Family history of coronary heart disease as a risk factor for developing coronary heart disease

- *a literature study*

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ABSTRACT

Background and aims: Family history of coronary heart disease (CHD) has been proposed to be an important risk factor for developing CHD, but much remains to be explored on whether any increased risk is independent of other established risk factors, and how the risk is dependent on other aspects such as the age and gender of the various family members. The aim of this study was to examine the literature on the subject, and investigate whether a family history can be seen as an independent risk factor, and how other aspects, such as age, gender and the number of affected relatives influences the risk association.

Methods: This study is a literature review. Articles were found either by repeated searches in PubMed in a period from autumn 2012 until spring 2015, using the following search terms: "family history AND coronary heart disease", "family history AND myocardial infarction", "coronary heart disease AND heritability" and "myocardial infarction AND heritability", or via the bibliography of relevant articles and UpToDate.com. 11 articles were included in the final analyses.

Results: The articles included in this literature review all showed that a family history of CHD was, at least in many scenarios, an independent risk factor for developing CHD. The studies that have adjusted for numerous established risk factors, generally find a modest effect of such an adjustment. CHD occurring at a younger age and family histories with more than one affected relative appears to be of greater importance. Other investigated aspects, such as the effect of gender, show inconsistent results.

Conclusion: Family history of CHD is a risk factor for developing CHD that can be independent of other established risk factors. However, it cannot be interpreted as a binary risk factor that the index individual either has or has not. There appears to be greater risk with increasing number of affected relatives and with the CHD event occurring at a younger age. Gender of the index individual and affected relative may be of importance, but more research is needed to establish the exact pattern of this effect. Socioeconomic factors are an underexplored potential confounding factor. More research is needed to establish the degree to which the effect of a family history can be explained by established risk factors, the social environment and genetic mechanisms.

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BACKGROUND AND AIMS

According to the latest Global Burden of Disease study, coronary heart disease (CHD) remains the leading cause of death worldwide, accounting for 1 in 4 deaths (1). Much attention is therefore devoted to finding and investigating the relative importance of both modifiable and non-modifiable risk factors for developing CHD. The INTERHEART study found that at a population level, 90% of the risk for a first-time myocardial infarction (MI) could be explained by nine potentially modifiable risk factors: smoking, dyslipidemia, hypertension, diabetes, abdominal obesity, psychosocial factors, daily consumption of fruits and vegetables, regular alcohol consumption, and regular physical activity (2), and at least one of these are found in more than 85% of patients with CHD (3-5).

Several international studies have also suggested that a family history CHD in first-degree relatives, is an independent risk factor for developing CHD in the index person (6-16). Questions about illness in the family has long been a standard feature of the medical interview, and are used to assess the individual patient's risk of certain illnesses both currently and in the future, and the doctor will often ask explicitly about any accumulation of heart disease in the family (17). But what does a positive family history actually mean for the index individual's risk of developing CHD? How much of a risk increase has been observed in the studies that have been done on this subject? And does it matter which family member that developed CHD? It could be that this will depend on whether it is one of the parents or one of the siblings that were affected, or the age at which CHD occurred. Given that family members share a certain degree of both genes and environmental exposures, we must also try to assess whether any observed association could be explained by other confounding factors.

The aim of this study is to investigate the importance of a family history of CHD in parents and/or siblings as a risk factor for the index patient's risk of developing CHD and/or CHD mortality. I will try to elucidate what studies have shown regarding the importance of CHD in different family members, for instance the difference between a family history of CHD in parents compared to siblings. I will also discuss whether family history on the evidence currently available in the literature appears to be an independent risk factor, or if it the estimates could be influenced by residual confounding.

METHODS

This study is a literature review. The process of finding relevant literature was conducted over a period from autumn 2012 until spring 2015. Articles were found by the following two strategies: The first consisted of repeatedly searching PubMed for relevant articles, using the following search terms: "family history AND coronary heart disease", "family history AND myocardial infarction", "coronary heart disease AND heritability" and "myocardial infarction AND heritability". All of these search terms generated a large number of results, and the titles of the articles were then screened for relevance. The other main approach to finding relevant studies, was by using the bibliography of already included articles and the online resource UpToDate.com.

