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Association between a polygenic and family risk score on the prevalence and incidence of myocardial infarction in the KORA-F3 study

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ABSTRACT

Background and aims: Genetic risk scores for common diseases as myocardial infarction (MI) gain increasing attention for individual's risk prediction. One might wonder if assessing family history becomes redundant. It was the aim of this study to evaluate the amount of shared information between family history and genetic risk scores and to assess their independent and combined effects on prevalent and incident MI risk.
Methods: A genome wide polygenic risk score (PGS) and one family risk score (FamRS) were calculated in a population-based study from Southern Germany (n = 3071) with up to 11 years of follow-up. Logistic and Cox Regression models were used adjusting for lifestyle and classical risk factors.
Results: A right shift in MI risk for increasing values of PGS was found, with.
considerably increasing ORs along the top quantiles of PGS (OR = 3.03 for top 10%; OR = 5.55 for top 2.5%). The PGS was not associated with incident MI cases, though. The FamRS was significantly associated with both prevalent and incident MI cases with an OR of 2.9 for participants with a strong positive family history compared to average. ORs and HRs did hardly change in a combined model including both measures, indicating independent contribution to MI risk. The simultaneous addition of PGS and FamRS to a model including classical risk factors significantly enhanced prediction for prevalent cases and non-cases ($p = 3.28 \times 10^{-5}$).
Conclusions: These findings emphasize that both genetic information and family history are relevant for the determination of MI risk and that neither of them can replace the other.

1. Introduction

Coronary artery disease (CAD) represents a leading cause of death worldwide and has therefore a considerable impact on healthcare systems [1]. It is well known that the aetiology of CAD shows a high grade of intricacy, including both genetics and environmental factors like cigarette smoking, sedentary lifestyle or unhealthy diet [2,3]. Although lifestyle factors are of considerable importance for CAD pathogenesis, it should be emphasized that also genes play a significant role for the evaluation of disease risk, as a heritability of up to 50% has been reported for CAD [4]. Until some time ago only mutations in few genes such as the *LDL* receptor or the *LPA* gene have been reliably linked to CAD risk [5,6], but with the help of genome-wide association studies (GWAS) it has been possible to identify numerous genetic variants significantly associated with CAD susceptibility [2]. However, it should be noted that most of these variants only have a small effect size [2], which means that rather an accumulation of risk alleles is responsible for elevated CAD risk, whereas the isolated effect of a single risk increasing variant is negligible in most cases. One possibility to determine CAD risk based on genetic information is the calculation of a polygenic risk score (PGS). Such a score takes into account all potential risk alleles with their respective impact on genetic susceptibility for CAD [5]. One novel approach for the development of a PGS has been introduced by Khera et al. [7], who used a large-scale GWAS to derive a PGS for CAD and four

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other diseases. The PGS for CAD (PGS000013) contains 6,630,150 genetic variants and exhibits a high-quality performance of risk prediction in the UK Biobank population [7]. Moreover, it has been highlighted that approximately 8% of the investigated individuals are at greater than threefold elevated risk for CAD according to this PGS, which corresponds to risk levels of disease-causing monogenic mutations [7]. This has been a remarkable demonstration of the potential capacity of a PGS to identify individuals who are particularly at risk to develop CAD.

Another approach for the evaluation of CAD risk is to consider the family history of individuals regarding this disease. One way to do so is the calculation of a family history score (FamRS), as suggested by Williams et al. [8] The FamRS is not only based on the information if first degree relatives (e.g. parents and/or siblings) are affected by the disease, but also takes into account the age of first diagnosis and the number of family members, where disease status is known [8]. The inclusion of age into the formula is of considerable importance, as early cases of disease suggest particularly high risk in these families and provide more weight for the score. Furthermore, the number of applicable family members is considered, because in big families more disease cases can be expected than in small families. The main advantage of the usage of a FamRS may be the fact that it potentially includes information about both genetics and environmental factors, which lead to the clustering of disease in families [8]. It has been demonstrated that family history is significantly associated with both incidence and prevalence of CAD and can be used to identify a small proportion of the population, which is at substantial higher risk compared to those with discreet family history [8]. Alternatively, family history for CAD can be defined by a simplified approach by asking "whether mother or father have ever been affected by CAD". Such an approach to estimate family history would be much easier in clinical practice but may not always be able to approximate the information content of the FamRS in a sufficient manner [8,9].

In the study at hand, we investigated whether PGS and FamRS are associated independently with the prevalence and incidence of MI in the KORA-F3 population, respectively. Key issues are the question of whether PGS and FamRS identify individuals with significantly elevated susceptibility for MI in addition to established risk factors (e.g. those of the Framingham study [10]) and whether they are associated with each other. This will allow us to determine to what extent family risk can explain genetic risk and *vice versa.* Moreover, the performance of FamRS compared to alternative variables for family history of MI is evaluated.

