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Contribution and interaction of polygenic predisposition and family history of coronary heart disease in predicting cardiovascular risk

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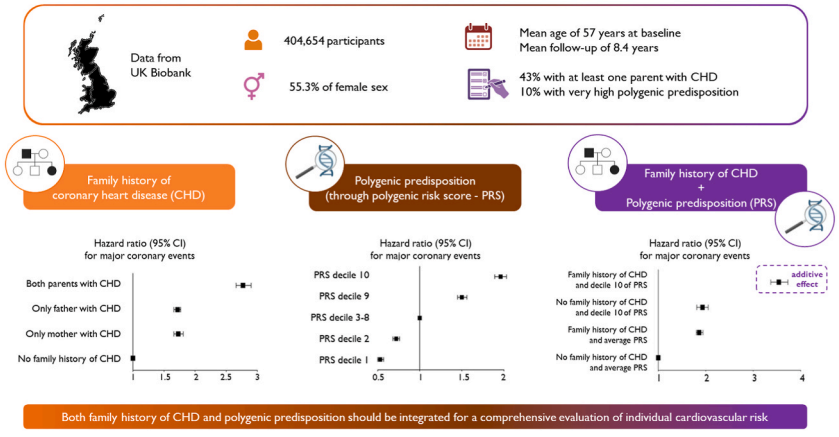
HIGHLIGHTS

- Polygenic risk and parental history independently increase lifetime coronary event risk.
- Their effects remain after mutual adjustment, indicating complementary value.
- Combined high genetic risk and family history markedly raise cardiovascular risk.
- These associations persist across LDL, blood pressure, and diabetes levels, showing added predictive value.

GRAPHICAL ABSTRACT



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ABSTRACT

Background and aim: Inherited susceptibility to coronary heart disease (CHD) can be conceptualized by considering family history and polygenic predisposition. This study aimed to clarify the role of these two components in predicting individual lifetime risk.

Methods: In the UK Biobank, information about family history of CHD (having one or both parents with CHD) was recorded at enrolment. To assess each individual's polygenic predisposition, we employed a previously validated polygenic risk score (PRS). Adjusted Cox models were used to analyse the impact of family history and PRS on major coronary events (MCE).

Results: We included a total of 404,654 participants (mean age 57 years; 55.3 % females). Both family history and PRS were found to be dose-related with the lifetime risk of MCE. Having a parental history of CHD or having a

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very high PRS (10th decile) exhibited a similar increasing effect, in terms of lifetime risk of MCE (12 % with hazard ratio [HR]: 1.86, 95 % confidence intervals [CI]: 1.80–1.94, and 14 % with HR: 1.93, 95 %CI: 1.81–2.05, respectively). The presence of a very high PRS, on top of a positive parental history of CHD, further increased the risk (20 % with HR: 3.54, 95 %CI: 3.37–3.73). Even after stratifying by LDL-C levels, both family history and polygenic predisposition complementary and additively contributed to MCE risk increase.
Conclusions: Family history and polygenic predisposition are both impactful predictors of MCE risk, demonstrating an additive effect that underscores the importance of considering these factors alongside cardiovascular risk factors for a comprehensive assessment of individual cardiovascular risk.

1. Introduction

Cardiovascular diseases (CVD), despite remarkable successes in the past decades in the treatment and prevention, still represent the leading cause of death and premature disability in developed countries [1]. In this field, understanding the basis of coronary heart disease (CHD) can significantly enhance the management and prevention strategies. Family and twin studies, animal models, and gene association studies suggest a genetic basis for CHD, supporting the hypothesis that genes contribute to CHD development and progression, as well as to the response to risk factor modification and lifestyle choices [2]. For this reason, individuals with a genetic predisposition to atherosclerosis are at the greatest risk for developing CHD, especially at early ages. Therefore, by identifying genetic factors that contribute to CHD, healthcare providers can develop more personalized treatment plans, implement targeted prevention programs, and potentially identify at-risk individuals earlier [3].

There are mainly two ways to conceptualize inherited risk of CHD: family history and polygenic predisposition.

Family history of CHD is an important risk factor for the development of a future cardiovascular (CV) event [4]. Researchers from the Framingham Study reported that having CVD in at least one parent doubled the 8-year CVD risk among men and increased the risk among women by 70 %. Current prevention guidelines advise integrating premature family history of CHD into risk assessments to inform treatment decisions. However, this approach is inconsistently included in short-term risk prediction models, likely due to uncertainties about its independent contribution alongside classical risk factors and genetic predisposition to cardiovascular risk prediction [5].