Over this 2,5 year period, a large number of abstracts were read in order to assess whether the research applied to this study. If the abstracts appeared to be relevant, the articles were then read in full, and out of those articles, ten were analyzed in detail, and are presented in the Results section of this review, and form the basis for the discussion on the topic, where other research obviously also will be drawn on.

This is a research question were randomized controlled trials are not an option, and the included studies are all various forms of cohort studies. The results of cohort studies are prone to be influenced by confounding factors. Cohorts were the researchers had access to detailed information on numerous risk factors were preferred, as this allowed the researchers to adjust for the effect of these potential confounders.

Due to the limitations in the space available for the study, I will mostly restrict myself to reporting the adjusted, rather than crude or merely age-adjusted, results. Given the multitude of potential confounding on the association between exposure and outcome in this research question, I believe the adjusted results to be of greater interest.

Exposure and outcome

To limit the scope of this review, I have restricted myself to articles where CHD specifically was at least one of the investigated exposures and outcomes, rather than the broader concept of cardiovascular disease. Even when narrowing it down to CHD, there is still a considerable variation in what constitutes both a family history and an endpoint of CHD. Given that this will influence the number of participants in each group, it could influence the results. I will therefore for each article reviewed present clearly how CHD was defined as both exposure and outcome.

Unless otherwise noted, the effect estimates (odds ratio, hazard ratio, etc.) are compared to a reference group of those with no family history, and numbers in parenthesis after effect estimates are 95% confidence intervals.

RESULTS

The earliest study to investigate family history of CHD as a risk factor for CHD, and adjust for other risk factors, identified in the literature search performed for the present study, was conducted by Barrett-Connor and Khaw, and presented in Circulation in 1984 (9). The results were based on a cohort of 4014 men and women from the community of Rancho Bernado, California. Participants were investigated between 1972 and 1974 and followed for 9 years. Exposure was self-reported family history of heart attack in parents, siblings or children. Participants with a positive family history were asked to indicate whether this occurred before or after age 50. Outcome was mortality (all-cause, cardiovascular and due to ischemic heart disease), as reported on death certificate. A Cox proportional hazards model was used to determine the independent contribution of a positive family history to the three different categories of mortality. Only results for CHD mortality will be presented here. For men, the researchers found (after adjustment for age, systolic blood pressure, smoking, obesity, cholesterol and diabetes) that a family history of heart attack conferred an independent relative risk for death from CHD of 1.56 (p<0.05). The corresponding independent relative risk for women was 0.87. This study was pioneering work, in that it was one of the first to examine this question and adjust for the other established risk factors, and the first to examine the independent effect of family history on mortality in women.

Bachmann et al. (7) investigated 49 255 men from the Cooper Center Longitudinal Study, a prospective study at the Cooper Clinic in Dallas, Texas, that has lasted for over 40 years. Patients are recruited from all over the US, but the study population consists of less than 5% non-whites. All men between 20 and 90 years of age who had undergone a complete clinical examination and completed a family history questionnaire between 1970 and 2006 were included. The exposure was thus self-reported CHD in a sibling, aunt or uncle, parent or grandparent, where the definition of CHD included angina, myocardial infarction, angioplasty or coronary artery bypass surgery. Respondents were additionally asked to indicate whether the CHD event occurred before or after the relative was 50 years of age. The type of event and which family member that was afflicted were not defined. The outcome investigated was both CVD and CHD mortality, for the purpose of this literature study, only results on CHD mortality will be reviewed. CHD mortality was defined by ICD-9 codes 410-414, or their equivalents in ICD-8 or ICD-10. Participants were followed from the date of initial examination until death or end of follow-up through 2006. They then investigated the risk of CHD mortality associated with a family history of CHD, both early and late onset, and over different lengths of follow-up (0-10 years, 10-20 years and >20 years). Using a Cox proportional hazard model, where those with no family history were the reference group, the researchers found after multivariable (age, systolic blood pressure, serum total cholesterol, body mass index, smoking and diabetes mellitus) no significant risk increase with a late family history: HR 1.25 (0.88-1.76), 1.15 (0.91-1.46) and 1.00 (0.78-1.29) in the three categories of follow-up respectively. For an early family history the corresponding HR were 1.32 (0.76-2.31), 1.59 (1.13-2.22) and 1.43 (1.05-1.95). Thus, the results indicate a significant risk increase associated with premature CHD in one or more family members over a follow-up of more than 10 years, but not for shorter follow-up. Men with a family history of premature CHD were found to have a lifetime risk of CHD mortality of 13.7%, compared to 8.9% for those with no family history. Strengths of the study were a long follow-up and detailed information on and adjustment for numerous risk factors, although no socioeconomic risk factors were included. Weaknesses were the lack of specificity concerning both which type of CHD and which family member that was ill. The lack of female subjects and ethnic diversity also makes the results less applicable to the population at large.

