the relatives' diagnoses systematically through nationwide registries, including the hospital discharge registry (available from 1968 onward), causes of death registry (from 1964), and the Finnish Cancer Registry (from 1953). FH_{1st} and FH_{2nd} leverage the genetic relatedness within FinnGen: out of 306,418 individuals, we identified 39,444 with first-degree relative pairs based on the KING kinship coefficient[33] (see supplemental material and methods for details; 60.3% women; mean age 53.0, SD 16.5; parent-offspring relationship in 19,261 individuals, full-sibling relationship in 20,183). For breast cancer, we studied only women (15,281 individuals, mother-daughter relationship in 7,770; full sisters in 7,511), and for prostate cancer, only men (9,473 individuals; father-son relationship in 3,932; full brothers in 5,541). Similarly, we identified 47,154 individuals with a second-degree relative in the dataset (63.2% women, mean age 47.5, SD 15.0; N = 18,973 for breast cancer; N = 12,355 for prostate cancer). Parental causes of death (FH_P) were linked through the causes of death registry available from 1964 to 2019, and we excluded 78,436 whose parents had both died before 1964 or who had missing data on both parents (e.g., due to emigration), resulting in 227,982 individuals (mean age 53.6, SD 15.1; N = 133,653 for breast cancer; N = 94,329 for prostate cancer; 70,225 [30.1%] with one and 73,299 [32.2%] with two dead parents). See Figure S1 for study flow diagram.

Family history and risk of disease

First, we systematically evaluated the effects of FH on risk of disease. Figure 1 shows the prevalence of the diseases and the prevalence and effect sizes for positive FH. The most common diseases were cardiometabolic diseases, followed by knee osteoarthritis and hypothyroidism. Positive FH_{1st} was significantly associated with higher risk of disease in all diseases except stroke. The effect sizes ranged from odds ratio (OR) 3.25 (95% confidence interval, CI, 2.41–4.37) in chronic kidney disease to OR 1.17 (0.98–1.39) in stroke (Table S4). For FH_{2nd}, 18 of 24 diseases showed evidence of an association, with their effect sizes ranging from OR 1.85 (1.19–2.89) in colorectal cancer to OR 1.17 (1.09–1.25) in hypertension (Table S5). Compared to FH_{1st}, the effect sizes for FH_{2nd} were on average 69.1%

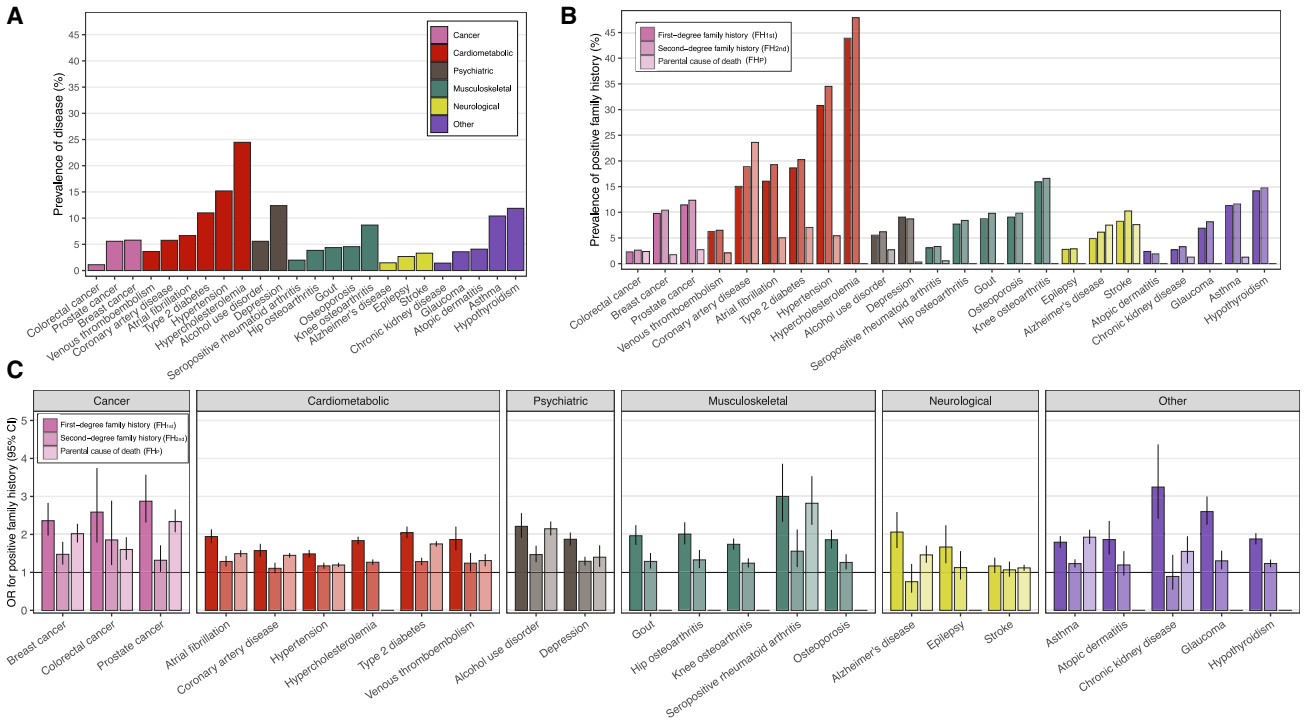

Figure 1. Disease prevalence and prevalence and effect sizes of positive family history

(A) Disease prevalence in individuals for whom we studied risk of first-degree family history.

