Supplemental Material to

Association between a Polygenic and Family Risk Score on the prevalence and incidence of Myocardial infarction in the KORAF3 study

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Supplemental Methods

Definition and Calculation of the FamRS

The FamRS was calculated with an algorithm based on the information of a standardized interview. For each first-grade relative disease status regarding myocardial infarction (MI) was requested. During the interview, all participants were asked if their father/mother/brother/sister ever experienced a MI and if the MI occurred before or after an age of 60 years.

To account for the age of onset, the following weights were included into the formula:

- Weight = 2 if age < 60
- Weight = 1 if age ≥ 60
- Weight = 1.5 if age of first disease onset is not known

The observed values (O) for each participant were calculated by taking the sum of the weights for all first-grade relatives. The expected values (E) were derived from the mean values of the weights for father, mother, brothers, and sisters for each 10-year age group, respectively. These mean values were appropriate reference values because KORA F3 is a population-based study. Therefore, the number of diseased versus healthy controls and the respective family histories behind these individuals should be representative for the whole population.

The FamRS was then calculated as suggested by Williams and colleagues[1]:

If $|O - E| > 0.5$ then,

$$\text{FamRS} = \frac{|O - E| - 0.5}{\sqrt{E}} \times \frac{|O - E|}{O - E}$$

or if $|O - E| \leq 0.5$, then FamRS = 0. And if FamRS is ≥ 1.0 with only one affected person in the family, FamRS is set to 0.99.

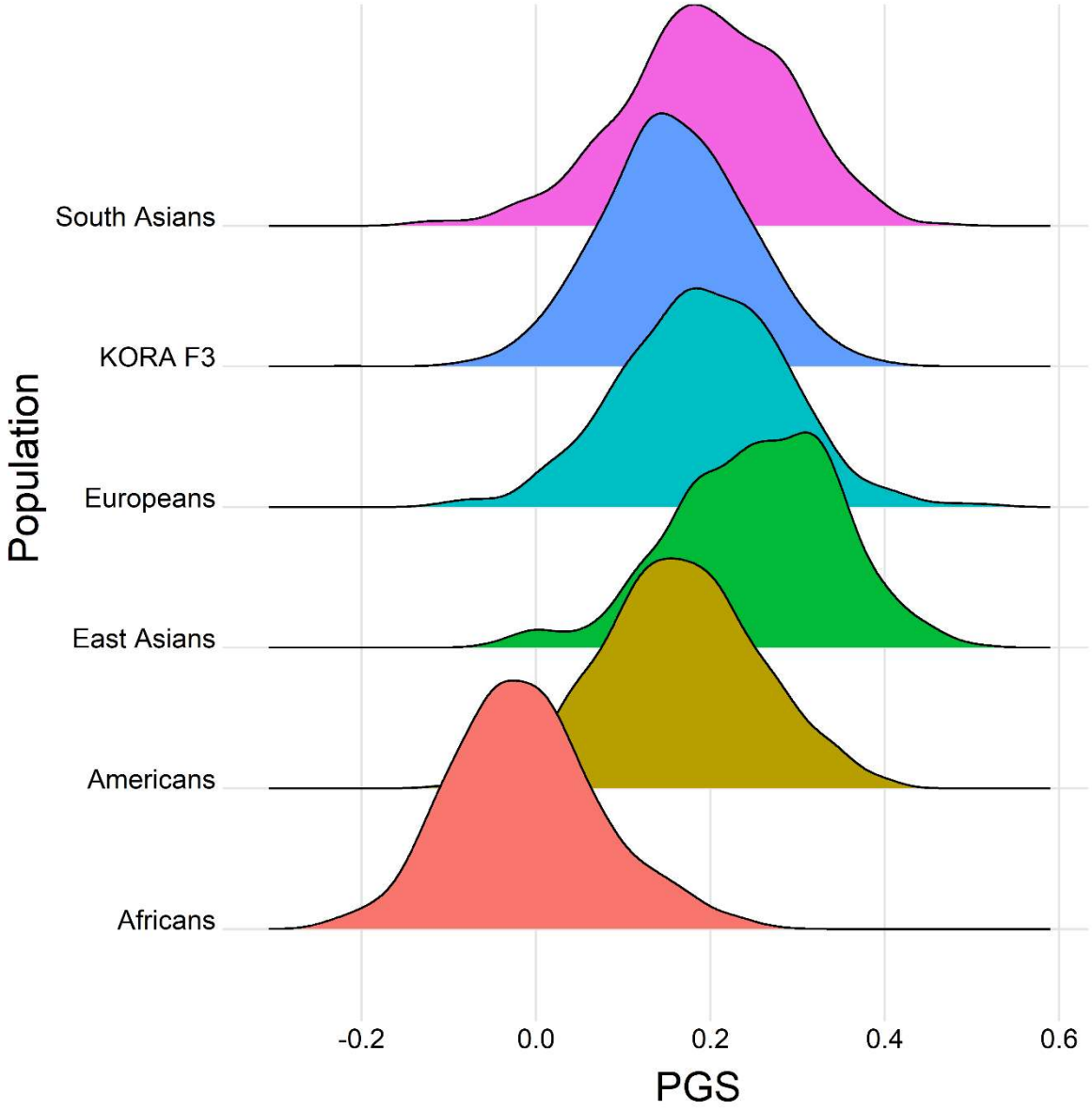
The calculated FamRS is a continuous variable and can be used as such for analytical purposes. But for better illustration and interpretation a categorization of the FamRS, as recommended by Williams et al. [8] has been performed, as follows: protective (FamRS < −0.5), average (−0.5 to +0.5), positive (> +0.5 to +1.0), strong positive (> +1.0 to +2.0), and very strong positive family history (> +2.0). These categories can be interpreted like this: Protective refers to no events in a big family; average refers to no events in an average or small sized family or one event at an higher age in a large family; positive refers to one event at any age in families of