2. Patients and methods

2.1. Description of the KORA-F3 study

The "**Co**operative Health **R**esearch in the Region of **A**ugsburg" (KORA) is a population-based adult cohort study carried out in Germany and was started as part of the WHO "**Moni**toring of Trends and Determinants of **Ca**rdiovascular Diseases" (MONICA) project [11]. The participants of the MONICA-Survey S3 were inhabitants of Southern Germany aged 25–74 years, as they were invited in 1994/95 [11]. The follow-up study KORA-F3 took place from 2004/05 and comprised 3184 individuals [9]. A morbidity and mortality follow-up was conducted in 2016. The applied study methods included a standardized computer-assisted interview, a standardized self-administered questionnaire, a physical examination and blood sampling [9,11]. The information regarding the occurrence and the age of first onset of MI among parents and siblings of the study participants was obtained by a standardized interview [9]. After exclusion of those with missing values in family history and genetic data 3071 participants of the KORA-F3 study remained in the analysis dataset. The study was approved by the Ethics Committee of the Bavarian Medical Association (KORA-F3 1994/95: EC No. 03097 and 2016 EC No. 08064), and written informed consent was obtained from all participants [12]. Requests to access the dataset can be made using the digital tool KORA.PASST in accordance with the informed consent given by the study participants (https://www.helmholtz-munich.de/epi/research/cohorts/kora-cohort/data-use-and-access-via-korapasst).

2.2. PGS definition

Genotype data was obtained using the Illumina Omni 2.5 and Illumina Omni Express array. Genotypes were imputed using the HRC reference panel [13] and the Michigan imputation server [14]. With that method, about 40 Mio SNPs over the whole genome are available for each of the KORA F3 study participants.

In the present study, a genome wide polygenic score, developed by Khera et al. [7], was used for estimation of genetic risk. This PGS was chosen, since it considers a large number of SNPs (6,630,150), scattered over the whole genome without limitation by *p*-value or to candidate genes and due to its good performance in the UK Biobank population.

The weights (log Odds Ratios from previous GWAS on MI) for the 6,630,150 SNPs included in the PGS were derived from the Polygenic Score Catalog [15] as score number "PGS000013". The PGS was calculated using PGS-Calc (https://github.com/lukfor/PGS-calc) by summing up the respective weights times genotypes for each individual in KORA F3 study.

2.3. FamRS definition

The FamRS was calculated based on the information of a standardized interview as suggested by Williams et al. [8] FamRS considers the number of affected family members among close relatives and accounts for the age of disease onset [8]. An elaborate description of FamRS calculation and a detailed definition of FamRS categories is provided in Supplementary Materials.

2.4. Definition of MI events and covariates

MI events were self-reported at the baseline examination S3 in 1994/95. During follow-up, up to 2016 MI events were identified and validated using self-reports based on standardized questionnaires, the KORA Myocardial Infarction Registry and death certificates based on standardized procedures [16,17]. A prevalent MI is defined as an MI event before or reported at the F3 examination in 2004/05. Consequently, these are partially validated and partially self-reported by participants.

Incident MI cases analysed here refer to the first occurrence of a fatal or non-fatal MI after the F3 examination in 2004/05 in participants free of disease. Definition of other covariates can be found in Supplementary Materials.

2.5. Statistical methods

To determine whether differences in mean values between cases and controls are significant, Welch two sample t-tests and Wilcoxon tests were used for normally and non-normally distributed data, respectively (tested using Shapiro-Wilks-test and qq-plots). Differences in categorical variables were determined by Chi-square tests.

For the evaluation of the association of PGS, FamRS and other family history variables with prevalent MI cases logistic regression models were used. In addition, correlation between PGS and FamRS was determined using Spearman correlation coefficient.

Furthermore, Cox regression using the package survival [18] in R was applied to investigate the association of PGS, FamRS and other family history variables with MI incidence. PGS and FamRS are mainly treated as continuous variables and odds ratios/hazard ratios (OR/HR) given for one standard deviation increase. Additional models are given for specific categorizations: in percentiles for PGS and average, positive, very strong positive family history for FamRS.

For all regression analyses the following adjustment models were used, adjusted for age and sex, hypertension, BMI, healthy diet score (as

recommended by Winkler et al. [19]), alcohol consumption, smoking and physical activity and one further model, which adjusts for the risk predictors for hard CHD (myocardial infarction or coronary death), as outlined by the Framingham study [10], age, sex, smoking, HDL cholesterol, total cholesterol, systolic blood pressure and antihypertensive treatment. The second model focuses on the lifestyle factors influencing MI risk, whereas the third represents the "main model" since it includes the traditional risk factors.

The predictive capacity of PGS and FamRS was determined by continuous Net Reclassification Index (NRI) and Integrated Discrimination Improvement (IDI) using the function improve Prob in package Hmisc [20]. In this context, the third adjustment model was used as the baseline model. All analyses were performed using the programme R version 4.0.3 and 4.1.0. In general, p-values<0.05 were considered to be statistically significant.