(B) Prevalence of first-degree family history (left column), second-degree family history (middle column), and parental cause of death (right column).

(C) Effect size of first-degree family history (left column), second-degree family history (middle column), and parental cause of death (right column) with respective diseases. For parental causes of death, we studied 15 out of the 24 diseases.

Sample size in (A): total N = 39,444, N = 15,281 for breast cancer, N = 9,473 for prostate cancer. Sample sizes in (B) and (C): first-degree family history as in (A); second-degree family history total N = 47,154, N = 18,973 for breast cancer, N = 12,355 for prostate cancer; and parental causes total N = 227,982, N = 133,653 for breast cancer, N = 94,329 for prostate cancer. Odds ratios (ORs) were obtained from logistic regression models adjusted for sex (except for breast and prostate cancer), birth year, genotyping array, cohort, and the first ten genetic principal components of ancestry.

lower (SD 25.0%; calculated from log odds), i.e., a third of the effect of FH_{1st}. For FH_P, out of the 24 diseases, we studied 15 diseases that are well captured by causes of death and used information from all recorded causes of death (immediate, contributing, and underlying causes of death on the death certificate). For all 15 diseases, we observed an association between FH_P and risk of disease, with effect sizes ranging from OR 2.82 (2.25–3.53) in seropositive rheumatoid arthritis to OR 1.12 (1.04–1.20) in stroke (Table S6). Compared to FH_{1st}, the effect sizes for FH_P were on average 30.1% lower (SD 22.4%), i.e., two-thirds of the effect of FH_{1st}.

Overlap of family history and polygenic risk

Next, we compared the overlap between FH and PRSs. We constructed 24 genome-wide PRSs with uniform methodology using PRS-CS,[31] one for each disease (Table S2). We first compared the effect sizes per standard deviation (SD) increase for PRS and FH_{1st} (Figure 2, Table S4). The PRS was associated with elevated risk in all 24 diseases. The higher the PRS, the higher the proportion of positive FH (Figure S2). Effect sizes for the PRS ranged from OR 2.33 (95% CI 2.10–2.58) in prostate cancer to OR 1.12 (1.05–1.20) in epilepsy. Adjusting the PRS effect size with FH_{1st}, the change in effect size was small (mean decrease as log odds −3.0%, SD 1.3%). Adjusting the effect of FH_{1st} with PRS led to a mean decrease of −10.3% (SD 6.0%), i.e., PRS explained one-tenth of first-degree family history. No decrease in effect size was observed for PRS adjusting with FH_{2nd} (Table S5). We observed similar results for FH_P (Table S6; effect size decrease adjusting PRS effects with FH_P −0.7%, SD 0.6%; vice versa −14.5%, SD 9.2%). Proportional decreases in log odds by disease for all definitions of FH are in Figure 3. FH generally explained a much smaller fraction of the effect of PRS than vice versa. A similar pattern was observed categorizing the PRS and comparing high PRS (>90th percentile) to the rest of the distribution (Table S7 and Figure S3). A high PRS conferred on average similar effect sizes as FH_{1st}. The effect sizes particularly in common cancers and cardiometabolic diseases were higher for the PRS, whereas the effect sizes for psychiatric diseases were higher for FH_{1st}.

As early-onset FH is considered a particularly important familial risk factor, we also assessed the impact of FH_P divided into tertiles of age at death. The largest effect size was observed for FH_P with the lowest age tertile, in line