small or average size or one early event in large families; strong positive refers to one early or two events at any age; and very strong positive refers to two or more events at an early age.[1]

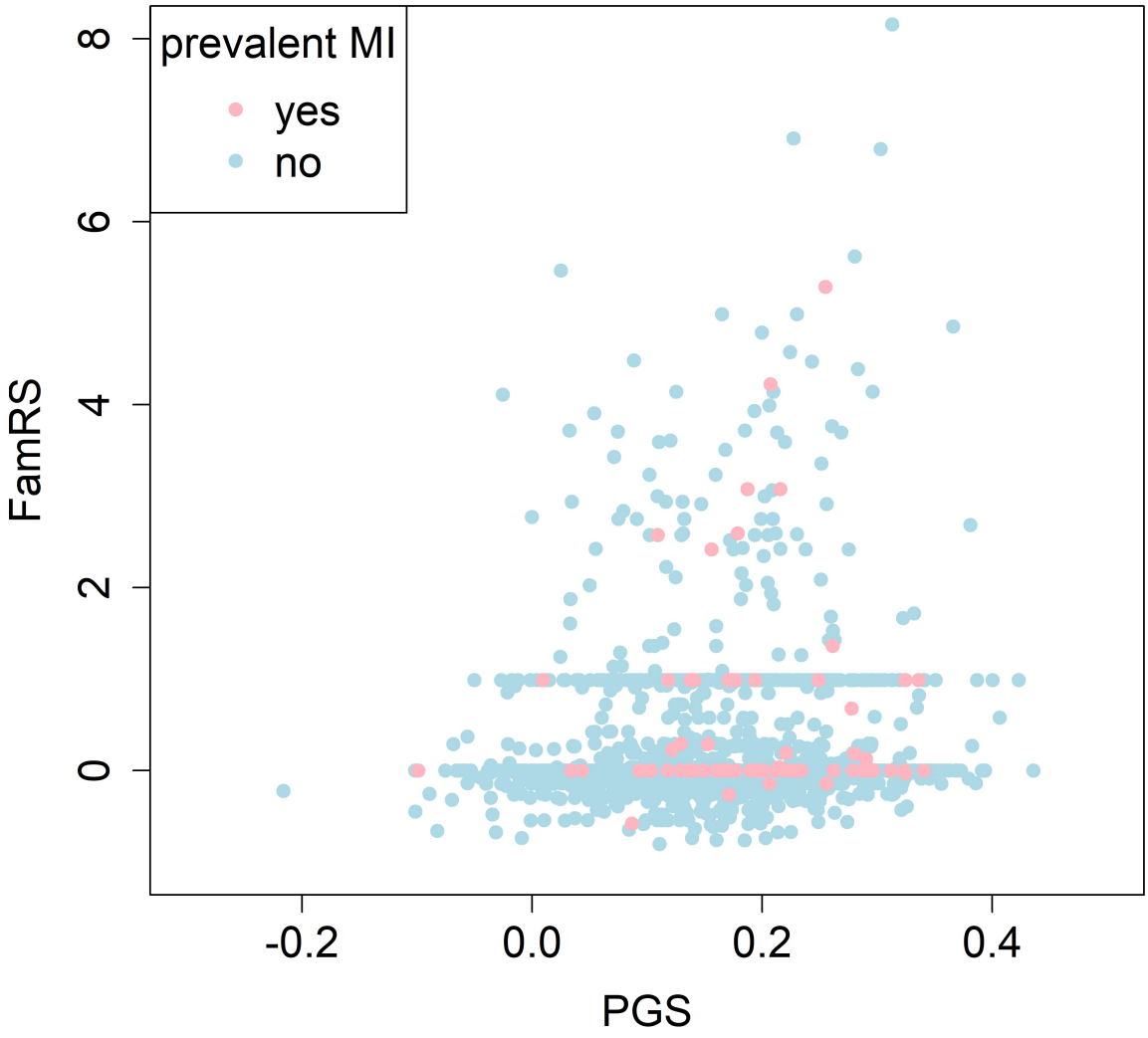
Because of the small number of study participants with a protective (n = 37) and strong positive (n = 27) family history, it has been decided that the protective cases were added to the average and the strong positive cases to the positive family history category. Therefore, in this study average family history refers to a FamRS≤0.5 and positive family history to 0.5< FamRS≤2.

Another categorization used was the definition of a "general positive family history" by FamRS, which is true if FHS>0.5, thereby including the positive, strong positive and very strong positive cases. This roughly translates into one or more events at any age in small and average sized families or at least one early event in a big family or alternatively, two or more events at any age in a big family.