3. Results

3.1. Descriptive statistics

The KORA F3 study cohort consisted of 3071 participants with a mean age of 57 ± 13 years and with 1575 (51.3%) women. The baseline characteristics of the study population, as a whole and separated in men and women, are provided in Supplementary Table 1. 78 individuals exhibited a prevalent MI at the beginning of the study with mean age 58.6 ± 11.8 years at the prevalent MI events, whereas 116 incident MI events were recorded during the study (mean age incident MI 74.5 ± 11.3 years). A comparison of selected variables by MI prevalence is shown in Supplementary Table 2, showing a significant difference in mean values of the PGS ($p = 1.65 \times 10^{-4}$).

The distribution of the PGS for the KORA F3 population was compared with five reference populations, whose samples were derived from the 1000 genomes project [21] (Supplementary Fig. 1), showing similarity to the distribution in Americans and Europeans.

Density plots illustrate a consistent right shift in PGS to higher values

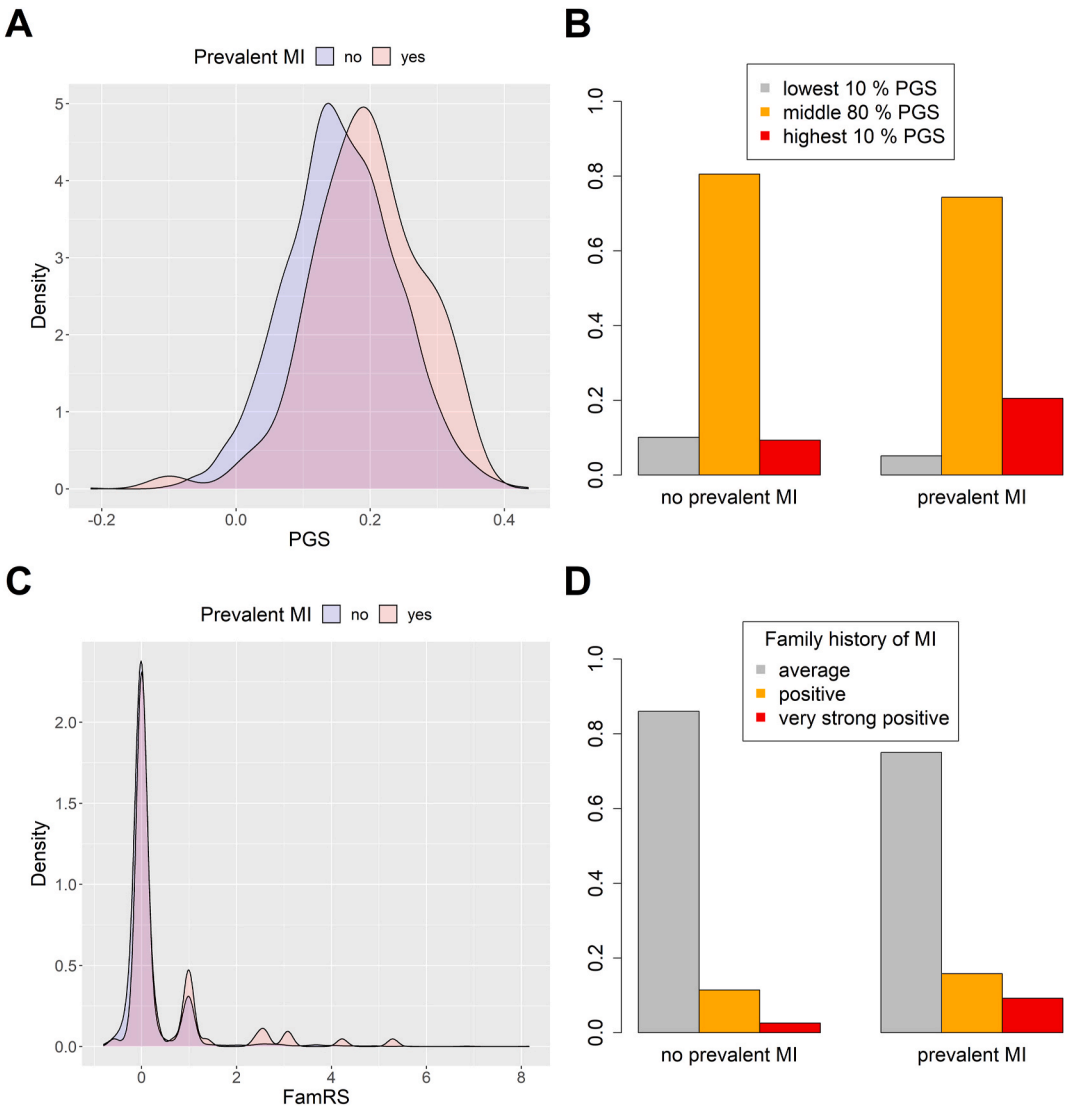

Fig. 1. PGS and FamRS distribution, stratified for prevalent MI cases yes/no.
(A) Density plots of PGS stratified by MI prevalence. The red shaded curve represents the prevalent cases, whereas the blue shaded curve stands for study participants, who had no MI before the study. (B) Comparison between study participants with and without prevalent MI by distinct percental categories of PGS. (C) Density plots of FamRS stratified by MI prevalence with the same colour code as in (A). (D) Comparison between study participants with and without prevalent MI by distinct categories of FamRS. Average family history refers to a FamRS≤0.5, positive family history to 0.5<FamRS≤2 and very strong positive family history to a FamRS>2. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