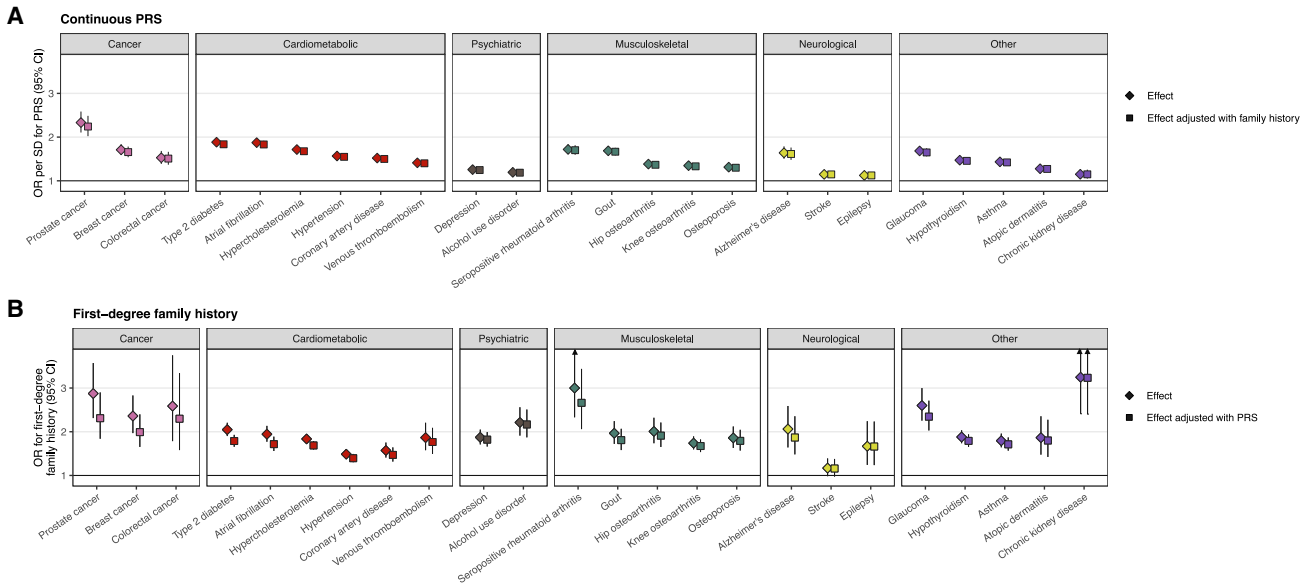

Figure 2. Cross-adjustment effects for first-degree family history (FH_{1st}), and respective polygenic risk scores (PRS)
(A and B) The impact of adjusting the PRS effect with first-degree FH_{1st} (A) and vice versa (B). The diamonds represent the unadjusted effects and the squares the adjusted effects. The PRS explained on average 10% of the effect of FH_{1st}, but FH_{1st} only 3% of the PRSs. The PRS effect is shown per one SD increase. Total N = 39,444, N = 15,281 for breast cancer, N = 9,473 for prostate cancer. Odds ratios (ORs) were obtained from logistic regression models adjusted for sex (except for breast and prostate cancer), birth year, genotyping array, cohort, and the first ten genetic principal components of ancestry.

with early-onset FH being a stronger risk factor than late-onset FH. Adjusting the PRS with this FH_P divided into age tertiles had no impact on the effect sizes of the PRSs. Adjusting this FH_P by PRS resulted in the largest effect size decreases for the youngest age tertile, but the decreases were overall small. These show that the PRS was independent of both early- and late-onset FH_P (Table S8 and Figure 4).

With formal interaction testing, we did not identify any systematic interactions between FH and PRS (Figure S4), which was further supported by observing similar PRS effect sizes in individuals with positive and negative FH_{1st} (Figure 5).

Moreover, we compared the performance of our contemporary genome-wide PRSs to previously published PRSs containing a smaller number of variants, obtained from PGS Catalog (https://www.pgscatalog.org/). Genome-wide PRSs had on average larger effect sizes (mean absolute difference in log odds 0.13 larger for genome-wide PRSs), whereby they also explained on average a larger proportion of the effect size of family history than the smaller PRSs (Figure 6).

Polygenic risk in individuals with a positive family history

Next, having assessed the overlap between FH and the PRSs, we estimated how high and low PRSs impact disease risk in individuals with positive FH_{1st}. Looking at cumulative incidence of risk of disease with the PRSs divided into three groups (high PRS >90%, average PRS 33%–90%, and low PRS <33%), we observed that a low PRS systematically compensated for the impact of positive FH_{1st}, and individuals with a combination of high PRS and positive FH_{1st} had a particularly high risk (Figure 7). Survival curves for a broader set of diseases and survival curves stratifying individuals with no FH_{1st} into similar PRS groups are in Figures S5 and S6.

Concordance of high polygenic risk in relatives

Lastly, we assessed concordance—detection of a high PRS among first- and second-degree relatives, relevant for cascade screening in relatives of individuals with high PRS. We evaluated two questions: (1) "What is the probability of having high PRS, if a relative has high PRS?" and (2) "How does this probability differ with relative's disease status?" For (1), on average 33.7% of the first-degree and 19.8% of second-degree relatives had a similarly high PRS (Figures S7 and S8). For (2), the concordance was somewhat higher with positive FH_{1st} than with negative FH_{1st}, with an average difference of 2.5% (range 0.0%–7.9%). For FH_{2nd}, no difference with disease status was observed (average 0.6%).

Discussion

Covering a large proportion of the burden of non-communicable diseases in adults, we systematically compared the overlap of polygenic risk and different types of family history, showing that they provide independent and complementary information of inherited disease susceptibility in all 24 studied diseases. PRS explained on average 10% of the effect of FH_{1st}, but FH_{1st} only 3% of the PRSs, and the