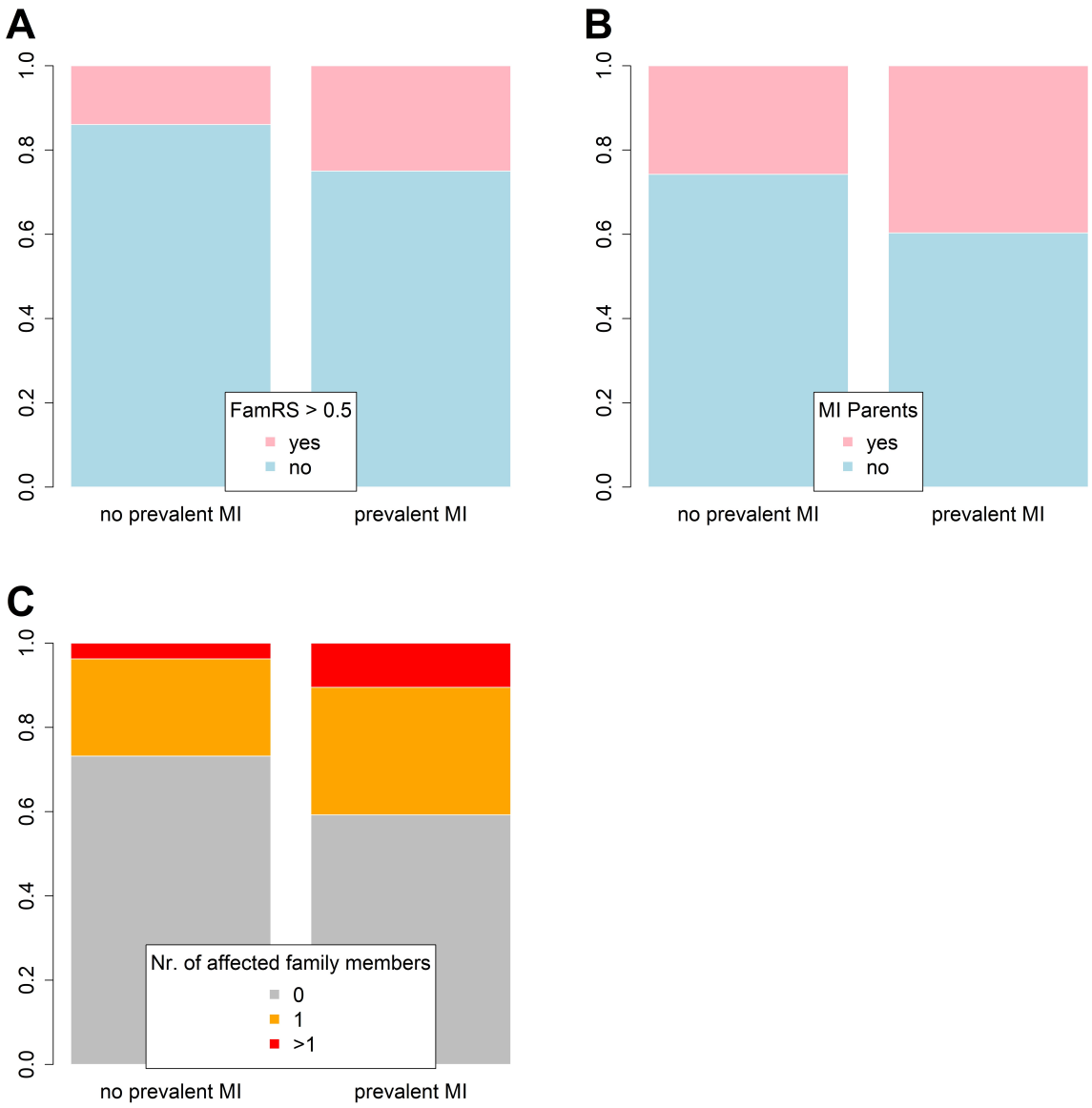
Supplemental Figures



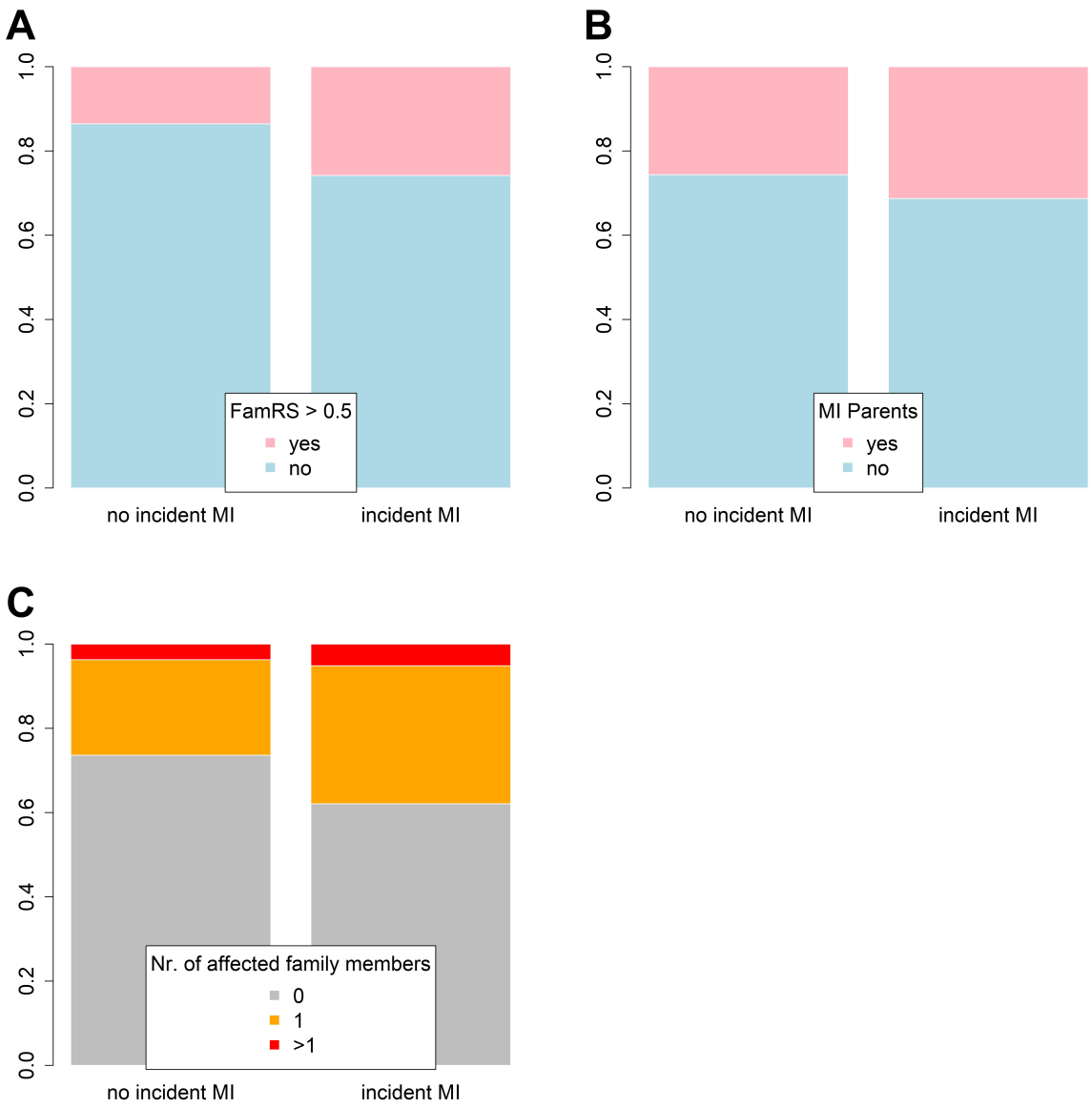
Supplemental Figure 1: Comparison of the distribution of a PGS for CAD among different populations. The applied risk score was PGS000013 from the Polygenic Score Catalog.[2] The samples for all populations except KORA F3 were derived from the 1000 genomes project.[3]



Supplemental Figure 2: Correlation plot for a polygenic score for CAD and a family risk score for MI. The light pink dots stand for study participants, who already had a MI before the beginning of the study, whereas the light blue dots represent study participants, who did not have a MI before the study.



Supplemental Figure 3: Comparison between different variables describing family history for MI stratified by the prevalence of MI. (A) Percentage of study participants with (light pink) or without (light blue) a general positive family history (FamRS > 0.5) for MI stratified by the prevalence of MI among these individuals. **(B)** Comparison between study participants with and without a prevalent MI regarding the information if their parents had a MI (light pink) or not (light blue), respectively. **(C)** Percentage of study participants with the specified number of family members affected by MI stratified by the prevalence of MI among these individuals.



Supplemental Figure 4: Comparison between different variables describing family history for MI stratified by the incidence of MI. (A) Percentage of study participants with (light pink) or without (light blue) a general positive family history (FamRS > 0.5) for MI stratified by the incidence of MI among these individuals. **(B)** Comparison between study participants with and without an incident MI regarding the information if their parents had a MI (light pink) or not (light blue), respectively. **(C)** Percentage of study participants with the specified number of family members affected by MI stratified by the incidence of MI among these individuals.