for individuals with a prevalent MI (Fig. 1A). Furthermore, the study participants were categorized due to their PGS into three categories: lowest 10%, middle 80%, and highest 10% of PGS. 20.5% of the cases fall into the overall top 10% of PGS, whereas among the controls only 9.3% belong to this category (Fig. 1B). In contrast, only 5.1% of the MI cases are part of the lowest 10% of PGS, whereas slightly more than 10% of the controls can be assigned to this group (Fig. 1B). In contrast, the equivalent analysis of the incident MI cases could not show a significant difference ($p = 0.389$) in the mean value of PGS between cases and controls according to a two-sided *t*-test and no consistent right shift in PGS (Fig. 2A). In addition, Kaplan-Meier curves, illustrating MI incidence during the observation period of the KORA F3 study stratified by the previously introduced percental categories of PGS, show only marginal and non-significant differences in MI incidence between these categories (Fig. 2B, Log Rank test $p = 0.50$).

FamRS of the KORA F3 population shows a highly skewed distribution. Of note, over 75% of study participants have no remarkable family history regarding MI and therefore have a FamRS of zero or below. Approximately 14% of the population (437 individuals) show a general positive family history of MI (FamRS>0.5) and 2.8% of the study participants (86 individuals) display a very strong positive family history of MI (FamRS>2).

Concerning the prevalent MI cases, a significant ($p = 4.02 \times 10^{-5}$) difference in mean values of FamRS has been found in comparison to the corresponding controls (Supplementary Table 2). Moreover, density plots comparing the distribution of FamRS separately for cases and controls indicate a higher relative occurrence of MI among individuals with higher FamRS values (Fig. 1C). Consistently, a comparison of FamRS categories between individuals with and without prevalent MI shows that study participants with prevalent MI are much more likely to exhibit a positive (0.5<FamRS≤2) or a very strong positive (FamRS>2) family history in comparison to those with an average family history (FamRS≤0.5) (Fig. 1D).

For incident MI cases, a significant ($p = 0.002$) difference in mean values of FamRS between cases and controls has been determined by a Wilcoxon test. Accordingly, it has been found that those with a positive family history are overrepresented among incident cases (Fig. 2C). In addition, two Kaplan-Meier curves for individuals with and without a

