Association between Family History and Coronary Heart Disease

Death across Long-Term Follow-Up in Men:

The Cooper Center Longitudinal Study

Running title: Bachmann et al.; Family history and coronary heart disease

Justin M. Bachmann, MD1; Benjamin L. Willis, MD, MPH2; Colby R. Ayers, MS3;

Amit Khera, MD, MSc1; Jarett D. Berry, MD, MS1

1Division of Cardiology, Dept of Internal Medicine, 3Reynolds Cardiovascular Clinical Research Center, University of Texas Southwestern Medical Center; 2Cooper Institute, Dallas, TX;

Correspondence:
Jarett D. Berry, MD, MS
University of Texas Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, TX 75390-9047
Tel:  214-645-7541
Fax:  214-645-7501
E-mail:  jarett.berry@utsouthwestern.edu

Journal Subject Codes:  [8] Epidemiology; [89] Genetics of cardiovascular disease; [135] Risk factors
Abstract:

Background - Family history of coronary heart disease (CHD) has been well studied as an independent risk factor for CHD events in the short-term (<10 years). However, data are sparse on the association between family history and risk for CHD across long-term follow-up.

Methods and Results - We included 49,255 men from the Cooper Center Longitudinal Study. Premature family history (pre-FHx) of CHD was defined as the presence of angina, myocardial infarction, angioplasty or bypass surgery in a relative age <50 years. Cause-specific mortality was obtained from the National Death Index. The association between pre-FHx and cardiovascular disease (CVD) or CHD death was compared across three unique follow-up periods (0 to 10, >10 to 20, and >20 years). Lifetime risk was estimated using a modified survival analytic technique adjusted for competing risk with non-CVD death as the competing event. After 811,708 person-years of follow-up, there were 919 CHD deaths and 1,456 CVD deaths. After adjustment for traditional risk factors, pre-FHx was associated with CHD mortality across 10-20 years [1.59 (1.14-2.22)] and > 20 years [1.43 (1.05-1.95)] with wider confidence intervals at 0-10 years [1.32 (0.76-2.31)]. Similar findings were observed for CVD mortality. Compared to men without a family history of CAD, pre-FHx was associated with approximately a 50% higher lifetime risk for both CHD and CVD mortality (13.7% vs. 8.9% and 21% vs. 14.1%, respectively).

Conclusions - Pre-FHx was associated with a persistent increase in both CHD and CVD mortality risk across long-term follow-up, resulting in significantly higher lifetime risk estimates.

Key words: cardiovascular disease risk factors; coronary heart disease; family history
Introduction

Family history of coronary heart disease (CHD) is a well-recognized risk factor, with multiple prospective studies demonstrating a consistent, independent association with CHD. While definitions vary, it is well established that the strength of the association between family history and CHD is greatest with earlier age of presentation of CHD in the family member (i.e. premature family history). Current prevention guidelines recommend that premature family history be incorporated into the risk estimation process that guides treatment decisions, and family history can be easily and systematically queried in the clinical setting. However, family history is included in some, but not all short-term risk prediction equations because of its relatively modest contribution to short-term risk.

Although risk in the short-term (i.e. 10 years) represents a well-established approach to guide treatment decisions, it may not completely reflect the burden of CHD risk across the lifespan. Specifically, a risk factor that promotes a small but consistent increase in CHD risk can translate into substantial differences in risk across the lifespan despite a more modest increase in short-term risk.

To our knowledge, the association between a family history of CHD and long-term risk for CHD has not been studied. Therefore, we sought to determine the association between the presence of a family history of CHD and both CHD and cardiovascular disease (CVD) mortality across short-term (0-10 years), intermediate-term (>10-20 years) and long-term (>20 years) follow-up. We also sought to determine the association between the presence of a family history of CHD and the lifetime risk for both CHD and CVD mortality.
Methods

Study sample and definitions

The Cooper Center Longitudinal Study (CCLS) is an ongoing, prospective study at the Cooper Clinic in Dallas, TX that began over 30 years prior to date.\textsuperscript{16-18} The Cooper Clinic is a preventive medical practice that focuses on periodic health examinations. Patients come from all 50 states and are referred by their employer, personal physician or self-referred. Less than 5\% of patients are non-white. For the present study we included all men between the ages of 20 and 90 who underwent a complete clinical examination and completed a family history questionnaire at the Cooper Center between 1970 and 2006 (n=49,956). After excluding 701 men with a prior myocardial infarction, we had a final study sample of 49,255. Women were excluded from the present study due to the small number of CHD endpoints in each decade of follow-up (6 CHD deaths at 0-10 years, 27 CHD deaths at >10-20 years, and 32 CHD deaths at >20 years), particularly when stratifying by family history status.