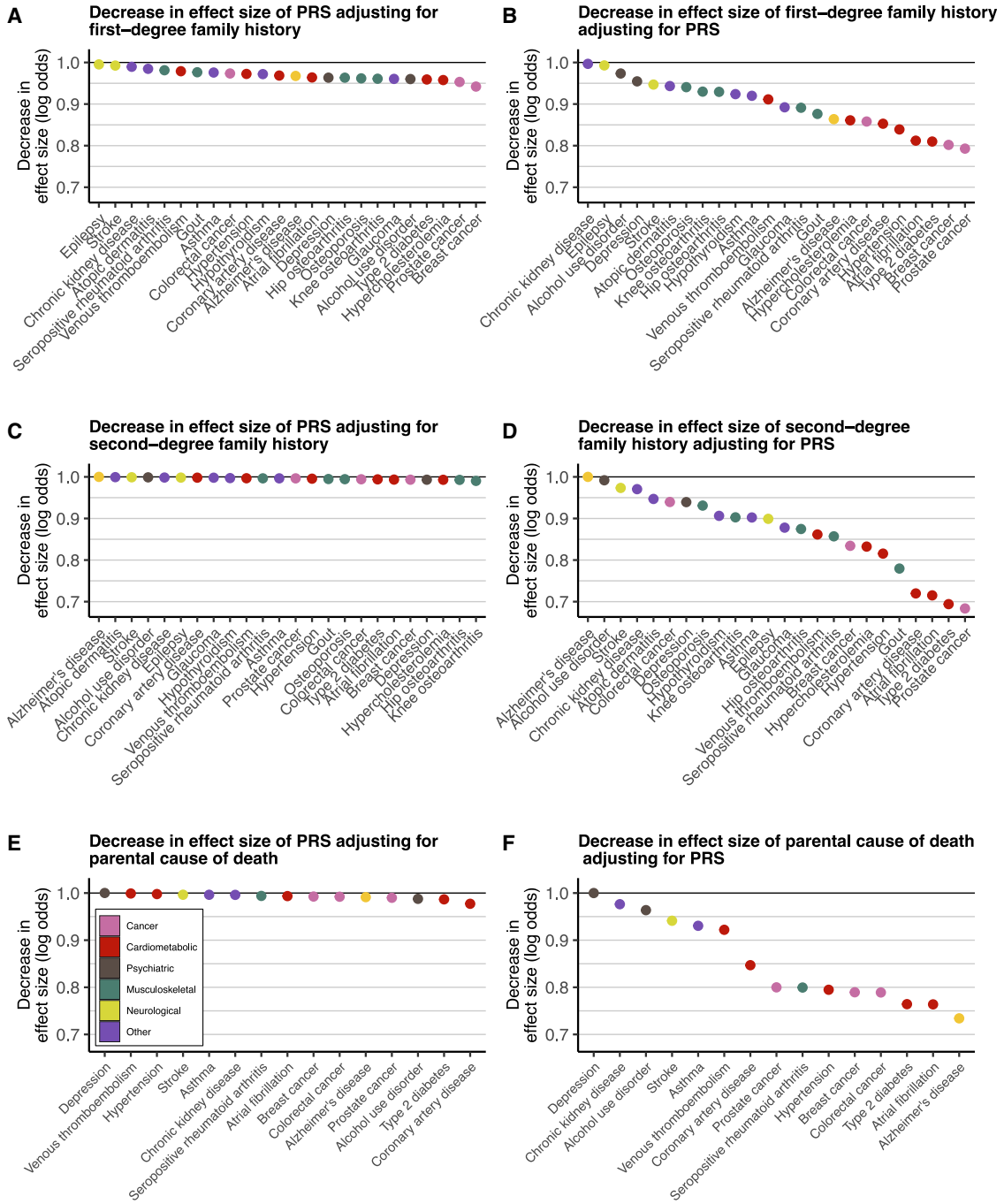

Figure 3. Cross-adjustment effect size decreases

(A–F) Proportional decreases in log odds by disease for first-degree family history, FH_{1st} (A and B), for second-degree family history, FH_{2nd} (C and D), and parental causes of death, FH_P (E and F). The left column (A, C, and E) represents decreases in effect size of high polygenic risk score (PRS, per SD) adjusting for family history. The right column (B, D, and F) represents decreases in effect size of family history adjusting for high PRS. The y axis represents the decrease in the effect size, calculated by dividing the log odds from the adjusted logistic regression model with the log odds from the non-adjusted model. For instance, in (A), the y axis represents the following quantity: (log odds of PRS adjusting for FH_{1st}) / (log odds of PRS without adjusting for FH_{1st}). In (D), the proportion of Alzheimer's disease was set at 1.00 as we did not observe any association for second-degree family history of Alzheimer's disease.

PRSs were independent of both early- and late-onset family history. The PRS estimates stratified risk similarly in individuals with and without positive FH: a high PRS conferred a considerably elevated risk, whereas a low PRS compensated for the effect of FH.