On the other hand, an increasing body of evidence have illustrated the potential use of polygenic risk scores (PRSs) for identifying individuals at an elevated risk of CHD [6,7], where the scores are based on the counts of the number of risk alleles carried. Moreover, additional studies have demonstrated that PRSs linked to CHD remain independent of family history [8], reinforcing the idea that family history might effectively encapsulate inherited genetic predispositions along with shared environments, habits and behaviours.

Due to this synergy, the combined factors of family history and polygenic predisposition hold significant promise for improving risk prediction in cardiovascular diseases. By integrating both genetic inheritance and individual genetic predisposition, they offer a comprehensive approach to identifying individuals at heightened risk for cardiovascular events.

Our study aimed to clarify the role of parental family history of CHD and polygenic predisposition in predicting an individual's lifetime risk of cardiovascular events development. In addition, we sought to understand whether these two risk factors exert independent effects and how they interact in shaping cardiovascular risk prediction.

2. Materials and methods

2.1. Study population

A total of 445,719 participants enrolled in the UK Biobank with complete genetic and principal component data who self-identified as being of white ancestry were evaluated. The UK Biobank is a prospective observational study of approximately 500,000 volunteer adults aged 40–69 years recruited from 22 sites across the United Kingdom between 2006 and 2010. Biochemical measurements, physical examination data, and medical histories were assessed at the time of study enrolment. Participants underwent genotyping with one of two closely related custom arrays (UK BiLEVE Axiom Array or the UK Biobank Axiom Array) consisting of over 800,000 genetic markers, with additional genotypes imputed using the Haplotype Reference Consortium resource, the UK10K panel, and the 1000 Genomes panel. The KING toolset was used to identify up to third-degree relatedness based on kinship coefficients >0.044. The UK Biobank protocol was approved by the Northwest Multi-Center Research Ethics Committee, and all study participants provided written informed consent. Participants consented to long-term follow-up through linkage to their electronic health records, enabling the study of incident disease events over time. Secondary use of data for this study was approved by the Massachusetts General Hospital institutional review board 2013P001840. For the purposes of this study, only subjects with information on both family history of CHD and individual genetic predisposition were selected, resulting in a total of 404,654 subjects.

2.2. Family history of CHD

For each subject, the family history of CHD was assessed at the time of enrolment in the UK Biobank. Available information includes whether parents (mother, father, or both) of each subject experienced a CHD event.

2.3. Genetic risk scores

A previously developed PRS for cardiovascular disease predisposition, already available within the UK Biobank database, was utilized. The UK Biobank resources category 301 provides access to standard PRS and enhanced PRS for 28 diseases and 25 quantitative traits, with the standard set (centered and variance-standardized) calculated for all participants in the UK Biobank using algorithms trained on external data only [9]. For CVD, the PRS was developed using a Bayesian framework that integrated genetic data across multiple ancestries (European, South Asian, East Asian, and African). This approach leveraged results from nine different genome-wide association studies, encompassing a total of 233,928 cases and 1,606,361 controls. Based on this, a standard PRS was computed for all UK Biobank participants (UK Biobank field 26223). CVD was broadly defined and included a range of diagnoses and clinical events: CAD, ischemic heart disease (broad and narrow definitions), ischemic stroke (excluding haemorrhagic subtypes), and CHD events. Diagnoses were identified through hospital records using ICD-9 codes (410–414, 434, 436, and 42979), as well as through self-reported data on myocardial infarction, angina, ischemic stroke, and transient ischemic attack (UK Biobank field 20002, codes 1075, 1074, 1082, 1583; field 6150, codes 1, 2, 3). Cardiovascular procedures were also captured through both self-reports (field 20004, codes 1070, 1071, 1105, 1109, 1095, and 1514) and hospital data using OPCS-4 procedure codes (K40–K46, K47.1, K49–K50, and K75). The Enhanced PRS, incorporating additional layers of optimization, was centrally computed by the UK Biobank and made publicly available to researchers as part of

the PRS Release.