Sesso and co-workers (12) used data from two large cohort studies, the Physicians' Health Study and the Women's Health Study, to investigate maternal and paternal history of myocardial infarction as a risk factor for various forms of cardiovascular disease. A total of 20515 men and 37985 women were included. The exposure was self-reported history on myocardial infarction in either mother or father, and respondents were additionally asked to provide the age when it occurred. Cox proportional hazards models estimated the relative risk (RR) and 95% confidence intervals for the outcomes myocardial infarction, stroke and total CVD, as assessed by annual questionnaires and medical records. Once again, only the results for myocardial infarction will be discussed here. After multivariate (age, body mass index, smoking status, exercise and alcohol intake for both sexes, as well as some gender specific additional factors), the RR for maternal, paternal and both maternal and paternal history of myocardial infarction were 2.14 (1.64-2.79), 1.58 (1.33-1.89) and 1.98 (1.41-2.78) respectively. The higher magnitude of risk for maternal compared to paternal history was significantly different in men (p=0.01), but not women (p=0.13). This was another large cohort study, with detailed information on established cardiovascular risk factors. Some limitations should also be noted: Socioeconomic status is not acknowledged as a potential confounder. This is also self-reported family history, which has certain limitations and implications that will be addressed later.

Using data from four large Danish registries, Nielsen et al. (11) conducted a retrospective nationwide register-based cohort study, where they identified siblings and children of all Danish citizens diagnosed with a myocardial infarction in the period 1978-2010 (n=333 344) and whether any of these first-degree relatives also had had a myocardial infarction. The diagnoses of myocardial infarction were obtained from the Danish National Patient registry, with ICD-10 codes I21 and I22, or equivalent from ICD-8. Both fatal and non-fatal events were included. Using a Poisson-model, rate ratios for myocardial infarction for the first-degree family members was calculated. After adjustment in a multivariate model (hypertension, hypercholesterolemia, diabetes, treatment with aspirin, chronic obstructive lung disease, cerebrovascular disease, peripheral vascular disease and renal disease), they found a rate ratio of 3.23 (2.76-3.93) if you had a sibling with myocardial infarction, 2.06 (1.89-2.23) with myocardial infarction in mother and 1.64 (1.55-1.72) with myocardial infarction in father. The strengths of this study include the size of the cohort, and the fact that it was validated coronary events in both index persons and relatives. Important weaknesses should however be noted, such as a lack of information on the important risk factors smoking status, obesity and lack of exercise. Like most of the other studies on this topic, they did not include socioeconomic status in their analyses.

Andresdottir, Sigurdsson, Sigvaldason and Gudnason of the Icelandic Heart Association's research institute and Landspitali University Hospital investigated a prospective cohort of 9328 men and 10 062 women examined in a period from 1967 to 1998 (6). The exposure was self-reported family history of myocardial infarction in father, mother or siblings. Outcome was CHD, which encompasses both a verified diagnosis of myocardial infarction, sudden cardiac death, as well as the need for coronary revascularization, either by coronary artery bypass graft of percutaneous transluminal coronary angioplasty. All these data were available from registries maintained by the Icelandic Heart Association. Hazard ratios for developing CHD were calculated by Cox regression. The risk period was from the date of examination until diagnosis of end-points, death or end of follow-up through 1998. To investigate the effect of conventional risk factors (age, BMI, cholesterol, triglycerides, systolic blood pressure, erythrocyte sedimentation rate, glucose tolerance, smoking history, use of antihypertensive medication, level of education and physical activity) the association between family history and CHD, they adjusted for risk factors one at the time, and eventually

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calculated the risk percentage attributable to family history. This was done by using family history as a categorical variable, and calculating the attributable risk percentage. After multivariate adjustment, the hazard ratio for CHD given a family history of myocardial infarction in one or more first-degree relatives was 1.66 (1.51-1.82) for men and 1.64 (1.43-1.89) for women. The researchers also found that family history could be attributed to 15.1% of the cases of CHD in men, and 16.6 % in women, independent of other established risk factors. Strenghts of this study included a near total follow-up, detailed information on several established risk factors, inclusion of an indicator of socioeconomic status in the form of education level. However, as will be discussed later, the latter is probably not sufficient if one is to properly investigate the importance of socioeconomic position. Additionally, HDL-cholesterol was not included in the study. The problems concerning self-reported family history obviously also applies to this study.