Our results are in line with previous disease-specific reports observing at most a modest attenuation in the effect of FH adjusting for PRS in cardiometabolic diseases, cancers, and depression.[11,15,17–27,34] We extend these by a systematic comparison across 24 common diseases, using

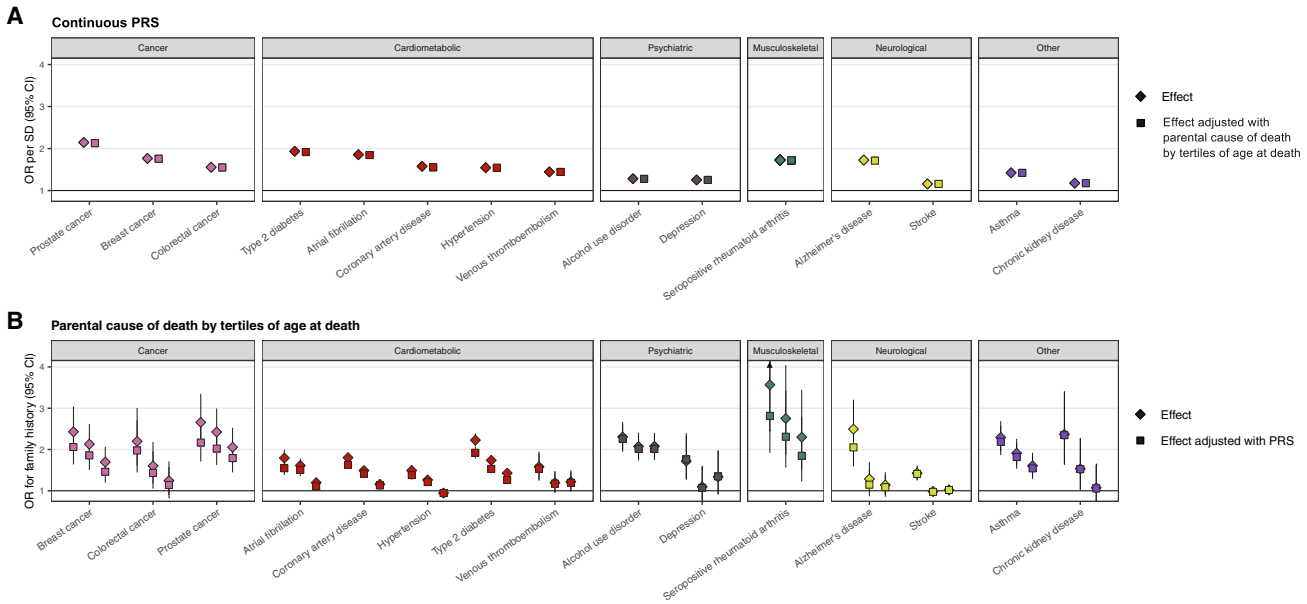

Figure 4. Polygenic risk is independent of both early- and late-onset family history

(A and B) As early-onset family history is considered a particularly important familial risk factor, we also assessed the impact of FH_P divided into tertiles of age at death. (A) Adjusting the effect of polygenic risk score (PRS; per SD) by parental causes of death (FH_P) divided into tertiles of age at death had no impact on the effect sizes of the PRSs. (B) Adjusting the effects FH_P by tertiles of age at death by PRS resulted in the largest effect size decreases for the youngest age tertile; however, for most diseases the difference by age tertile was small. The diamonds represent the unadjusted effects and the squares the adjusted effects. In (B), the effect sizes from lowest to highest age at death are displayed from left to right, and the reference group for each disease is individuals with negative FH_P. Sample size: total N = 227,982, N = 133,653 for breast cancer, N = 94,329 for prostate cancer. Odds ratios (ORs) were obtained from logistic regression models adjusted for sex (except for breast and prostate cancer), birth year, genotyping array, cohort, and the first ten genetic principal components of ancestry. Age limits for tertiles of FH_P and the number of individuals with parental cause of death in each tertile are reported in Table S8.

genome-wide PRSs generated with uniform methodology, by measuring FH uniformly through nationwide healthcare registries, and by leveraging genetic relatedness. Our results show that effects of FH and polygenic risk scores are independent, indicating that these measures complement each other for assessment of inherited disease risk. Compared to prevention guidelines that do not recommend use of PRS when FH is available,[3] these results provide important data supporting the use of PRS for improving risk assessment of several diseases with major public health importance.

The largely independent effects have several potential explanations. In addition to capturing shared DNA, FH measures non-genetic exposures and behaviors shared by families. In contrast, PRSs capture each person's unique combinations of common, disease-associated genetic variants, including genetic risk variation not shared by the relatives. PRSs can be measured in any phase of life, whereas FH relies on disease events having actualized in relatives with most utility in late-onset diseases. FH also assigns a similar risk for all relatives of the same degree, despite everyone carrying a unique set of genetic variants measurable through PRSs. Our observation of independent effects is also in line with earlier reports showing the importance of FH of breast and ovarian cancers in individuals with high-risk variants in *BRCA1* and *BRCA2*.[35]

Genetic information is typically considered in clinical care only when evidence-based prevention strategies to attenuate risk are available.[36] For instance, risk assessment of cancers has long tradition of comprehensive ascertainment of FH to identify familial clustering[37] when targeted interventions and screening tools are available.[2,38] Our results indicate that PRSs could be used to refine risk assessment of breast, prostate, and colorectal cancer, even when information about FH is available. In glaucoma, a high PRS and FH had equal and largely independent effects, but only FH is currently used for assessing risk of glaucoma in individuals with ocular hypertension.[39] The risk of coronary artery disease and type 2 diabetes can be decreased by lifestyle interventions and medications, and FH is commonly used for assessing their risk.[3,40] For both diseases, we observed larger effects for high PRS than for FH. Moreover, a high PRS may identify individuals more likely to benefit from preventive treatments: for coronary artery disease, a high PRS can result in higher relative efficacy of statins and disclosing PRS risk together with traditional risk factors can motivate lifestyle changes.[41–43] In contrast, stroke PRSs and FH show lower effect sizes than other cardiovascular diseases, likely owing to the heterogeneity of the disease and differing etiological patterns of stroke subtypes.[44,45]