Supplementary Tables

Supplemental Table 1: Baseline characteristics of the KORA F3 study, for all participants and separated by gender. Continuous variables are shown as mean ± SD and [25 %, 50 %, 75 %] percentiles.

Variable	All participants: 3,071	women: 1,575 (51.3 %)	men: 1,496 (48.7%)
Age[a] (in years)	57.4 ± 12.9 [46.0, 57.0, 67.0]	57.1 ± 12.7 [47.0, 57.0, 67.0]	57.7 ± 13.1 [46.0, 58.0, 68.0]
Prevalent MI [a], n (%)	78 (2.7 %)	25 (1.7 %)	53 (3.7 %)
Incident MI[b], n (%)	116 (4.2 %)	41 (2.8 %)	75 (5.6 %)
Smoking Current smoker, n (%) Ex-smoker, n (%) Never-smoker, n (%)	 542 (18.7 %) 1,078 (37.1 %) 1,283 (44.2 %)	 259 (17.5 %) 410 (27.6 %) 814 (54.9 %)	 283 (20.0 %) 668 (47.0 %) 469 (33.0 %)
Alcohol consumption [g/day]	15.5 ± 19.6 [0.0, 6.6, 22.9]	8.0 ± 11.9 [0.0, 2.9, 13.6]	23.3 ± 22.8 [4.1, 20.0, 37.1]
Total cholesterol [mg/dl]	218 ± 40 [191, 216, 243]	220 ± 40 [193, 218, 245]	216 ± 40 [189, 215, 241]
HDL cholesterol [mg/dl]	58.8 ± 17.1 [46.0, 56.0, 69.0]	65.1 ± 16.9 [53.0, 63.0, 75.0]	52.1 ± 14.7 [42.0, 50.0, 60.0]
LDL cholesterol [mg/dl]	128 ± 32.6 [105, 127, 148]	127 ± 34 [103, 125, 147]	129 ± 31 [107, 128, 149]
Triglycerides [mg/dl]	165 ± 126 [88, 136, 201]	137 ± 83 [79, 117, 176]	194 ± 154 [104, 157, 236]
Lipid-lowering-agent, n (%)	333 (10.9 %)	156 (9.9 %)	177 (11.8 %)
BMI [kg/m^2]	27.7 ± 4.6 [24.4, 27.1, 30.3]	27.3 ± 5.2 [23.5, 26.6, 30.5]	28.0 ± 3.9 [25.3, 27.6, 30.1]
Healthy diet score favourable (≥ 16 HDS) normal (14 – 15 HDS) unfavourable (≤ 13 HDS)	 1,513 (55.7 %) 464 (17.1 %) 737 (27.2 %)	 930 (66.0 %) 215 (15.3 %) 264 (18.7 %)	 583 (44.7 %) 249 (19.1 %) 473 (36.2 %)
Physical activity active (≥ 1h/week), n (%) inactive, n (%)	 1,589 (51.7 %) 1,482 (48.3 %)	 806 (51.2 %) 769 (48.8 %)	 783 (52.3 %) 713 (47.7 %)
Hypertension, n (%)	1,535 (50.1 %)	712 (45.4 %)	823 (55.1 %)
Systolic blood pressure [mmHg]	131 ± 20.0 [117, 129, 143]	127 ± 20 [112, 124, 140]	135 ± 19 [123, 133, 146]
Diastolic blood pressure [mmHg]	82 ± 11 [75, 81, 89]	80 ± 10 [73, 79, 86]	84 ± 11 [77, 84, 91]
Antihypertensive, n (%)	965 (31.5 %)	497 (31.6 %)	468 (31.3 %)
PGS	0.16 ± 0.08 [0.10, 0.16, 0.21]	0.16 ± 0.08 [0.10, 0.16, 0.21]	0.16 ± 0.08 [0.10, 0.16, 0.21]
FamRS	0.18 ± 0.68 [0.00, 0.00, 0.00]	0.21 ± 0.72 [0.00, 0.00, 0.00]	0.16 ± 0.65 [0.00, 0.00, 0.00]

n: Sample size of analysis dataset.