One of the studies that have investigated this question using a different design than cohort studies, is the INTERHEART study, a multinational case-control study that after exclusion for missing risk factors consisted of 12,149 cases and 14,467 control matched for age and sex between February 1999 and March 2003 (10). Index individuals were identified when admitted to coronary care units having verified myocardial infarction (2). Information on parental history of myocardial infarction was obtained from a structured questionnaire. Multiple logistic regression models were used to examine the risk of myocardial infarction associated with a parental history of myocardial infarction. Nine important risk factors had been identified in an earlier phase of the INTERHEART study: abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, physical activity, fruit and vegetable consumption and alcohol consumption. In addition to these, the researchers adjusted for age, sex, region, and in sub-group analyses even for genetic risk factors. After adjustment for the complete set of risk factors, the study found the following odds ratios for risk of myocardial infarction associated with parental history of myocardial infarction: OR 1.57 (1.34-1.86) for maternal history, OR 1.45 (1.25-1.68) for paternal history and 2.28 (1.64-3.17) for those with both maternal and paternal history. Genetic variants was found to be have very limited ability to predict risk, independent of serum lipid levels. The strengths of this study is that it is the only study on the subject identified in the research for this review that is transnational, contained information on genetic variants known to be associated with CHD, and it also on indicators of socioeconomic position, as well as psychosocial factors. Since this is a case-control study, there is a possibility of recall bias skewing the results.

In a study from 2012, Zöller et al. investigated the familial risk of CHD in families with several affected siblings, and compared it to the spousal risk to investigate genetic and non-genetic familial contribution (15). They used a data set of over 11.8 million individuals constructed by linking several national Swedish registers. Siblings were identified and the data set was linked to National Census data to ascertain occupational group, and to the Swedish Cause of Death Register and the Swedish Hospital Discharge Register for information on the outcomes of CHD or CHD mortality, as defined by ICD-10 I20-I25, or earlier equivalents. Standardized incidence ratios were then calculated for individuals whose siblings were hospitalized or died due to CHD, and compared with standardized incidence for ratios for those who did not have affected siblings. This was then repeated for spouses. The following individual variables were adjusted for in the analyses: sex, age, socioeconomic/occupational group and area of residence (urban vs. rural). Person years at risk were calculated from start of follow-up on January 1 1964 until hospitalization or death from CHD, death, emigration or end of follow-up through 2008. Adjusted standardized incidence ratio varied somewhat with the age at which CHD had occurred, the sex of the siblings and the number of affected sibling probands. For all age-categories of time of CHD in probands,

and both sexes of siblings, the standardized incidence ratio for CHD (either hospitalization of death) was 1.82 (1.27-2.60) for hospital admission for CHD, and 1.61 (1.10-2.36) for death from CHD. The combined figures for both sexes concerning standardized incidence ratio for CHD given hospitalization for CHD in a sibling ranged from 1.49 (1.04-2.13) with one affected sibling proband to 7.66 (4.99-11.74) with four or more siblings. When these calculations were repeated for spouses of individals who suffered hospitalization or death due to CHD, the researchers found a significant, but nearly negligible, increased risk for hospitalization or death from CHD, with standardized incidence ratios of 1.07 (1.07-1.07) and 1.01 (1.00-1.02) respectively. The strengths of this study include the vast number of cases, the use of verified events and adjustment for socioeconomic factors. Some weaknesses should be noted, such as lack of adjustment for important risk factors like smoking, BMI and cholesterol levels.