Due to the heterogeneity in fasting status at the time of blood sampling in UK Biobank, measured low-density lipoprotein cholesterol (LDL-C) levels are subject to substantial within-person variability and may not accurately reflect habitual exposure. To address this, we used a genetic score for LDL-C. To construct the genetic LDL-C score, we identified a total of 100 exome variants previously associated with LDL-C levels at genome-wide significance ($p < 5 \times 10^{-8}$) and exhibiting low linkage disequilibrium with each other ($r^2 < 0.1$). For each variant, the exposure allele was defined as the allele associated with lower LDL-C levels. A weighted genetic score was then computed for each participant by summing the number of LDL-C–lowering alleles carried at each variant, weighted by the effect size of each allele on LDL-C (expressed in mg/dL), conditional on the association of all other variants included in the score. These effect sizes were estimated in UK Biobank participants without cardiovascular disease (see Supplementary Table 1) [10].

Similarly, a genetic score for systolic blood pressure (SBP) was constructed using 61 exome variants previously associated with SBP at genome-wide significance and also in low linkage disequilibrium ($r^2 < 0.1$). The exposure allele was defined as the allele associated with lower SBP. For each participant, the weighted SBP score was calculated by summing the number of SBP-lowering alleles, weighted by their conditional effect on SBP (in mm Hg) among UK Biobank participants free of cardiovascular disease (see Supplementary Table 2) [10].

2.4. Study outcome

The primary outcome was the time to first major coronary event (MCE), defined as the first occurrence of myocardial infarction or coronary revascularization after study enrolment. Only incident events were considered, based on the standard UK Biobank outcome classification system, which distinguishes between prevalent and incident cases using centrally processed hospital records, primary care data, and self-reported diagnoses. Participants with prior history of MCE at baseline were excluded from the analysis (**Supplementary Methods**).

Table 1
Baseline characteristics, measured at the time of enrolment in UK Biobank.

Characteristics	
No. participants	404,654
Age, y (SD)	57.09 (8.00)
Female sex, %	55.30
TC, mg/dL (SD)	221.14 (44.02)
LDL-C, mg/dL (SD)	138.1 (33.5)
ApoB, mg/dL (SD)	103.44 (23.75)
HDL-C, mg/dL (SD)	56.4 (14.82)
TG, mg/dL (IQR)	131.17 [92.64–189.63]
SBP, mmHg (SD)	137.54 (18.56)
CRP, mg/L (IQR)	1.31 [0.65–2.72]
BMI, Kg/m2 (SD)	27.34 (4.76)
Lipid-lowering therapy, %	16.75
Anti-hypertensive therapy, %	20.02
Diabetes,%	4.18
Smoker, %	6.93
Family history of CHD	
None	57.51
One parent	35.03
Both parents	7.46
PRS	
Decile 1	10.05
Decile 2	10.06
Average (deciles 3 to 8)	60.02
Decile 9	9.93
Decile 10	9.94

[a]Characteristics are presented as means and standard deviations (SD) for normally distributed variables, median and interquartile ranges (IQR) for non-normally distributed variables (TG and CRP), or percentages for dichotomous variables. TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; ApoB: apolipoprotein B; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides; SBP: systolic blood pressure; CRP: c-reactive protein; BMI: body mass index; CHD: coronary heart disease; PRS: polygenic risk score.

2.5. Statistical analysis

Initially, the separate impact of family history of CHD and polygenic predisposition on the risk of incident MCE was assessed using Cox proportional hazards models. These models were adjusted for sex and the first 10 principal components of ancestry, with age serving as the time scale, accounting for censoring and the ongoing accrual of events. The lifetime risk of MCE was then visualized using Kaplan-Meier curves, categorized by the presence of parental family history of CHD (none, one parent, both parents with an event) and polygenic cardiovascular predisposition (divided into five groups: the first group comprised individuals in the 1st decile of the PRS, the second group included those in the 2nd decile, the third group combined individuals in deciles 3rd through 8th, the fourth group included those in the 9th decile, and the fifth group comprised individuals in the 10th decile).

Furthermore, adjusted Cox proportional hazards models were employed to estimate the combined effect of parental family history and polygenic predispositions in predicting the individual lifetime risk of MCE. As a final analysis, the previous survival model was applied by first stratifying the population into tertiles based on the LDL-C instrumental genetic variable, in order to assess whether the impact of these factors on MCE lifetime risk is independent of the known impact of LDL-C on cardiovascular risk. Hazard ratios (HR) and corresponding 95 % confidence intervals (95 % CI) were calculated for these estimates. The same procedure was applied to tertiles of genetically instrumented SBP, as well as to self-reported diabetes status at baseline, treated as a binary variable.