The CCLS undergoes annual review by the institutional review board of the Cooper Institute and the current study was approved by the institutional review board of University of Texas Southwestern Medical Center at Dallas.

Measurements

All participants underwent a comprehensive clinical examination including self-reported personal medical history and smoking habits, physical examination, and measurement of blood pressure, fasting blood glucose, and cholesterol. Details of anthropometric and laboratory measurements and other variable definitions have been described previously.\textsuperscript{17} Diabetes mellitus (DM) was defined by self-report or a fasting blood glucose >125 mg/dL. Smoking habits (current smoker or not) were obtained from a standardized questionnaire. Systolic and diastolic
blood pressures were measured in standard fashion with a sphygmomanometer.

**Definition of family history**

Participants completed a standardized questionnaire regarding their family history status. A positive family history was defined as the presence of angina, myocardial infarction, angioplasty or coronary artery bypass surgery in a sibling, aunt or uncle, parent or grandparent (excluding cousins, relatives by marriage, and half relatives). If a patient had a family member with a history of CHD, they were asked to indicate whether the event occurred prior to age 50 (pre-FHx) or thereafter (late-FHx); if not, they were defined as having no family history (no-FHx). The three categories of family history (no-FHx, pre-FHx and late-FHx) were mutually exclusive. No specific information was recorded in the questionnaire regarding the type of CHD event or family member.

**Outcome**

Participants were followed from the date of initial examination until death or end of follow-up on December 31, 2006 (range of follow-up period, 0.01 to 36 years) using data from the National Death Index. Coronary heart disease (CHD) mortality was defined as the primary cause of death indicated by International Classification of Diseases, Ninth Revision (ICD-9) codes 410-414 or equivalent codes from International Classification of Diseases, Eighth Revision or International Classification of Diseases, Tenth Revision. Cardiovascular disease (CVD) mortality was defined as ICD-9 codes 390.0 to 458.9 or their equivalents from ICD-8 or ICD-10.

**Statistical analysis**

The follow-up period was partitioned into 3 unique, mutually exclusive time periods: 0 to 10 inclusive, >10 to 20 inclusive, and >20 years. For example, a participant surviving for 25 years provided 10 years of follow-up for the first follow-up interval (0 to 10 years), 10 years of follow-
up for the second interval (>10 to 20 years), and 5 years of follow-up for the third interval (>20 years). Family history was characterized as a single categorical variable with three levels (no-FHx, pre-FHx and late-FHx) and a Cox proportional hazards model was constructed for each follow-up period, using no-FHx as the referent group. The model was multivariable and included age, systolic blood pressure, serum total cholesterol, body mass index, smoking and DM. Secondary analyses with further adjustment for fitness were also performed.

Finally, to estimate lifetime risk for CHD mortality, we applied a modified survival analytic technique that has been previously described. In this type of analysis, participants contributed information on CHD death and death free of CHD for each age attained during follow up. Since the Kaplan-Meier cumulative incidence does not reflect the competing risk for death from other causes prior to development of CHD, adjustment was made for this competing risk to yield a true remaining lifetime risk for CHD. Lifetime risk estimates were calculated separately for each family history category (no-FHx, pre-FHx and late-FHx) beginning at age 45 and 55 years. Similar analyses were performed to estimate the lifetime risk for CVD mortality. All statistical analyses were performed using SAS for Windows (release 9.2; SAS Institute, Inc., Cary, NC).