In a 2009 paper in the Circulation Cardiovascular Genetics (8), Banerjee and co-workers used data from the Oxford Vascular Study, to analyze the presence of a positive family history in patients presenting with acute coronary syndrome (unstable angina, NSTEMI or STEMI), with special emphasis on sex-specific effects. 623 probands (203 women and 420 men) were included in the analyses. Proband acute coronary syndrome was verified, and based on medical records, whereas family history was self-reported, using a structured questionnaire. Several analyses were performed. For our purposes, the most relevant is a logistic regression, with premature acute coronary syndrome in the proband, and the independent variables sex of proband, current smoking, hyperlipidemia and positive maternal history of premature myocardial infarction (defined as occurring before the age of 65). For women, maternal history of premature myocardial infarction conferred an adjusted Hazard ratio of 2.82 (1.16-6.85). For men, a similar family history did not constitute a significant risk increase, adjusted Hazard Ratio was 1.48 (0.94-2.34). For both men and women, this placed premature maternal history as a more important risk factor than hyperlipidemia, but markedly less than current smoking. The attention awarded to possible sex-specific mechanisms was the main strength of this study, which was otherwise limited somewhat by lack of statistical power, possibly due to low number of respondents. Scarce access to other established cardiovascular risk factors, and socioeconomic factors should also be kept in mind when analyzing the results.

In a prospective cohort study of 10 288 men and 12 553 women recruited from the Norfolk region of the United Kingdom, Sivapalaratnam et al. investigated self-reported family history of premature (<55 or <65 years of age for men and women respectively) or non-premature CHD in first-degree relatives. It is not entirely clear how the researchers defined CHD, it appears only to have been asked about myocardial infarction. Outcome was CHD in the index individual, counting both hospital admissions and death from CHD. For this purpose CHD was defined as "eg, unstable angina, stable angina or myocardial infarction". Results were adjusted for a modified Framingham Risk Score, which took into account age, sex, total cholesterol, HDL cholesterol, systolic and diastolic blood pressure, smoking and diabetes. Those with no family history were compared to the respondents with premature and non-premature family history. Only premature was significant for both parental and sibling history. Adjusted relative risk for CHD was 1.43 (1.22-1.68) with a premature parental history, and 1.43 (1.15-1.77) for premature sibling history. The researchers then investigated the value of adding information on family history to the Framingham Risk Score. The study had the advantage of having detailed information on established risk factors, but as has been mentioned for other studies with similar designs, there are problems with a self-reported family history. The imprecise definition of CHD is another weakness with this study.

In a recent study published in American Journal of Cardiology, researchers from Mt Sinai and collaborating institutions investigated family history as a risk factor in a low-risk population, defined by having a coronary artery calcium score of 0 (16). Coronary calcium score is a measure of calcification in the coronary arteries, and is performed by chest computed tomography (CT). A coronary calcium score of 0, has been shown to indicate a 10-year risk of a cardiac event of around 1%. The participants were recruited from 6 centers spread across the United States as part of the Multi-Ethnic Study of Atherosclerosis, a longitudinal, population-based survey of 6,814 men and women initially free of clinical cardiovascular disease. 3,185 were included in the present study. Baseline surveys were conducted between 2000-2002, with a median follow-up of 10 years. Exposure was self-reported family history of myocardial infarction in a first-degree relative. For our purposes, the relevant end point was that of CHD events, which in a previous article from the Multi-Ethnic Study of Atherosclerosis had been defined as a verified event of myocardial infarction, death from coronary heart disease, definite angina followed by coronary revascularization, definite angina not followed by coronary revascularization, and probable angina followed by coronary revascularization (18). Cox proportional hazards models were used to estimate the effect of family history on the risk of incident CHD. Following adjustment for age and gender, a family history of CHD was significantly associated with CHD events, with a Hazard Ratio of 1.60 (1.08-2.38). After additional adjustment for ethnicity, Framingham Risk Score, and baseline use of aspirin or statin, this risk was attenuated to non-significant levels. Since the association with CVD events remained significant, the researchers speculated that the low number of CHD events could be the explanation for this. One reason for this is probably the fact that for this low-risk and relatively small cohort, a follow-up time of 10 years is probably insufficient for a CHD, given that it usually develops over decades.

DISCUSSION

The ten articles reviewed above all found a family history of CHD to be a risk factor for developing CHD. Given that the statistical methods and thus outcome measures have varied somewhat, they are not necessarily directly comparable. Most articles also operate with different categories of family history (eg. premature vs. non-premature, paternal vs. sibling, etc). In a review of the available literature on the risk of developing CHD associated with a positive family history of the wider concept of "atherosclerotic cardiovascular disease", the researchers estimated that it ranged from 15-100 % in various cohorts, with most cohorts showing a 40-60 % increase (19).