All statistical analyses were conducted using Stata (version 16; StataCorp). Statistical significance was defined as a 2-tailed p-value (p) < 0.05.

3. Results

3.1. Participant characteristics

The cohort consists of 404,654 participants from the UK Biobank with a mean age of 57 years, of which 55.30 % are female (Table 1). The lipid profile shows mean levels of total cholesterol of 221.14 mg/dL and LDL-C at 138.1 mg/dL. Regarding family history of CHD, 35.03 % have one parent with a history of event, and 7.46 % have both parents affected. The PRS distribution reveals that 60.02 % of participants fall within the average range, with approximately 10 % each in the lowest and highest deciles. All participants were followed from study entry for a median duration of 8.4 years (mean 8.4 years, standard deviation 3.1

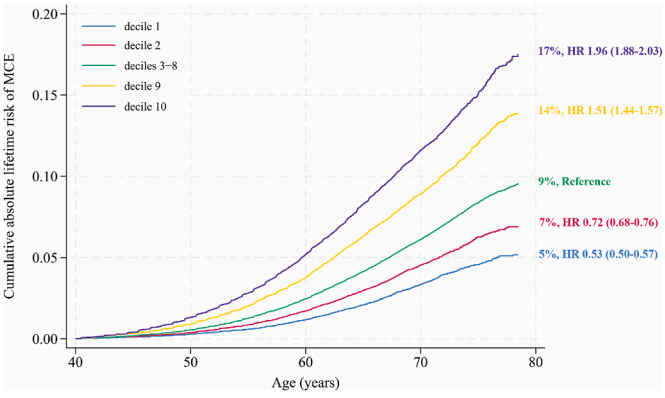
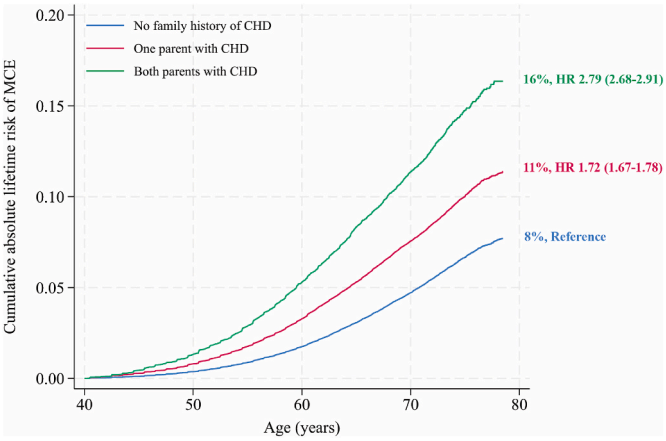


Fig. 1. Association between polygenic risk score for coronary artery disease and lifetime risk of major coronary event. Model estimates are expressed as hazard ratios (HR) and 95 % confidence intervals (95 %CI).



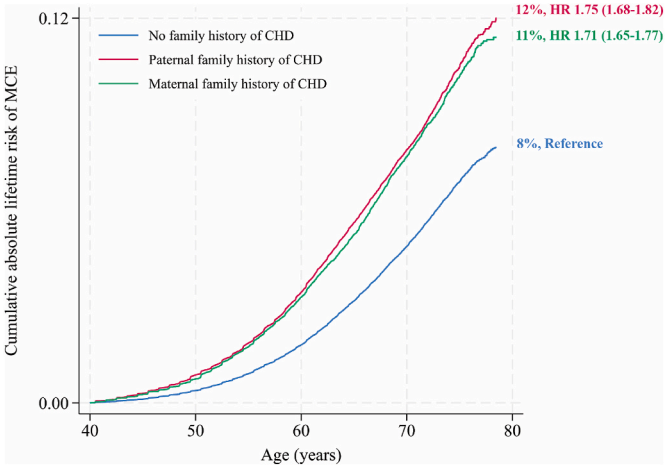


Fig. 2. Association between family history of coronary heart disease (CHD) and lifetime risk of major coronary event. Model estimates are expressed as hazard ratios (HR) and 95 % confidence intervals (95 %CI). Panel A: Dose-response relationship between family history of CHD and the lifetime risk of major coronary events. Panel B: Impact of maternal and paternal family history of CHD on the lifetime risk of major coronary events.

years). Follow-up time was calculated as the time from study entry until the occurrence of a MCE, death, or censoring.