[a] at the beginning of the KORA F3 study.

[b] during participation of the KORA F3 study.

Supplemental Table 2: Comparison of baseline characteristics by MI prevalence. Continuous variables are shown as mean ± standard deviation and [25%, 50%, 75%] percentiles.

Variable	prevalent MI (n = 78)	no prevalent MI (n = 2,826)	p-value
Age[a] (in years)	67.7 ± 9.8 [62.0, 69.5, 75.0]	57.2 ± 12.9 [46.0, 57.0, 67.0]	**1.29×10^{-12}** [b]
Sex women, n (%) men, n (%)	 25 (32.1 %) 53 (67.9 %)	 1459 (51.6 %) 1367 (48.4 %)	**9.77×10^{-4}**
Smoking Current smoker, n (%) Ex-smoker, n (%) Never-smoker, n (%)	 10 (13.0 %) 50 (65.0 %) 17 (22.0 %)	 532 (18.8 %) 1028 (36.4 %) 1266 (44.8 %)	**1.69×10^{-6}**
Alcohol consumption [g/day]	14.7 ± 19.4 [0.0, 6.6, 22.9]	15.4 ± 19.6 [0.0, 6.6, 22.9]	0.541 [#]
Total cholesterol [mg/dl]	191 ± 41 [164, 191, 214]	219 ± 40 [192, 217, 243]	**3.39×10^{-9}** [b]
HDL cholesterol [mg/dl]	48.6 ± 15.0 [37.2, 47.0, 60.0]	58.9 ± 17.1 [47.0, 56.0, 69.0]	**1.52×10^{-7}** [b]
LDL cholesterol [mg/dl]	111 ± 31 [91, 105, 127]	129 ± 33 [106, 127, 149]	**3.31×10^{-6}**
Triglycerides [mg/dl]	172 ± 96 [114, 154, 199]	166 ± 128 [88, 135, 201]	0.078 [#]
Lipid-lowering-agent, n (%)	47 (60.3 %)	272 (9.6 %)	**$< 2.2 \times 10^{-16}$**
BMI [kg/m^2]	29.4 ± 4.9 [25.9, 30.0, 32.1]	27.6 ± 4.6 [24.4, 27.1, 30.2]	**0.001** [#]
Healthy diet score favourable (≥ 16 HDS) normal (14 – 15 HDS) unfavourable (≤ 13 HDS)	 39 (68.4 %) 9 (15.8 %) 9 (15.8 %)	 1,383 (55.2 %) 431 (17.2 %) 691 (27.6 %)	0.098
Physical activity active (≥ 1h/week), n (%) inactive, n (%)	 31 (39.7 %) 47 (60.3 %)	 1,473 (52.1 %) 1,353 (47.9 %)	**0.04**
Hypertension, n (%)	56 (71.8 %)	1390 (49.3 %)	**1.46×10^{-4}**
Systolic blood pressure [mmHg]	129 ± 22 [115, 130, 143]	131 ± 20 [117, 129, 143]	0.635 [#]
Diastolic blood pressure [mmHg]	77 ± 11 [68, 78, 84]	82 ± 11 [75, 81, 89]	**2.46×10^{-4}** [b]
Antihypertensive, n (%)	68 (87.2 %)	850 (30.1 %)	**$< 2.2 \times 10^{-16}$**
PGS	0.19 ± 0.08 [0.14, 0.19, 0.25]	0.16 ± 0.08 [0.10, 0.15, 0.21]	**1.65×10^{-4}**
FamRS	0.47 ± 1.03 [0.00, 0.00, 0.39]	0.17 ± 0.66 [0.00, 0.00, 0.00]	**4.02×10^{-5}** [b]

Bold font: Significant p-value (<0.05).
Chi-square test was used for categorical variables, t-test or Wilcoxon test (indicated with [b]) for continuous variables.
n: Sample size.
[a] at study start.