Results

Baseline characteristics

Among 49,255 men in the study sample, 7,832 (16%) had a late-FHx whereas 3,203 (6.5%) had a pre-FHx. Baseline characteristics of the study sample are shown in Table 1, demonstrating similar overall levels of traditional risk factors with and without a family history of CHD. After a median follow-up of 16 years, there were 919 CHD deaths and 1,456 CVD deaths across
811,708 person-years of follow-up, with a large number of person-years and events across all periods of follow-up (Table 2).

**Family history of CHD and risk at 0-10, >10-20 and >20 years follow-up**

The associations between late-FHx and CHD, CVD and all-cause death across short-term, intermediate-term, and long-term follow-up are shown in Table 3. The association between late-FHx and CHD mortality was strongest in the short-term (0-10 years) with no apparent association across intermediate and long-term follow-up. Findings were similar in both age adjusted and multivariable-adjusted models and for both CHD and all-cause mortality.

The associations between pre-FHx and CHD, CVD and all-cause death across short-term, intermediate-term, and long-term follow-up are also shown in Table 3. Pre-FHx was associated with both CVD and CHD mortality across intermediate-term (>10-20 years) and long-term (>20 years) follow-up in both age-adjusted and multivariable adjusted models, with a similar pattern of results in short-term follow-up but with wider confidence intervals. Secondary analyses with additional adjustment for cardiorespiratory fitness levels demonstrated similar results (data not shown). In addition, we stratified our analyses by high (>10% 10-year risk) and low (<10% 10-year risk) Framingham Risk Score (FRS) groups. The magnitude of the association between pre-FHx and CHD mortality at >20 years follow-up was similar in high (HR 1.45, CI 0.89-2.34) and low (HR 1.37, 0.91-2.06) FRS groups but with wider confidence intervals as expected.

**Family history and lifetime risk of CVD mortality**

For men at age 55 years, the presence of a pre-FHx was associated with a 6.9% higher lifetime risk for CVD mortality (Figure 1). For men at age 45 years, pre-FHx was associated with a 4.7% higher lifetime risk for CVD mortality (Figure 2). Similar findings were observed for men at both ages for lifetime risk for CHD mortality (Age 55: 13.7% with pre-FHx vs. 8.9% with no
family history; Age 45: 8.1% vs. 5.5%). In contrast, there was no apparent difference in the lifetime risk for either CHD or CVD mortality between the no-FHx and late-FHx groups (data not shown).

**Discussion**

In the present study, we observed several important findings. First, the association between pre-FHx and both CHD and CVD mortality relative to overall mortality was consistent across short-term (0-10 years), intermediate term (>10-20 years), and long-term (>20 years) follow-up. In contrast, the presence of late-FHx was associated with an increased risk in the short-term with no apparent association across later follow-up periods. In addition, the presence of pre-FHx was associated with an approximately 5% absolute and 50% relative difference in the lifetime risk for CVD and CHD mortality. These findings suggest that the presence of a pre-FHx of CHD represents a clinically significant increase in CHD and CVD risk across the lifespan.

Current prevention guidelines recommend the use of short-term risk estimation (i.e. 10 years) to guide treatment decisions (i.e. statin therapy)\(^5,20-25\) Although these risk prediction algorithms have some limitations, the ability to improve their performance through the addition of novel risk markers has had only limited success.\(^26\) In particular, the addition of premature family history to a traditional risk factor model was not associated with a significant improvement in risk classification.\(^4\)

In contrast, lifetime risk estimation has been proposed as a novel strategy to provide clinically meaningful improvements in risk prediction.\(^12,14,27\) Most US adults age 50 and under are at low short-term risk for CHD (i.e. less than 10%), however, more than one-half have a high lifetime risk.\(^12,28\) This discordance reflects the dominant effects of age in short-term risk
equations as well as the sustained contribution of modest risk factor levels on CHD risk across the remaining lifespan.\textsuperscript{13,29,30} Therefore, extending the time horizon for risk estimation beyond the 10-year window to include the remaining lifespan represents a novel approach to risk estimation that could have important clinical implications.