3.2. Separate effect of polygenic predisposition and parental family history of coronary heart disease on the lifetime risk of MCE

The inherited risk captured by the PRS significantly impacts the lifetime risk of MCE, showing an increasing trend from the lowest decile (HR: 0.53, 95 %CI: 0.50–0.57) to the highest decile (HR: 1.96, 95 %CI: 1.89–2.03), compared to an average PRS (deciles 3 to 8), indicating a dose-response relationship between polygenic predisposition and MCE risk (Fig. 1).

Considering the family history, having only one parent with a history of CHD results in a 72 % increased risk of developing the condition (HR: 1.72, 95 % CI: 1.67–1.78). Additionally, having both parents with a history of CHD approximately doubles the risk (HR: 2.79, 95 % CI: 2.68–2.91), indicating a dose-response relationship between parental family history of CHD and MCE risk (Fig. 2, panel A).

When additionally adjusting for SCORE2 and LDL-C, the associations of both PRS and family history of CHD with MCE remained consistent and significant (data not shown).

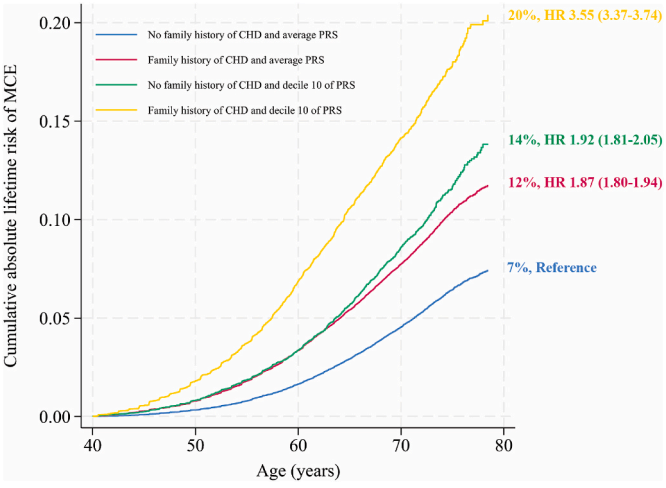


Fig. 3. Comparison and combined effect of family history of CHD and PRS on lifetime risk of major coronary events. Model estimates are expressed as hazard ratios (HR) and 95 % confidence intervals (95 %CI). CHD: coronary heart disease; PRS: polygenic risk score.

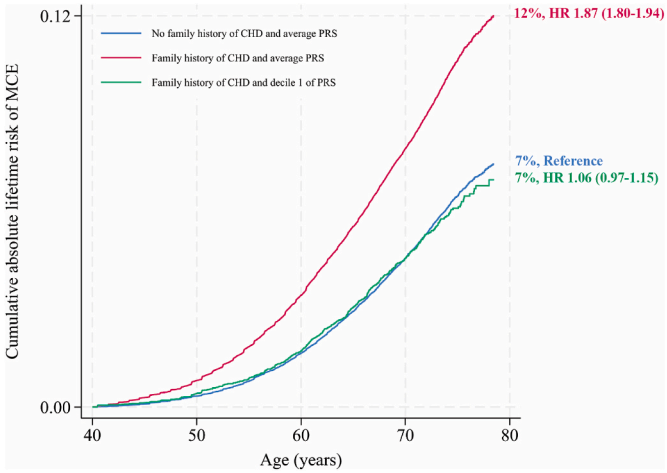


Fig. 4. Combined effect on lifetime risk of MCE of positive family history of CHD and low level of polygenic predisposition. Model estimates are expressed as hazard ratios (HR) and 95 % confidence intervals (95 %CI). CHD: coronary heart disease; PRS: polygenic risk score.

A further evaluation was performed for family history of CHD. Having either the mother or the father with a history of CHD increases the lifetime risk of MCE by approximately the same amount (HR: 1.71, 95 %CI: 1.65–1.77 and HR: 1.75, 95 %CI: 1.68–1.82, respectively, p-value for the difference >0.05), suggesting that maternal and paternal family history of CHD contribute roughly equally to the individual risk (Fig. 2, panel B).

3.3. Interaction between family history of CHD and polygenic predisposition in modulating risk

We observed also a borderline significant interaction between PRS and family history (interaction term p = 0.043). However, the effect size was modest. Indeed, we observed a slight attenuation in hazard ratios after mutual adjustment (Supplementary Table 3). For example, the HR for individuals with both maternal and paternal history decreased from 2.79 to 2.64 after adjustment for PRS, and the HR for the highest PRS quintile decreased from 1.96 to 1.90 after adjusting for family history. However, both effects remained highly significant, and their magnitudes largely preserved.