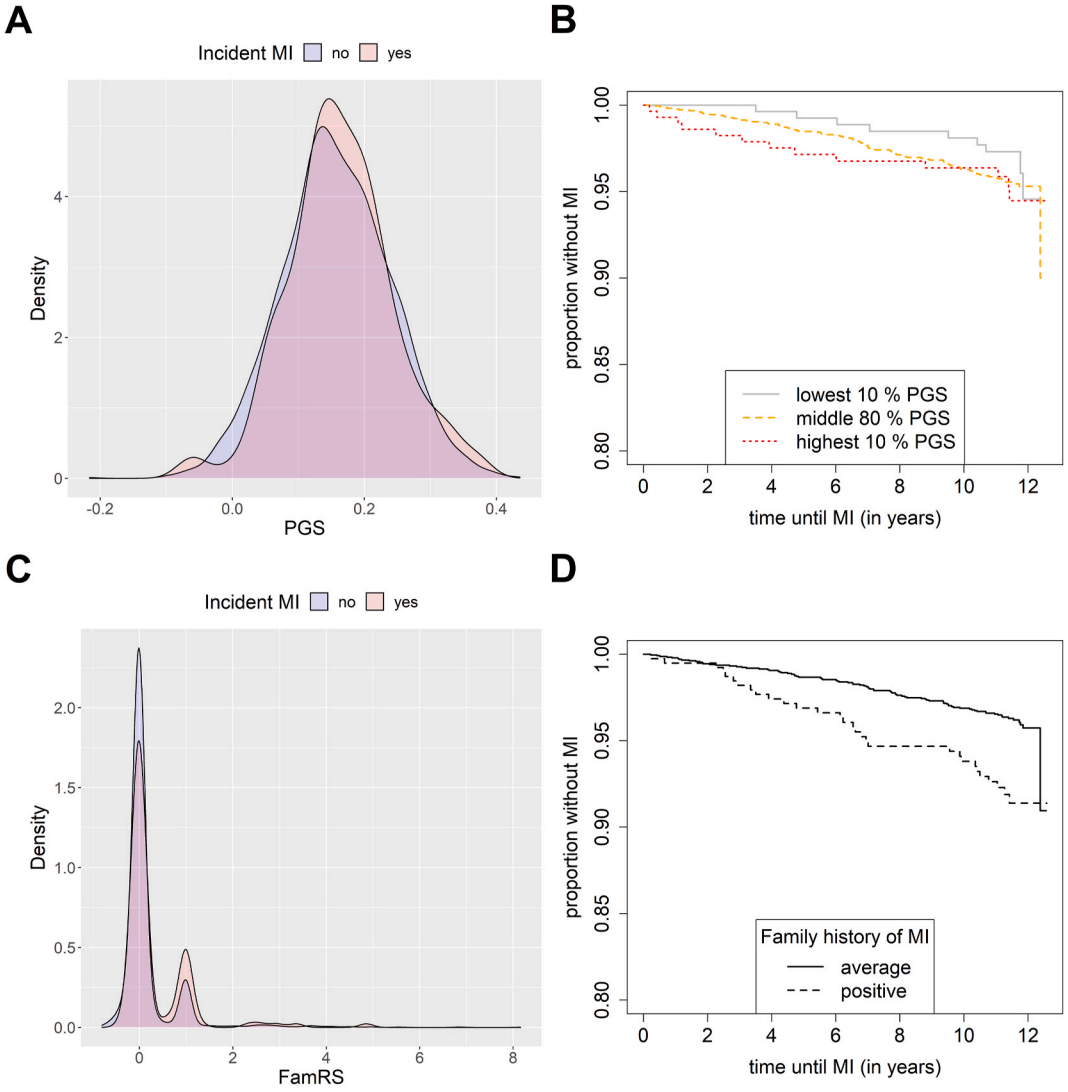

Fig. 2. PGS and FamRS distribution, stratified for incident MI cases yes/no.
(A) Density plots of PGS stratified by MI incidence. The red shaded curve represents the incident cases, whereas the blue shaded curve stands for event-free controls. (B) Kaplan-Meier curves illustrating the MI incidence for subgroups of distinct percental categories of PGS. (C) Density plots of FamRS stratified by MI incidence with the same colour code as in (A). (D) Kaplan Meier curves for MI incidence by average *versus* general positive family history of MI. Average family history refers to FamRS≤0.5 and (general) positive family history to a FamRS>0.5. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

general positive family history visualize a notable difference regarding MI incidence rate between these two groups (Fig. 2D, Log Rank test $p = 2 \times 10^{-4}$).

Although the correlation is significant ($p = 3.41 \times 10^{-4}$), PGS and FamRS correlate only marginally with each other (Spearman correlation coefficient = 0.065, adjusted $R^2 = 0.005$), which was illustrated in a correlation plot (Supplementary Fig. 2).

3.2. Comparing estimates for family history

A comparison between distinct variables for family history of MI has been performed for participants with and without prevalent (Supplementary Fig. 3) and incident MI (Supplementary Fig. 4). General positive family history (FamRS>0.5) detected 25% of prevalent MI cases compared to approximately 40% for both "MI among parents" and "one or more affected family member" and a similar result was obtained for incident MI cases with the exception that "MI parents" identifies only 31% of cases. In addition, logistic regression was carried out to compare the three estimates for family history concerning their association with MI prevalence (Supplementary Table 3). All three variables exhibited a strong positive association with prevalent MI cases. This remained significant after correction for the Framingham risk predictors (model 3) with similar ORs of general positive family history and MI among parents (OR = 2.08 and OR = 2.10, respectively).

Furthermore, Cox regression was carried out for a similar comparison of family history estimates regarding incident MI cases (Supplementary Table 4). The variables general positive family history (FamRS>0.5) and number of affected family members demonstrated a significant positive association with incident cases for all investigated models. On the other hand, MI among parents was not consistently significant for the incident cases. For instance, MI among parents shows comparatively low HRs and is not significant for the model, which adjusts for the Framingham risk predictors (HR = 1.53, $p = 0.057$), whereas FamRS>0.5 is significant for this model and displays a pronounced increment in MI risk (HR = 2.27, $p = 1.25 \times 10^{-4}$). Thus, we decided to use the FamRS as variable for family history for the subsequent investigations.

3.3. Association with prevalent MI

PGS was significantly associated with risk of prevalent MI (Supplementary Table 2), which was quite independent of other risk factors and was shown to remain significant even after correction for the Framingham risk predictors (model 3, OR = 1.66). This OR translates into a 66% higher chance for someone to have a prevalent MI for each standard deviation increase in PGS. Moreover, ORs for the top percentages of PGS were calculated using the same covariates as in model 3 (Fig. 3A). The top 15, 10, 5 and 2.5% of PGS show ORs of 2.76, 3.03, 3.61 and 5.55 in comparison to the remainder of the population, respectively.

Similarly, FamRS demonstrated a strong association with prevalent MI cases according to logistic regression (Table 1) and this association was still significant after adjustment for classical risk factors and the Framingham risk predictors (model 3, OR = 1.29). Furthermore, ORs of 1.78 and 2.90 were ascertained for positive and very strong positive family history according to model 3 (Fig. 3B). Logistic regression analyses including both PGS and FamRS simultaneously have been performed to evaluate if these two risk scores influence each other (Table 1). In the combined analysis both PGS and FamRS maintained their significant association with prevalent MI cases and odds ratios only marginally changed. The OR for PGS even slightly increased, if restricted to those participants with average FamRS (OR = 1.74, $p = 5.9 \times 10^{-4}$). If separated into men and women, higher OR are observed in men than in women (Men: $OR_{PGS} = 1.79$, $OR_{FamRS} = 1.36$; Women: $OR_{PGS} = 1.44$, $OR_{FamRS} = 1.16$ in the combined model, adjustment model 3). Odds Ratios do not differ significantly between men and women, though.