The degree to which this association was found to independent of other risk factors varied somewhat. In most studies this was found to be the case, but there was important differences in which risk factors that were adjusted for. I will in the following section discuss some of the issues where the effect size and pattern of the risk association between family history and CHD in the index individual remains unclear, and where the findings can differ in the various articles.

Independence from other risk factors

It is a noticeable pattern that in several of the studies, the difference between crude, or merely adjusted for age and sex, and the fully adjusted estimates are moderate at most. For instance, Sesso and co-workers (12) found that relative risk conferred by a combined maternal and paternal history of myocardial infarction was 1.89 (1.60-2.23) in the age-adjusted estimates, and 1.85 (1.56-2.19) after multivariate adjustement. A similar pattern was seen for the female participants. In the INTERHEART study (10), odds ratio for myocardial infarction in the presence of a maternal and paternal history of myocardial infarction was 2.43 (1.96-3.01) unadjusted, and after adding age, sex, region, 9 established risk factors and genotype score, the odds ratio was reduced to 2.28 (1.64-3.17). A final example is the article by Nielsen et al.(11), where the difference in rate ratio between unadjusted risk associated with a maternal history was a reduction from 2.40 (2.20-2.60) to 2.06 (1.89-2.23). The only article where adjustment attenuated the risk to non-significant levels was in the small sample-size study by Cohen et al. (16), as described above.

In other words, there appears to be a pattern where the effect of a family history of CHD on the risk of developing CHD is relatively independent of the effect of other established risk factors. This could be interpreted in at least two ways: First, it could be because family history constitutes a genetic or environmental risk that is independent of other risk factors such as cholesterol metabolism. Or it could be that there is an as-of-yet unidentified confounding factor that influences the observed association.

As family members in addition to shared genes, also will share living habits and environment, the question of family history as a risk factor for CHD is laden with potentially confounding factors. To be able to decipher the true magnitude of the risk that is attributable to family history, we need to be able to separate it from the effect of other risk factors that will be shared in a family, such as smoking status and cholesterol metabolism. A limitation that applies to all of the included studies is that information on relatives' CHD risk factors, such as smoking status, was not included in the analyses. Also, the exposure of the index individuals to these risk factors were only assessed at a single point in time, which may not capture the true magnitude of their adverse or protective effects over decades of exposure and lead to residual confounding.

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Effect of CHD in parents compared to siblings

The excess risk of CHD mortality associated with a positive family history seems to vary by which family member that was affected (11, 12). Nielsen et al. found that after multivariate adjustment, the rate ratio for developing myocardial infarction in the presence of myocardial infarction in a sibling was 3.23 (2.76-3.93), compared to 2.06 (1.89-2.23) and 1.64 (1.55-1.72) with a maternal and paternal history respectively (11). Thus, CHD in siblings appear to confer a greater risk than CHD in a parent. Several explanations are possible for this; one is that siblings usually have more environmental exposures in common than parents and offspring, which might lead to more similar patterns of disease.

However, in the study by Sivapalaratnam and co-workers (13), no difference was found between a parental and sibling history of premature CHD. Hazard ratios adjusted for the Framingham Risk Score was 1.43 (1.22-1.68) for a parental history, and 1.43 (1.15-1.77) for a sibling history. There are no apparent differences in study design that can explain the different findings of these two studies. It is interesting to note that in the latter study, the adjusted hazard ratios were greater than the unadjusted, whereas for a sibling history, the hazard ratios were attenuated by adjustment. This suggests that the effect of confounding factors is different for a parental and a sibling history.

As shown here, not much work has been done on the relative importance of a parental compared to at sibling history of CHD as risk factors for developing CHD. From the studies that are available at the time of this literature review, it is not possible to draw any conclusions on whether one is more important than the other.