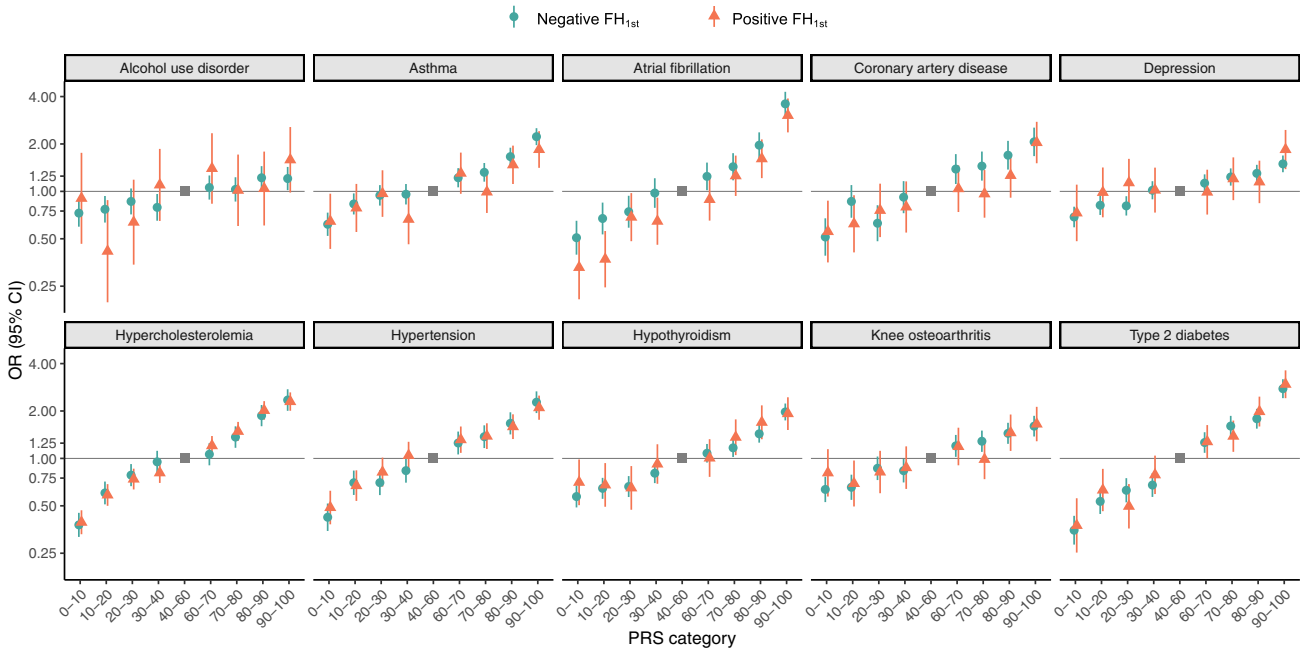

Figure 5. Effect sizes of polygenic risk scores stratified by first-degree family history (FH_{1st})
The effect sizes were calculated for the 10 most prevalent diseases. The gray box represents the reference category.

This study has multiple strengths. FH was assessed systematically and comprehensively by using linkages to high-quality nationwide registries, including hospital discharges, causes of death, and medication reimbursement registries and by overcoming several limitations of self-reported FH, such as recall bias, sensitivity to wording, and inter-individual differences in knowledge about FH.[5,6,46] We report effects of FH for disorders challenging to capture precisely from self-reported data, such as alcohol use disorder and atrial fibrillation, and show effects for diseases less studied in the field of PRSs, including glaucoma and hypothyroidism. Unlike FH, extremes of PRSs can also be used to identify individuals at particularly high or low risk. Moreover, our contemporary genome-wide PRSs had on average much larger effect sizes than previously published PRSs that are based on a smaller number of variants. This observation highlights the complex genetic architecture of common diseases and is in line with earlier reports on individual diseases.[29,30] FinnGen's wide age range is a key strength of the study, allowing systematic comparison of polygenic risk and FH across 24 diseases. Our results are also supported by quantitative genetic theory.[47,48] Average concordances of a high PRS among first- and second-degree relatives was 33.7% and 19.8%, in line with estimates on cardiometabolic diseases in UK Biobank[49] and in agreement with theoretically derived concordance estimates of 32.4% and 19.3%.[48] Moreover, the study provides catalogue of risk estimates for both FH of disease and PRSs in a large-scale biobank study.