3.4. Association with incident MI

Table 2 shows the results of the respective Cox regression models. PGS was not associated significantly with risk of incident MI in a continuous fashion. On the other hand, FamRS demonstrated a strong association with incident MI cases. This relationship was significant even after adjustment for the Framingham risk predictors (model 3, HR = 1.16). A combined Cox regression with PGS and FamRS barely changes the outcome of both variables.

3.5. Net reclassification

Adding PGS to the baseline model consisting of the Framingham risk predictors could correctly increase MI probability for those with a prevalent MI and decrease probability for non-cases in approximately 60% of participants, respectively ($NRI_{events} = 0.221$, $NRI_{non\text{-}events} = 0.204$). This results in an overall NRI of 0.424 ($p = 1.65 \times 10^{-4}$). The corresponding IDI was 0.018 ($p = 3.15 \times 10^{-3}$). Adding solely FamRS to the baseline model could merely ameliorate prediction for non-cases according to the same predictive measures ($NRI_{non\text{-}events} = 0.68$, $NRI_{events} = -0.42$, NRI = 0.26, $p = 0.013$; IDI = 0.008, $p = 0.23$).

The simultaneous addition of PGS and FamRS to the baseline model

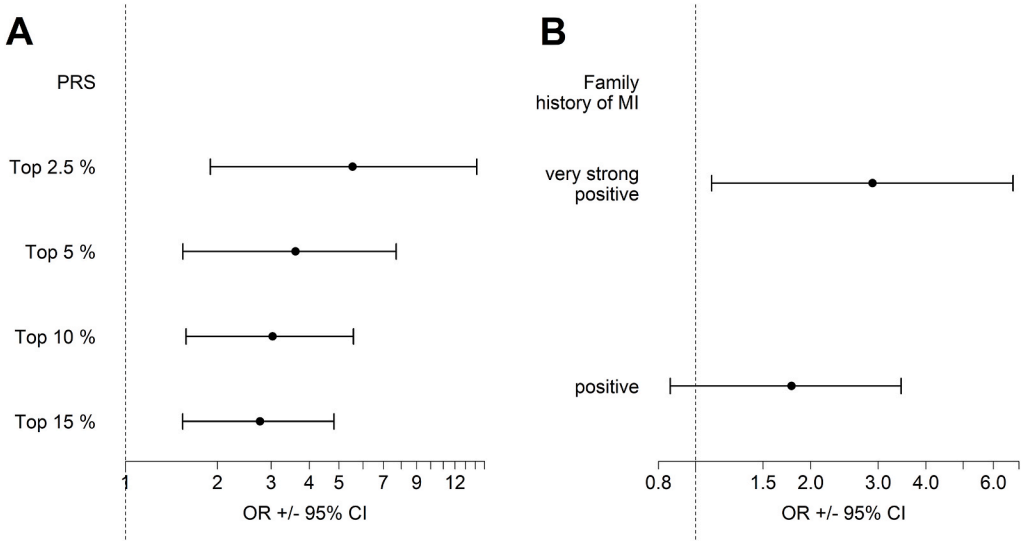

Fig. 3. Illustration of odds ratios (ORs) ± 95% confidence intervals (CI) of distinct categories of PGS and FamRS. (A) Risk for a prevalent MI according to certain top percentages of PGS against the remainder of the population (OR = 1 in each model). ORs and 95% CI were calculated by a logistic regression model adjusted for the Framingham risk predictors [10]. (B) Risk for a prevalent MI according to the family history of MI. Positive family history is defined as 0.5<FamRS≤2 and very strong positive as FamRS>2. ORs and 95% CI were calculated by a logistic regression model with those individuals with FamRS≤0.5 being the reference group. The model has been adjusted for the Framingham risk predictors [10].

Table 1
Results of Logistic regression analysis of the effect of PGS and FamRS on prevalent MI. Odds ratios are given per 1 standard deviation increase in PGS and FamRS.

	PGS only				FamRS only				Combined analysis						
										PGS			FamRS		
	n	OR	CI (95%)	*p*-value	n	OR	CI (95%)	*p*-value	n	OR	CI (95%)	*p*-value	OR	CI (95%)	*p*-value
M1	2904	1.676	[1.322–2.134]	**$2.33x10^{-5}$**	2886	1.290	[1.111–1.468]	**$2.75x10^{-4}$**	2886	1.649	[1.292–2.113]	**$6.61x10^{-5}$**	1.232	[1.059–1.405]	**$3.30x10^{-3}$**
M2	2543	1.792	[1.332–2.427]	**$1.35x10^{-4}$**	2528	1.284	[1.080–1.491]	**$1.95x10^{-3}$**	2528	1.720	[1.272–2.341]	**$4.84x10^{-4}$**	1.230	[1.032–1.434]	**0.012**
M3	2890	1.662	[1.280–2.170]	**$1.58x10^{-4}$**	2873	1.294	[1.094–1.501]	**$1.25x10^{-3}$**	2873	1.616	[1.243–2.115]	**$3.96x10^{-4}$**	1.261	[1.065–1.465]	**$4.04x10^{-3}$**

Bold font: significant *p*-value ($p < 0.05$).
Model M1: adjusted for Age + Sex.
Model M2: adjusted for Age + Sex + Hypertension + BMI + Healthy diet score + Alcohol consumption + Smoking + Physical activity (active/inactive).
Model M3: adjusted for the Framingham risk predictors [10]: Age + Sex + Smoking + HDL-Cholesterol + Total cholesterol + systolic blood pressure + Antihypertensive treatment.