In the present study, we extend our prior work in long-term risk estimation to include family history, demonstrating that pre-FHx is associated with a 5\% absolute and 50\% relative difference in the lifetime risk for CVD mortality. Prior literature from the CCLS\textsuperscript{11} and from other datasets\textsuperscript{13,14} suggests that this increment represents a clinically significant difference in lifetime risk and is similar to the effect of a major risk factor. For example, we recently observed that the presence of a major risk factor was associated with a lifetime risk for CVD mortality of 23\% compared to a lifetime risk of just 17\% among participants without a major risk factor.\textsuperscript{11} Similarly, compared to participants without a family history, the presence of a pre-FHx was associated with an increased lifetime risk of CVD death (8.4 vs. 13.1\% at age 45). Thus, when making treatment decisions, clinicians could consider the contribution of a premature family history to the lifetime risk of CVD as similar to a major risk factor.

The discordance between the clinical impact on short-term and long-term risk is not unexpected. For example, nonsense mutations in PCSK9 resulting in a 15\% reduction in LDL cholesterol was associated with a 47\% reduction in the risk of CHD.\textsuperscript{15} Thus, the more typical 1:1 relationship between cholesterol and CHD risk in clinical trials was increased three-fold, consistent with the cumulative effects of lower LDL cholesterol across the lifespan. Similarly, sustained exposure to the genetic factors involved in a premature family history could be expected to result in a significant, cumulative CHD risk over the lifespan.

Although the association between family history and CHD risk in the short-term (i.e. 10
years or less) has been well-studied,\textsuperscript{1, 6, 31-40} relatively limited data are available on the association between family history and long-term risk. In one study from the Swedish Twin Registry, the heritability of CHD death was assessed across different follow-up periods.\textsuperscript{41} An additional 10 years of follow-up was associated with a small but statistically insignificant decrease in the heritability of CHD death (0.66 vs. 0.57 in men; 0.44 vs. 0.38 in women). These data are consistent with our observations that a premature family history was associated with CHD and CVD death across longer-term follow-up.

In contrast to the results for pre-FHx, the association between late-FHx and CHD mortality attenuated over time. This is consistent with prior studies\textsuperscript{4, 6} and likely reflects the heterogeneous nature of self-reported family history which influences CHD risk through both genetic and environmental mechanisms.\textsuperscript{33, 37, 42} While premature CHD events likely have a greater genetic component, late CHD events may reflect a greater contribution of environmental factors and behaviors that are less heritable. Thus, the risk associated with the likely stronger genetic component of pre-FHx appeared to persist with time in contrast to the attenuation in risk observed with late-FHx.

Several limitations to our study should be acknowledged. First, the definition of family history of CHD in our study was broad (including grandparents, aunts and uncles) and was acquired within the context of a clinical study. However, these effects would tend to attenuate the observed association between family history and CHD risk, and a more rigorous definition of family history would be expected to have an even larger effect size. In addition, family history of CHD was obtained through patient report and was not validated. However, in the National Heart, Lung and Blood Institute Family Heart Study and other cohorts self-report of a family history of premature CHD has a sensitivity above 80% and a specificity approaching 90%.\textsuperscript{43-45}
In the Newcastle Family History Study the net bias in recall of family history of CHD was towards the null.\textsuperscript{46} Therefore, at a minimum, we believe that our data represent conservative estimates on the association between family history and long-term risk.

Second, the prevalence of pre-FHx and late-FHx is lower than comparative studies\textsuperscript{4} and likely reflects multiple factors, including the age restrictions in our definition of family history. Data on family size and the specific age at which a family member’s CHD or CVD event occurred were not available in the CCLS database, preventing us from exploring more traditional age cutpoints. As a result we were not able to use gender-specific age restrictions with higher age thresholds in women. Although our definition of family history may have resulted in some misclassification, the large sample size and long-term follow-up provided adequate statistical power to assess the association between family history and long-term CHD risk.

Third, the CCLS is a unique cohort of predominantly white participants with a lower risk factor burden and higher socioeconomic status as compared with the general population. Although the prevalence of prior CHD and traditional risk factors is lower,\textsuperscript{47} the effect of these risk factors is quite similar. For example, we have recently shown that the presence of a major risk factor in middle-age in the CCLS is associated with a comparable lifetime risk for CVD in other cohorts within the Lifetime Risk Pooling Project, a pooled analysis of 18 cohorts.\textsuperscript{11,14} Moreover, we believe that the overall healthy nature of the cohort represents an important strength, illustrating the contribution of family history to an otherwise low-risk population. Finally, our analyses were restricted to men because of the overall low prevalence of family history and the small number of events in women across the different follow-up periods.