The study was limited to individuals of European ancestry, among whom current PRSs have the highest utility.[50] Although our recording of FH_{1st} and FH_{2nd} was primarily based on only one relative, FH estimates are well in line with earlier reports from epidemiological cohorts and large registry studies (Table S9). For some diseases such as breast and prostate cancer, our effect sizes for FH were slightly larger than previously reported estimates, which may reflect the higher precision of registry-obtained family history compared to self-reported family history. As information on FH_P was available for all individuals, analyses on FH_P strengthen the results and conclusions by providing a complementary source of data that does not have the same limitations as the FH_{1st} and FH_{2nd}, which rely on inference of genetic relatedness. Not being able to account for family size may under- or overestimate the clinical impact of family history. Although the various registries are efficient in capturing disease diagnoses, milder disease forms such as mild osteoarthritis or atopic dermatitis may remain uncaptured. Similarly, common conditions such as depression or alcohol use disorder are often underreported unless severe or contributing to somatic pathologies. With over half of the study participants in the dataset ascertained from hospital biobanks or disease cohorts, the data are somewhat enriched in individuals with diseases, resulting in cumulative incidences that may not be fully generalizable to the population.

In conclusion, we studied the interplay of family history and genome-wide PRSs, systematically comparing effects across 24 common diseases. The effects of family history and PRS were largely independent, and the pattern was observed across the diseases. We demonstrate that polygenic risk and family history are not interchangeable measures of genetic susceptibility. Instead, they provide complementary information, bringing opportunities for a

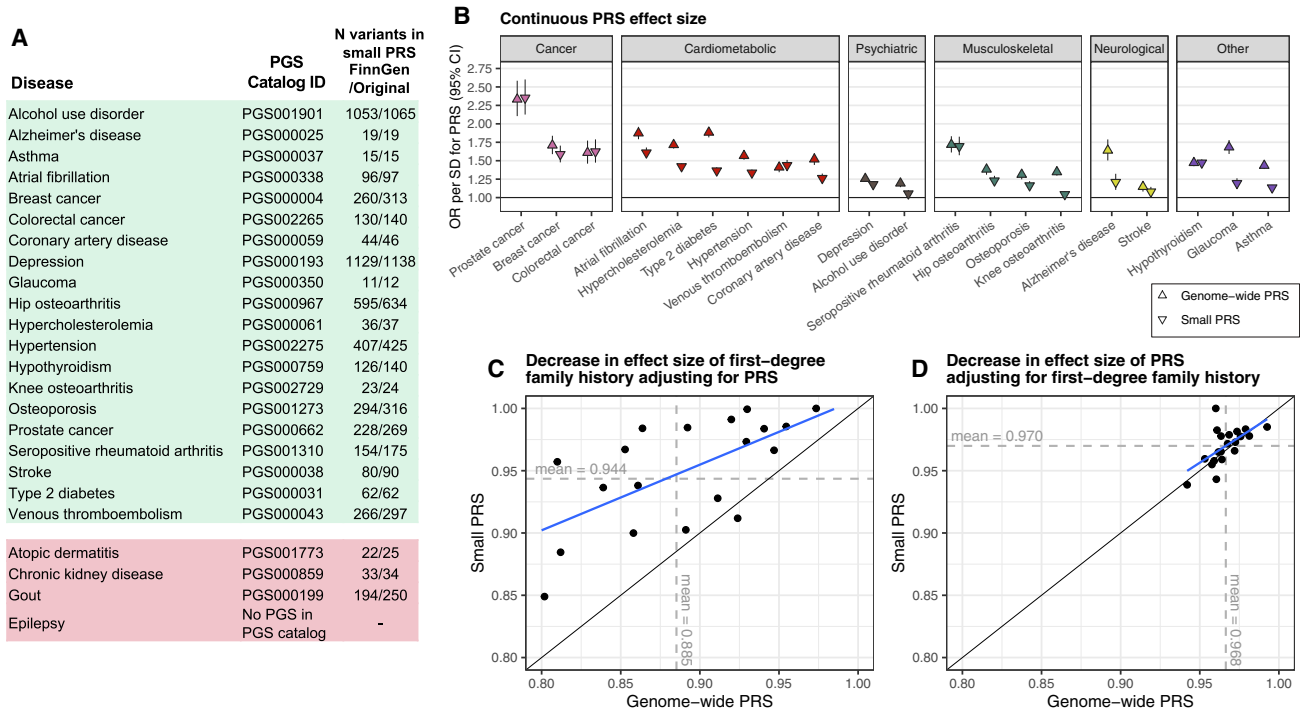

Figure 6. Comparison of our contemporary genome-wide PRSs to previously published PRSs containing a smaller number of variants
(A) Weights for the small PRSs were obtained from PGS Catalog (www.pgscatalog.org). The PRSs in green were associated with the respective endpoint in FinnGen, carried on to further comparisons. The PRSs in red showed no associations with their respective endpoints and were excluded from further analyses. No PRS for any type of epilepsy was found in PGS Catalog.
(B) Comparison of PRS effect sizes for the genome-wide PRSs and the small PRSs.
(C) Proportional decreases in effect size of first-degree family history adjusting with the PRS, showing adjustments with the genome-wide PRSs on x axis and adjustment with the small PRSs on y axis.
(D) Proportional decreases in effect size of PRS adjusting for first-degree family history, showing adjustments with the genome-wide PRSs on x axis and adjustment with the small PRSs on y axis. Similar to Figure 3, the proportional decreases in (C) and (D) represent decreases in log odds. Total N = 39,444, N = 15,281 for breast cancer, N = 9,473 for prostate cancer.

more comprehensive way of assessing inherited risk. A PRS can be calculated early in life to serve as risk indicator in individuals without family history of disease, while also providing effective risk stratification among individuals with positive family history.