Supplemental Table 3: Logistic regression of the effect of FamRS > 0.5, at least one parent with MI and Number of affected family members on prevalent MI.

	FamRS > 0.5			**MI Parents**			**Nr. of affected family members**		
	OR	CI (95 %)	p-value	OR	CI (95 %)	p-value	OR	CI (95 %)	p-value
Model 1	2.224	[1.263 – 3.762]	**3.88×10^{-3}**	2.355	[1.374 – 3.981]	**1.51×10^{-3}**	1.627	[1.181 – 2.171]	**1.60×10^{-3}**
Model 2	2.346	[1.229 – 4.297]	**7.20×10^{-3}**	2.651	[1.428 – 4.914]	**1.88×10^{-3}**	1.731	[1.217 – 2.388]	**1.26×10^{-3}**
Model 3	2.082	[1.144 – 3.655]	**0.013**	2.099	[1.191 – 3.652]	**9.18×10^{-3}**	1.604	[1.136 – 2.210]	**5.18×10^{-3}**

Bold font: Significant p-value ($p < 0.05$).
Model 1: adjusted for Age + Sex.
Model 2: adjusted for Age + Sex + Hypertension + BMI + Healthy diet score + Alcohol consumption + Smoking + Physical activity (active/inactive).
Model 3: adjusted for the Framingham risk predictors[4]: Age + Sex + Smoking + HDL-Cholesterol + Total cholesterol + systolic blood pressure + Antihypertensive treatment.

Supplemental Table 4: Cox regression of the effect of FamRS > 0.5, at least one parent with MI and Number of affected family members on prevalent MI

	FamRS > 0.5			**MI Parents**			**Nr. of affected family members**		
	HR*	CI (95 %)	p-value	HR†	CI (95 %)	p-value	HR‡	CI (95 %)	p-value
Model 1	2.268	[1.494 – 3.443]	**1.20×10^{-4}**	1.644	[1.069 – 2.526]	**0.023**	1.407	[1.101 – 1.798]	**6.32×10^{-3}**
Model 2	2.687	[1.628 – 4.436]	**1.11×10^{-4}**	1.971	[1.185 – 3.277]	**8.90×10^{-3}**	1.572	[1.191 – 2.074]	**1.40×10^{-3}**
Model 3	2.268	[1.493 – 3.447]	**1.25×10^{-4}**	1.527	[0.987 – 2.361]	0.057	1.371	[1.072 – 1.754]	**0.012**

Bold font: Significant p-value ($p < 0.05$).
Model 1: adjusted for Age + Sex.
Model 2: adjusted for Age + Sex + Hypertension + BMI + Healthy diet score + Alcohol consumption + Smoking + Physical activity (active/inactive).
Model 3: adjusted for the Framingham risk predictors[4]: Age + Sex + Smoking + HDL-Cholesterol + Total cholesterol + systolic blood pressure + Antihypertensive treatment.

Supplemental References

1. Williams RR, Hunt SC, Heiss G, et al. Usefulness of cardiovascular family history data for population-based preventive medicine and medical research (the Health Family Tree Study and the NHLBI Family Heart Study). *Am J Cardiol*. 2001;87(2):129-135.
2. Lambert SA, Gil L, Jupp S, et al. The Polygenic Score Catalog as an open database for reproducibility and systematic evaluation. *Nat Genet*. 2021;53(4):420-425.
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4. National Heart, Lung, and Blood Institute. Risk predictors for Hard Coronary heart disease (10-year risk) according to the Framingham heart study. https://framinghamheartstudy.org/fhs-risk-functions/hard-coronary-heart-disease-10-year-risk/. Accessed May 8, 2021.