In summary, we observed a persistent association between pre-FHx and both CHD and CVD mortality across intermediate-term (>10-20 years) and long-term (>20 years) follow-up.
We also observed that pre-FHx was associated with a clinically significant increase in the lifetime risk for both CVD and CHD mortality. We believe these findings could be useful to clinicians, providing a broader context with which to consider the effects of a premature family history on the lifetime risk of CVD.

**Acknowledgments:** We thank Dr. Kenneth H. Cooper for establishing the Cooper Center Longitudinal Study, the Cooper Center staff for collecting clinical data, and the Cooper Institute for maintaining the database.

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**Conflict of Interest Disclosures:** Dr. Berry is a member of the Speaker’s Bureau for Merck & Co. (significant). All other authors report no conflicts of interest.

**References:**


Table 1: Participant characteristics in the Cooper Center Longitudinal Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Family History</th>
<th>Late-onset Family History</th>
<th>Premature Family History</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=38,220</td>
<td>n=7,832</td>
<td>n=3,203</td>
</tr>
<tr>
<td>Baseline Age, years</td>
<td>45.1 (9.8)</td>
<td>43.2 (9.6)</td>
<td>40.5 (8.7)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>122.8 (13.7)</td>
<td>120.4 (13.5)</td>
<td>121.0 (13.2)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>82.1 (9.7)</td>
<td>80.3 (9.5)</td>
<td>80.7 (9.4)</td>
</tr>
<tr>
<td>Total Cholesterol, mg/dL</td>
<td>206.6 (40.2)</td>
<td>212.5 (40.1)</td>
<td>214.3 (40.4)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>139.2 (120.3)</td>
<td>139.2 (112.9)</td>
<td>145.1 (107.2)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.0 (4)</td>
<td>26.1 (3.5)</td>
<td>26.1 (3.6)</td>
</tr>
<tr>
<td>Diabetes, n, (%)</td>
<td>1740 (4.6%)</td>
<td>320 (4.1%)</td>
<td>161 (5%)</td>
</tr>
<tr>
<td>Smoking, n, (%)</td>
<td>6361 (16.6%)</td>
<td>1623 (20.7%)</td>
<td>702 (21.9%)</td>
</tr>
<tr>
<td>CHD deaths, n</td>
<td>582</td>
<td>230</td>
<td>107</td>
</tr>
<tr>
<td>Age-adjusted rate, per 1000 person-years</td>
<td>1.0</td>
<td>1.3</td>
<td>1.9</td>
</tr>
<tr>
<td>CVD deaths, n</td>
<td>905</td>
<td>2657</td>
<td>387</td>
</tr>
<tr>
<td>Age-adjusted rate, per 1000 person-years</td>
<td>1.6</td>
<td>2.2</td>
<td>2.9</td>
</tr>
<tr>
<td>All-cause deaths, n</td>
<td>2657</td>
<td>1057</td>
<td>407</td>
</tr>
</tbody>
</table>

Data presented as mean and standard deviation unless otherwise noted. Late onset family history indicates a diagnosis of coronary artery disease occurring after age 50 in a family member; premature family history indicates a diagnosis of coronary artery disease before age 50 in a family member. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease.

Table 2: Mortality rates by cause of death for 0-10, >10-20 and >20 years follow-up among 49,255 men in the Cooper Center Longitudinal Study

<table>
<thead>
<tr>
<th></th>
<th>0-10 years</th>
<th>&gt;10-20 years</th>
<th>&gt;20 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person-years, y</td>
<td>411,648</td>
<td>270,036</td>
<td>130,024</td>
</tr>
<tr>
<td>CHD deaths</td>
<td>203</td>
<td>356</td>
<td>360</td>
</tr>
<tr>
<td>Rate (per 1,000-person years)</td>
<td>0.49</td>
<td>1.32</td>
<td>2.77</td>
</tr>
<tr>
<td>CVD deaths</td>
<td>281</td>
<td>540</td>
<td>635</td>
</tr>
<tr>
<td>Rate (per 1,000-person years)</td>
<td>0.68</td>
<td>2.00</td>
<td>4.88</td>
</tr>
<tr>
<td>All-cause deaths</td>
<td>810</td>
<td>1499</td>
<td>1812</td>
</tr>
<tr>
<td>Rate (per 1,000-person years)</td>
<td>1.97</td>
<td>5.55</td>
<td>13.94</td>
</tr>
</tbody>
</table>