Table 2
Hazard ratios (HR) [95 % confidence intervals (CI)] for cardiovascular outcomes stratified by tertiles of low-density lipoprotein cholesterol (LDL-C) polygenic risk score (low, intermediate, high), by tertiles of systolic blood pressure (SBP) polygenic risk score, and baseline self-reported diabetes status.

Group	LDL-C genetic score		
	First tertile	Second tertile	Third tertile
	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)
No family history of CHD and average PRS	Reference	Reference	Reference
Family history of CHD and average PRS	1.89 (1.76–2.03)	1.87 (1.75–1.99)	1.81 (1.7–1.92)
No family history of CHD and decile 10 of PRS	1.83 (1.63–2.06)	1.95 (1.75–2.17)	1.97 (1.79–2.17)
Family history of CHD and decile 10 of PRS	3.1 (2.8–3.45)	3.63 (3.31–3.97)	3.66 (3.38–3.96)
Group	SBP genetic score		
	First tertile	Second tertile	Third tertile
	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)
No family history of CHD and average PRS	Reference	Reference	Reference
Family history of CHD and average PRS	1.84 (1.72–1.97)	1.99 (1.86–2.12)	1.78 (1.67–1.89)
No family history of CHD and decile 10 of PRS	1.98 (1.77–2.21)	2.06 (1.85–2.29)	1.75 (1.59–1.94)
Family history of CHD and decile 10 of PRS	3.59 (3.26–3.95)	3.69 (3.37–4.04)	3.34 (3.07–3.64)
Group	Self-reported diabetes		
	No	Yes	
	HR (95 % CI)	HR (95 % CI)	
No family history of CHD and average PRS	Reference	Reference	
Family history of CHD and average PRS	1.85 (1.78–1.93)	1.8 (1.62–2)	
No family history of CHD and decile 10 of PRS	1.9 (1.78–2.03)	1.75 (1.49–2.06)	
Family history of CHD and decile 10 of PRS	3.52 (3.33–3.72)	2.92 (2.54–3.35)	

[a]CHD: coronary heart disease; PRS: polygenic risk score.

3.4. Combined effect of family history and polygenic predisposition on the lifetime risk of MCE

Having at least one parent with a history of CHD or having a very high individual polygenic predisposition (i.e., belonging to the PRS decile 10) exhibited a similar increasing effect, in terms of lifetime risk of MCE (12 %, with HR: 1.87, 95 %CI: 1.80–1.94, and 14 %, with HR: 1.92, 95 %CI: 1.81–2.05, respectively) (Fig. 3). Moreover, the presence of a very high polygenic predisposition, on top of a positive parental history of CHD, further increased the risk (20 %, with HR: 3.55, 95 %CI: 3.37–3.74) (Fig. 3), suggesting that the contributions of family history and polygenic predisposition are additive in determining the lifetime risk of MCE. However, when considering those with low genetic predisposition and a positive family history, they have a lifetime risk comparable to individuals showing an average predisposition with no family members with history of CHD (7 %, with HR: 1.06, 95 %CI: 0.97–1.15) (Fig. 4). This further implies that parental family history and polygenic scores provide complementary information in determining individual cardiovascular risk.

3.5. Cumulative lifetime risk of major coronary events by strata of cardiovascular risk factors

Stratifying the population by tertiles of the LDL-C instrumental variable (LDL-C tertile 1: 127.15 ± 29.88 mg/dL; LDL-C tertile 2:139.20 ± 31.93 mg/dL; LDL-C tertile 3: 147.93 ± 35.17 mg/dL), we confirmed that a positive family history and individual genetic predisposition still have an additive effect on the lifetime risk of MCE beyond LDL-C levels (Table 2). For example, even in subjects in the lowest LDL-C tertile, the lifetime risk of MCE increased from 6 % to 10–12 % when at least one parent had CHD or when the polygenic predisposition was high. This risk is higher than that observed for subjects in the highest LDL-C tertile who have neither a family history nor a polygenic predisposition; the risk becomes 16 % when both factors are present. Similar patterns were observed when stratifying the population by tertiles of genetically instrumented SBP and by baseline self-reported diabetes status. Across these strata, both a positive family history of CHD and high polygenic predisposition consistently demonstrated independent and additive effects on the lifetime risk of MCE, reinforcing the robustness of these associations beyond traditional risk factors.