Effect of age of index individual and affected relative

Both the age of the index individual and the relative that had a history of CHD could be of importance. The INTERHEART study found that the odds ratio for myocardial infarction, adjusted for age sex and region, was 1.67 (1.55-1.81) with a parental history in a parent older than 50 years old, and 2.36 (1.89-2.95) with a parent aged 50 or younger (10). This graded relationship persisted after additional adjustment for nine other established risk factors. Bachmann et al observed the same pattern (7); in their study only family history before the age of 50 was a significant risk factor, as described above. Sesso and co-workers divided their study population into five strata of age of onset of parental CHD, and found that cardiovascular risk for men was greatest with younger paternal ages at myocardial infarction, and that risk decreased as paternal age increased. A test for negative linear trend in paternal age found a p-value of <0.001. However, a paternal age at MI of 70-70 years still constituted a small, significantly increased risk of CVD (12). In the EPIC-Norfolk study, premature was defined as <55 years in men, and <65 years in women (13). This is, at least theoretically, a sensible approach, given that women on average develop CHD ten years later than men (20). It does however not appear to influence the results greatly, as there was a very similar pattern found in this study. After adjustment for the Framingham Risk Score, the relative risk conferred by premature and non-premature family history was 1.74 (1.56-1.95) and 1.30 (1.20-1.41) respectively. When comparing four different age categories more thoroughly, the researchers found an inverse relationship, with non-overlapping confidence intervals, between the age of onset of CHD in the first-degree relative and the index person's risk of CHD. Only family history occurring <75 in men and <85 in women was significant. In the Danish study by Nielsen et al. (11), a paternal history occurring before and after age 50, conferred a relative risk of 2.46 (2.18-2.79) and 1.53 (1.44-1.62) respectively. A similar pattern was observed for a maternal history. The importance of age is seen also for family history in siblings. Zöller et al. calculated a standardized incidence ratio for hospitalization for CHD of 2.60 (1.70-2.36) if

the sibling was <40, with successively lower ratios for each bracket of advancing age, reaching non-significant levels for siblings >70 (15).

Less studied is the effect of the age at which CHD occurred in the index individual. Sesso et al. (12), report to have analyzed it, and found the relative risk of CVD events given a parental history of myocardial infarction to be greater among subjects aged <60 years, but the data for these assertions are not shown. They do however hypothesize that this suggests that younger individuals are more likely to manifest the deleterious effects of a family history. No other studies included in this review have investigated this question, but the other INTERHEART study described above, by Yusuf et al. (2), similarly found that the population attributable risk for family history was 14.8% (11.7-18.5) for younger individuals (men <55, women <65), compared to 10.4 (8.3-13.0) in older.

Effect of number of relatives affected

Another factor that needs to be consider when asessing the importance of a family history as a cardiovascular risk factor, is the number of relatives that have been affected by CHD. Two of the included articles in this review have investigated this, with somewhat conflicting results. In the study by Zöller et al, that investigated sibling history as a risk factor, they found that there was a significant difference between having one sibling with CHD and two or more (15). This pattern was consistent for both the chosen outcomes (hospitalization and death) and for both genders. It was only for hospitalization in men where there was a significant risk increase with only one affected sibling: SIR 1.52 (1.06-2.18). In contrast, there was a substantial risk increase in all scenarios for those with two or more siblings, for instance the SIR for hospitalization in men with two, three and four affected siblings was 6.63 (4.55-9.66), 7.38 (4.91-11.08) and 7.06 (4.50-11.06) respectively. These figures also illustrate another pattern found for the other outcomes and genders, namely that the main difference was between with those with one affected siblings and those with more. There was no significant difference between two and four in any of the outcomes or genders.

Sesso and co-workers investigated this facet of the research question by comparing the effect of an isolated maternal or paternal history to a combined family history of CHD in both parents (12). For the outcome myocardial infarction, the relative risk after multivariate adjustment, for men with family history of myocardial infarction, compared to a reference group of those with no family history, was 2.14 (1.64-2.79) with a maternal history, 1.58 (1.33-1.89) for a paternal history and 1.98 (1.41-2.78) with both parents. The corresponding figures for women were 1.76 (1.09-2.87), 0.93 (0.60-1.45) and 2.49 (1.46-4.24). For men, one interpretation of the results is that a paternal history is less of a significant risk factor, and that this lowers the estimate for the combined family history. For women we also see that an isolated paternal history is less important, to the extent that it appears not to be a statistically significant risk factor. However, the estimates for a combined parental history are greater than a maternal history, although with overlapping confidence intervals. This suggests that there is an additive effect of having a family history in both parents, which is greater than the sum of its parts.

To summarize this section, there are certain indications that a family history affecting more than one relative is more significant as a risk factor than a family history restricted to one sibling or parent. However, this picture is not consistent, and more research needs to be done on this topic. If later research confirms increased effect of having more affected relatives, this might suggest that the heritability of CHD is an area of additive genetic effects.