Table 2
Results of the Cox regression analysis of the effect of PGS and FamRS on incident MI. Hazards ratios are given per 1 standard deviation increase in PGS and FamRS.

	PGS only				FamRS only				Combined analysis						
										PGS			FamRS		
	n	HR	CI (95%)	*p*-value	n	HR	CI (95%)	*p*-value	n	HR	CI (95%)	*p*-value	HR	CI (95%)	*p*-value
M1	2789	1.175	[0.971–1.423]	0.097	2773	1.173	[1.043–1.319]	**7.95×10^{-3}**	2773	1.155	[0.953–1.401]	0.143	1.155	[1.026–1.300]	**0.017**
M2	2484	1.222	[0.964–1.547]	0.097	2470	1.214	[1.059–1.390]	**5.31×10^{-3}**	2470	1.193	[0.941–1.513]	0.145	1.195	[1.043–1.369]	**0.010**
M3	2779	1.172	[0.966–1.423]	0.107	2763	1.158	[1.030–1.303]	**0.014**	2763	1.153	[0.948–1.401]	0.154	1.142	[1.014–1.285]	**0.028**

Bold font: significant *p*-value ($p < 0.05$).
Model M1: adjusted for Age + Sex.
Model M2: adjusted for Age + Sex + Hypertension + BMI + Healthy diet score + Alcohol consumption + Smoking + Physical activity (active/inactive).
Model M3: adjusted for the Framingham risk predictors [10]: Age + Sex + Smoking + HDL-Cholesterol + Total cholesterol + systolic blood pressure + Antihypertensive treatment.

enhances the prediction for both prevalent cases ($NRI_{events} = 0.211$) and non-cases ($NRI_{non\text{-}events} = 0.261$), which leads to an overall NRI of 0.472 ($p = 3.28 \times 10^{-5}$) and IDI of 0.024 ($p = 5.30 \times 10^{-3}$).

For incident cases, only FamRS was investigated, as PGS showed no significant association. FamRS could once more only make a positive contribution to the prediction of non-events ($NRI_{non\text{-}events} = 0.69$, $NRI_{events} = -0.46$, $NRI = 0.23$, $p = 5.77 \times 10^{-3}$; $IDI = 0.004$, $p = 0.12$).

4. Discussion

The PGS was shown to be significantly associated with MI prevalence in the KORA F3 population, independently of either lifestyle factors or Framingham risk predictors. A consistent right shift in MI risk for increasing values of PGS was found, revealing a risk gradient for MI along the top percentages of PGS with considerably increasing ORs. Moreover, addition of PGS yielded a significantly better NRI in comparison to a baseline model including the traditional risk factors. The results of the present investigation are in line with other research concerning the association between PGS and CAD [7,22]. For example, Khera and colleagues [7] showed an increasing risk for CAD along percentiles of PGS, especially in the right tail of the distribution, and they reported a several-fold increased risk for CAD for the top percentages of PGS. This is comparable to the magnitude of elevated risk for MI according to PGS, which was found in the present study. These findings strengthen the hope that a PGS – a risk estimate available from birth – could help identify individuals at considerably higher risk for MI early enough in terms of risk stratification to initiate preventive measures before they are affected by CAD [7,23,24].

In contrast, PGS was not associated with risk of incident MI. The poorer performance for incident cases in comparison to prevalent cases seems peculiar, but this finding has also been reported from comparable cohort studies [22,25], which reported weaker associations and risk predictions of the PGS regarding the incident or recurrent CAD cases.

The non-finding in our study might also be a power issue. We only have a power of 0.3–0.5 – depending on the assumptions - to detect a small risk increase such as a HR of 1.2. More promising results on a polygenic score as a predictor for incident cases and lifetime risk for CAD were found in cohort studies with much higher sample sizes [26,27].

Furthermore, the age difference between the prevalent and incident cases could play a role for this differential effect. The incident cases were on average more than 15 years older than the prevalent cases when experiencing their first MI event. This finding is of note, because it can be assumed that the risk-increasing effect of genetic variation, which is a risk exposure from birth, is particularly important for early MI cases, whereas the risk exposure from other risk factors, like cigarette smoking, usually starts much later in life. This hypothesis is supported by an investigation of Tada et al. [28], who reported that genetic risk for CHD could be particularly relevant for the CHD risk assessment among young individuals. Considering that both genes and lifestyle habits can contribute to the development of CAD [4], it can be speculated that the pathogenesis of a major proportion of the incident cases in this study is substantially influenced by lifestyle factors. Consequently, the overall relevance of the PGS for MI risk is veiled in this context.