Data and code availability

The FinnGen data may be accessed through Finnish Biobanks' FinBB portal (www.finbb.fi; email: info.fingenious@finbb.fi). Download links for the GWAS summary statistics used for constructing PRSs are provided in Table S2. The weights for our polygenic risk scores are available at PGS Catalog (https://www.pgscatalog.org/, publication ID PGP000364) with the PGS Catalog IDs listed in Table S2.

Supplemental information

Supplemental information can be found online at https://doi.org/10.1016/j.ajhg.2022.10.009.

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Author contributions

N.M., J.V.L, and S.R. conceived and designed the study. N.M. and P.d.B.P. carried out the statistical and computational analyses with advice from S.R. and J.V.L. Quality control of the data was carried out by N.M. and P.d.B.P. All authors provided critical input to interpretation of the data. The manuscript was written and revised by N.M. and S.R., with comments from all of the co-authors. All co-authors have approved the final version of the manuscript.

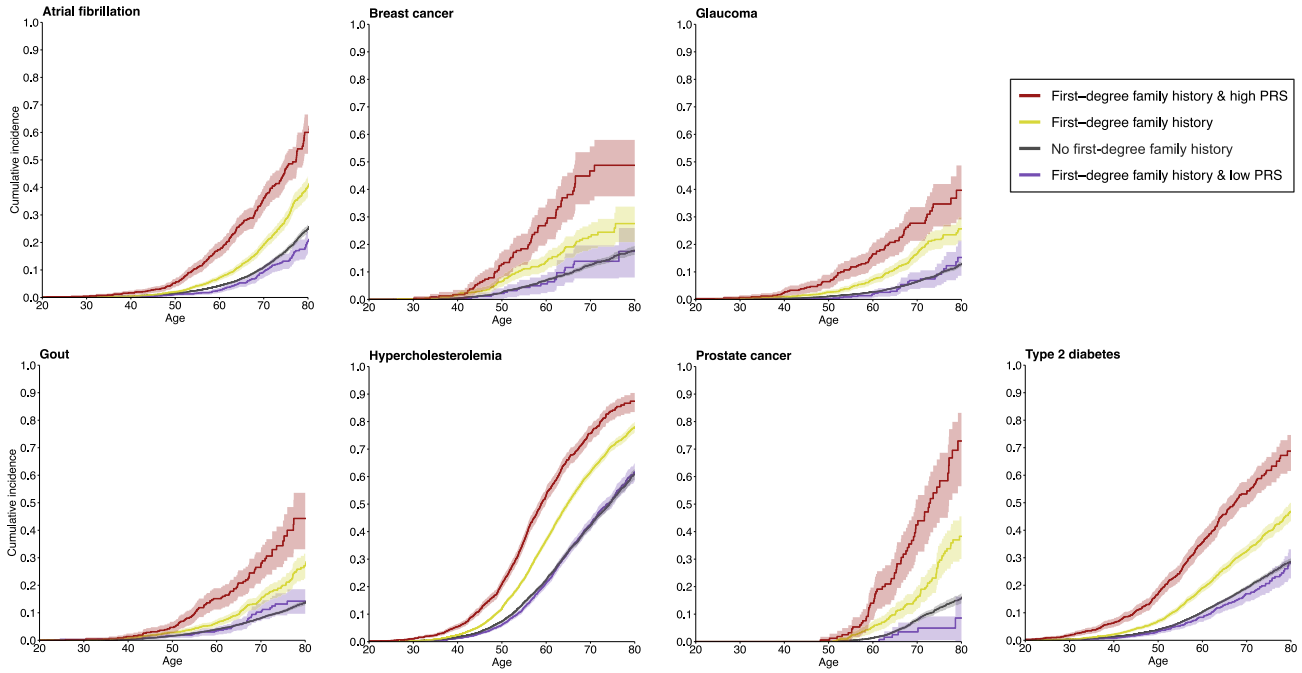

Figure 7. The impact of polygenic risk on disease risk in individuals with positive family history

The survival curves show cumulative incidences for individuals with positive first-degree family (FH_{1st}), stratified by level of polygenic risk score (PRS). High PRS was defined as top decile of the PRS distribution and low PRS as the bottom tertile of the PRS distribution. The figure shows results for the five diseases with the largest effect sizes for PRS, and for breast and prostate cancer. Survival curves for a broader set of diseases, and survival curves stratifying individuals with no FH_{1st} into similar PRS groups are in Figures S5 and S6. Total N = 39,444, N = 15,281 for breast cancer, N = 9,473 for prostate cancer. Analyses were performed for diseases with an OR >2 for high PRS in Table S7 and over 10 cases in each subgroup, excluding Alzheimer's disease due to its average onset late in life.

Declaration of interests

A.P. is a member of the Pfizer Genetics Scientific Advisory Panel.

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