CHD = coronary heart disease. CVD = cardiovascular disease.
Table 3: Multivariable and age-adjusted hazard ratios (95% confidence intervals) for premature family history*, late-onset family history* and CHD mortality, CVD mortality and all-cause mortality among men in the Cooper Center Longitudinal Study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>0-10 years follow-up</th>
<th>&gt;10-20 years follow-up</th>
<th>&gt;20 years follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No FHx</td>
<td>Late-FHx</td>
<td>Pre-FHx</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.25 [0.89, 1.76]</td>
<td>1.10 [0.87, 1.39]</td>
</tr>
<tr>
<td></td>
<td>p-value (Late-FHx vs. no FHx)</td>
<td>0.196</td>
<td>0.436</td>
</tr>
<tr>
<td></td>
<td>No FHx</td>
<td>Late-FHx</td>
<td>Pre-FHx</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.25 [0.88, 1.76]</td>
<td>1.15 [0.91, 1.46]</td>
</tr>
<tr>
<td></td>
<td>p-value (Late-FHx vs. no FHx)</td>
<td>0.210</td>
<td>0.250</td>
</tr>
<tr>
<td></td>
<td>No FHx</td>
<td>Late-FHx</td>
<td>Pre-FHx</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.40 [1.06, 1.86]</td>
<td>1.20 [0.99, 1.45]</td>
</tr>
<tr>
<td></td>
<td>p-value (Late-FHx vs. no FHx)</td>
<td>0.019</td>
<td>0.065</td>
</tr>
<tr>
<td></td>
<td>No FHx</td>
<td>Late-FHx</td>
<td>Pre-FHx</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.32 [0.95, 1.67]</td>
<td>1.21 [1.02, 1.44]</td>
</tr>
<tr>
<td></td>
<td>p-value (Late-FHx vs. no FHx)</td>
<td>0.115</td>
<td>0.132</td>
</tr>
<tr>
<td></td>
<td>No FHx</td>
<td>Late-FHx</td>
<td>Pre-FHx</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.30 [1.10, 1.54]</td>
<td>1.10 [0.98, 1.24]</td>
</tr>
<tr>
<td></td>
<td>p-value (Late-FHx vs. no FHx)</td>
<td>0.002</td>
<td>0.094</td>
</tr>
<tr>
<td></td>
<td>No FHx</td>
<td>Late-FHx</td>
<td>Pre-FHx</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.19 [0.90, 1.58]</td>
<td>1.20 [1.01, 1.43]</td>
</tr>
<tr>
<td></td>
<td>p-value (Pre-FHx vs. no FHx)</td>
<td>0.228</td>
<td>0.040</td>
</tr>
</tbody>
</table>

*Premature family history indicates a diagnosis of coronary artery disease prior to age 50 in a family member. Late-onset family history indicates a diagnosis of coronary artery disease occurring at or after age 50 in a family member.

CHD: coronary heart disease. CVD: cardiovascular disease. No FHx: No family history of CHD. Late-FHx: Family history of late-onset CHD. Pre-FHx: Family history of premature CHD.
Figure Legends:

**Figure 1:** Cumulative incidence of CVD death adjusted for competing risk (lifetime risk) for men according to family history status at 55 years of age. CHD = coronary heart disease; CVD = cardiovascular disease. “Family history of premature CHD” denotes a CHD event in a first-degree family member prior to age 50. N=26,447 for patients with attained age ≥55.

**Figure 2:** Cumulative incidence of CVD death adjusted for competing risk (lifetime risk) for men according to family history status at 45 years of age. CHD = coronary heart disease; CVD = cardiovascular disease. “Family history of premature CHD” denotes a CHD event in a first-degree family member prior to age 50. N=37,036 for patients with attained age ≥45.
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