4. Discussion

The results of this study conducted in the UK Biobank cohort show that: i) polygenic predisposition (measured by PRS) and parental history of CHD impact the lifetime risk of MCE, exhibiting a dose-response relationship; ii) the separate effect of parental history of CHD and very high polygenic predisposition is essentially equivalent in terms of increasing lifetime risk of MCE; and iii) family history provides, complementary and additive information to polygenic predisposition for characterizing individual CV risk (**Graphical abstract**).

Our findings are consistent with previous reports highlighting the independent roles of genetic predisposition and family history in CV risk prediction. Tada et al. reported that a 50-variant genetic risk score predicted incident CHD independently of traditional risk factors and self-reported family history [11]. More recently, Schnitzer et al. employed a genome-wide polygenic score and a family risk score to evaluate myocardial infarction risk in a smaller cohort, demonstrating their independent but complementary contributions [12]. Building on previous work, our study goes a step further by assessing lifetime CV risk and examining the combined predictive value of polygenic risk scores and family history across multiple CV risk factors, clearly demonstrating additive effects. This approach provides a broader and more clinically translatable perspective. A further novel contribution of our study is the demonstration that the predictive value of a positive family history of CHD does not differ by parental sex—that is, maternal and paternal history of CHD confer comparable risk. This assumption had not been empirically validated in large-scale studies to date.

The role of family history of CHD as a modifier of cardiovascular risk has been known for years. The Framingham study [13,14] and the InterHeart study [15], two of the landmark studies in cardiovascular epidemiology, demonstrated that family history of CVD can significantly influence future CVD risk, depending on the number and age of affected first-degree relatives. For instance, siblings of patients with CVD experience approximately a 40 % increase in risk, while offspring of parents with premature CVD face a 60 %–75 % increase in risk [16]. As a result, family history has been evaluated to determine how incorporating this factor could enhance the predictive accuracy of CV risk algorithms. It emerged as the only clinical risk factor that independently improves discrimination and reclassification of atherosclerotic CVD (ASCVD) when added to traditional Framingham risk factors [17]. Other evidence showed that the inclusion of family history of CVD in the traditional risk scores failed to improve risk prediction of CHD [18]. As a result, family history was incorporated into a few risk prediction algorithms (such as the Reynolds risk score, PROCAM, and QRISK [19–21]), while its inclusion in guideline-endorsed risk prediction models, like the American ASCVD Risk Estimator [22] and the European SCORE algorithm [23], has been limited. In European guidelines, family history is noted among the factors that might modify the estimated risk [24]. However, all guidelines agree on the fact that the systematic collection and interpretation of family history information is an appropriate initial screening approach to identify individuals with genetic susceptibility to CHD. The simplicity of collecting these data, which can be easily and

systematically queried in clinical settings, provides inexpensive and easy-to-obtain predictive information [4]. However, before adopting family history as a public health screening tool, several key issues must be addressed. First, family history needs to be consistently recorded in electronic health records to enhance risk prediction algorithms. Beyond a simple binary indicator (presence or absence of family history), more detailed information, like the number of affected relatives, their relationship to the patient, the severity and onset age of the disease, and whether they are first- or second-degree relatives, provide better insight. The use of any first-degree relative with ASCVD (mother, father, sibling) was shown to perform just as well as the assessment of premature family history in predicting cardiovascular events [25]. Regularly updating family history data also improves its predictive accuracy [26]. Nevertheless, this approach can be effective, particularly in intermediate-risk individuals, such as those with not very high cholesterol levels, or in young subjects [4]. In our study, we observed that lifetime risk of MCE is strongly modulated also by polygenic predisposition, beyond parental history of CHD. In the last 15 years, hundreds of genetic variants that affect the risk of CVD and stroke have been identified through genome-wide association studies (GWAS) [27]. Several studies have demonstrated that a PRS for CVD or CAD can enhance risk assessment when combined with traditional clinical risk scores [28,29]. These findings have led to discussions about incorporating PRS into clinical practice [30]. In the clinical setting, adding genetic information to traditional risk assessments significantly improves the identification of individuals at high risk for major CVD events, particularly among younger populations [31]. Current clinical risk scores only capture a portion of those who will later experience a major CVD event. The inclusion of genetic information has been shown to increase the relative number of cases identified as high risk, demonstrating not only a significant improvement but also the utility of various widely used clinical risk scores. Additionally, genetic data may lead to a downward revision of the risk estimate for some individuals, likely reflecting their lower inherited susceptibility. However, in clinical practice, studies suggest that genetic information should mainly be used to reclassify individuals at intermediate risk to higher risk, while those identified as high risk based on clinical factors should be treated accordingly, regardless of their polygenic score [31]. Although the integration of genetic information into risk assessment will offer several advantages, PRSs derived from genetic data can provide information for predicting disease risk, but they suffer from poor cross-population transferability [32]. Moreover, PRSs are more expensive and complex to obtain than a standard lipid panel or family history. However, where possible they should be integrated in the overall CV risk assessment, as they provide valuable information regarding genetic predisposition present from birth. This information can be ascertained early in life as part of a comprehensive risk evaluation [30].