Another topic of this investigation was the association of family history with MI. It has been reported previously that family history is an independent and meaningful risk factor for MI [4,29,30]. A family risk score, as recommended by Williams et al. [8], was used to describe the family history for MI, since it has been shown that such a score has advantages in comparison to common risk description variables for family history [8,9]. Nonetheless, the FamRS is not broadly used in clinical practice or in epidemiological research, because its calculation is rather complicated and obtaining the additional information is time-consuming. A more common approach is the simple yes/no discrimination if at least one parent was ever affected by a MI or counting the number of affected family members. All three family history variables were significantly associated with prevalent MI cases. However, FamRS was found to be the most appropriate variable for evaluating the family history of MI in this study, because it exhibited a consistently good performance for both prevalent and incident cases. Thus, FamRS should be considered to be included into clinical practice and epidemiological research more often. In accordance with these findings, there is increasing evidence that a more elaborate definition of

family history yields a higher benefit for the risk assessment of MI [31–33]. For example, Ranthe and colleagues [31], who followed a cohort of >4 m individuals, reported that a detailed family history significantly enhances MI risk estimation.

FamRS was positively and significantly associated with prevalent MI cases, independent of lifestyle and classical risk factors, and additionally improved net reclassification. Individuals with a very strong positive family history (FamRS>2), which means having two or more events in a family at an early age were shown to have an almost three times higher chance for MI than those with average family risk. For this target group, lifestyle adaptations and continuous monitoring should be encouraged, and more severe treatment regimens should be considered by healthcare providers.

It should be noted that in this context a recall bias cannot be excluded, since a better recall of parents' and siblings' disease status might be assumed for diseased participants [34]. For family history of MI or CAD, there is hardly evidence for such a bias, though. Studies comparing reported disease status of parents with validated records showed no difference in accuracy between cases and controls [35,36]. Only slight differences in recall rate between cases and controls with evident recall bias was found for siblings' histories of myocardial infarction [36]. Therefore, the impact of potential recall bias should be marginal, if at all.

On the other hand, first grade relatives' CAD or MI events were shown to be reported correctly in only 54–85% [35–38], which could rather lead to underestimation of the effect of family history."

This recall bias cannot play a role for incident cases, though, for which FamRS was also shown to be significantly associated and exhibited a similar increment in NRI. Individuals with at least a positive family history, which corresponds to one event at any age in families of small or average size or one early event in large families, have more than two times higher risk for incident events compared to someone with average family history.

Another key issue of this investigation is the relationship between PGS and FamRS. It has been found that PGS and FamRS correlate positively, but rather minimally with each other. The PGS cannot explain the variability of FamRS and the other way round as the adjusted R-squared of the linear regression model only amounts to 0.005.

Consequently, a logistic regression analysis including both PGS and FamRS simultaneously emphasizes that these two risk scores for MI are independently associated with MI prevalence. This finding is in line with an earlier investigation carried out by Tada et al. [28], who showed that two genetic risk scores are independent from self-reported family history and that both genetic assessment and family history data can improve risk estimation for CHD simultaneously [28].

Thus, it can be hypothesized that FamRS primarily contains information for the estimation of MI risk, which does not involve the shared genetic risk in a family. It can be argued that environmental and lifestyle conditions are rather similar within a family and that these factors contribute substantially to the risk estimation of FamRS, but do not influence the PGS. However, model 2, which focuses on the environmental/lifestyle factors, which are relevant for MI (e.g. smoking, diet, physical activity), did not attenuate the impact of FamRS or the other family history variables for both prevalent and incident cases. Therefore, the precise risk factors underlying the effect of FamRS are still elusive.

4.1. Conclusion

In a nutshell, both PGS and FamRS were found to be independent risk scores for the assessment of MI risk in addition to traditional risk factors, but with meaningful differences:

PGS was a strong risk estimator for the "early" prevalent MI cases. On the other hand, FamRS was highly informative for both MI prevalence and incidence but did not exhibit such a pronounced risk-increasing effect as compared to PGS concerning the prevalent cases. Consequently, it can be recommended that both PGS and FamRS or another appropriate variable for family history of MI should be considered to be implemented simultaneously into future research and guidelines for the assessment of MI risk.

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CRediT authorship contribution statement

Florian Schnitzer: performed data analysis and wrote the manuscript. **Lukas Forer:** and. **Sebastian Schönherr:** managed genotyping data and calculated the polygenic risk score. **Christian Gieger:** and. **Harald Grallert:** oversaw conduction of the KORA-F3 study. **Florian Kronenberg:** mainly contributed to the calculation and validation of the Family risk score and provided, input to all parts of the project and manuscript. **Annette Peters:** is the main contributor of the KORA-F3 study, oversaw the project and provided critical review of the manuscript. **Claudia Lamina:** designed and oversaw the project, performed data analysis, and reviewed the manuscript. All authors have read and approved the manuscript.

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.2022.05.014.

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