The rationale for the combined use of the two types of information stems from the fact that they have demonstrated an additive role in predicting MCE risk. This may be due to the partial complementarity of the information. Family history of disease can provide complementary information about disease risk: it represents both the result of inherited vulnerabilities (genetics) and behaviours embedded in close social structures, such as tobacco use, as well as dietary and exercise habits [33]. The independent and additive relationship observed between the PRS and family history in relation to CHD incidence can be explained by the complementary nature of the information they capture. While the PRS primarily reflects the genetic predisposition based on common genetic variants, it does not encompass rare variants, gene-gene interactions, or epigenetic factors. On the other hand, family history includes not only genetic factors but also shared environmental influences, behavioural factors, and possibly epigenetic modifications passed through generations, which are not captured by the PRS. Additionally, variability within families—such as siblings having different PRS despite sharing the same family history—further supports the idea that PRS can provide more individualized genetic risk assessment. Therefore, the two measures offer complementary information: PRS quantifies direct genetic risk, whereas family history reflects a broader spectrum of inherited and environmental risk factors [34]. This was shown to be true not only in cardiovascular fields. Hujoel et al. [35] developed a framework for predicting individuals' risk of disease conditional on both their polygenic risk scores and their family history, using data from the UK Biobank, finding that this approach increased prediction accuracy as compared to polygenic score alone across a broad set of simulations and empirical analyses, including analyses incorporating covariates. Together, family history and PRSs have the potential to enhance risk prediction in cardiovascular diseases. Some limitations of the study should be highlighted. First, participants in the UK biobank are a self-selected group who tend to be at lower risk of cardiovascular events than members of other populations. Future analyses should aim to replicate these findings in higher-risk populations and more diverse cohorts, including underrepresented age and ancestry groups. Second, this study focused on individuals of white/European ethnicity, and the generalizability of these findings to other ethnic groups requires further research. Third, additional limitations include the ascertainment bias associated with volunteer recruitment. Finally, it should be noted that the absence of information on the age at which parents experienced a CHD event limits the ability to determine whether the event was early-onset or not. Finally, previous studies have suggested that the relative impact of polygenic risk may be stronger in younger individuals, potentially reflecting the earlier expression of genetically driven disease in the absence of accumulated environmental exposures. While this is an important hypothesis, we were not able to explore it directly in our study, as the UK Biobank includes only individuals aged 40 years and older at baseline. Consequently, our findings cannot capture genetic effects in truly young populations or in early-onset CHD. This limitation highlights the need for future studies in younger cohorts to further characterize the age-specific predictive value of polygenic scores.

In conclusion, both a family history of cardiovascular disease and polygenic predisposition significantly contribute to an individual's lifetime cardiovascular risk. These factors do not simply overlap but have an additive effect, meaning their combined influence on risk is greater than the sum of their individual effects. Therefore, both family history and genetic predisposition should be integrated with LDL-C levels for a comprehensive evaluation of cardiovascular risk. Including these elements enables a more precise and personalized risk assessment, which can inform more targeted prevention and treatment strategies.

CRediT authorship contribution statement

Federica Galimberti: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft. **Elena Olmastroni:** Conceptualization, Methodology, Software, Data curation, Formal analysis, Writing – original draft. **Manuela Casula:** Writing – review & editing, Supervision. **Sining Xie:** Methodology, Software, Writing – review & editing. **Alberico L. Catapano:** Conceptualization, Writing – review & editing, Supervision.

Data availability statement

The data underlying this article are available from UK Biobank upon application.

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Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2025.120451.

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