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Sex differences in effect of a family history

Several of the studies included in this review presented analyses separately for men and women, allowing us to look into possible differences between men and women in the importance of family history for the index individual (6, 8, 10, 12, 15). This issue can be approached from at least three angles: First whether the sex of the index individual matters, secondly whether the sex of the affected family member is of importance, and lastly whether it matters if index individual and affected family member are of the same sex?

Regarding the first question, Andresdottir et al. (6) found no difference in their multivariate analyses, with the hazard ratios associated with a family history of myocardial infarction for male and female participants being 1.66 (1.51-1.82) and 1.64 (1.43-1.89) respectively. This was also the case in the study by Zöller et al. (15). These findings are contrasted by the previously mentioned findings by Banerjee, Barrett-Connor and Chow with respective co-workers (8-10), both found sex-specific differences in which family member that was affected. However, the findings in these studies are pointing in different directions. Banerjee et al. found greater risk with a family history for the female study population, unlike Barrett-Connor and Chow, where it was only in the male study population that they found significant effect. In the study by Sesso et al. (12) there were sex-specific differences, both with no clear pattern. In some categories of family history there was greater risk for men, in others for women. The latest ESC/EAS Guidelines for the management of dyslipidemias estimates the risk increase for an atherosclerotic cardiovascular event to be 1.7-fold in women and 2.0-fold in men, given a family history of premature CVD (21). The reason for this might be that middle-aged women have a lower background incidence of MI than men in the same age group, and thus require more genetic risk factors than men to develop CHD, consistent with the Carter-effect (8, 22).

The second issue, on the importance of the affected relative, can be assessed from the data presented in the the studies by Nielsen and Sesso et al., which both found that the risk generally was higher with affected female relative compared to male, although with overlapping confidence intervals (11, 12). Thus, a large degree of caution should be exercised in the interpretation of these results. If later studies were to replicate these findings, there is at least one theoretical explanation for the greater effect seen by family history in a female relative: As middle-aged women, given comparable risk factors, have lower risk of MI than men, a history of MI in the mother or sister may imply a higher CHD risk for the index person, than MI in a male relative (23).

Finally, does it matter if index individual and affected family member are of the same gender? In the study by Sesso et al., the results show that there is a greater effect with a paternal history for sons compared to daughters, but on the other hand the effect of a maternal history is also greater in sons, thus there is no clear effect of relative and index individual being of the same gender (12). However, such sex-specific effects are found in the study by Zöller and colleagues (15), were they highlight that the risk for hospitalization for CHD was higher for males than females if the proband was a man, with the SIR being 2.02 and 1.64 respectively. Similarly, the SIR for CHD was 2.04 for women and 1.34 for men if the proband was male. They do not present confidence intervals for these figures in the article, they are only described as overlapping. If we consider the full data presented in the supplementary material, we find that this is a consistent pattern for both hospitalization and death in most age groups, greater with a family history in a same sex relative in both men and women, although with generally overlapping confidence intervals.

Socioeconomic position

Risk of CHD has in numerous studies been shown to be associated with socioeconomic position (24-28), and it is possible that a positive family history could be of socioeconomic, rather than biological, origin. In this review, only the articles by Zöller, Andresdottir, and Chow et al., included socioeconomic position in their analyses, adjusting for single indicators, such as occupation or education (6, 15), or a sum score emphasizing psychological stress (10) respectively. The latter also found that the effect of family history was consistent across the regions and socioeconomic strata of their study population.

Educational level is the most widely used indicator of socioeconomic position in cardiovascular epidemiology, and has been shown to correlate with cardiovascular health (24, 29). However, public health researchers have increasingly emphasized the need to take the full life course into account to understand the origin and population distribution of diseases such as CHD (30, 31). Merely adjusting for single measures of social exposures at single points in time, could fail to capture the complex ways that social and behavioral factors confound associations between risk factors and disease, such under-adjustment may leave the analyses open to the effect of residual confounding (32), which for instance was the case in the observed inverse correlation between plasma levels of vitamin C and cardiovascular risk (32, 33). This could equally be an alternative explanation for the relationship between FH and CHD risk, and investigating the importance of life socioeconomic position for this association between family history and risk of developing CHD, and would be an important contribution to the existing literature.

Genetic contribution

The degree to which an effect of a family history of CHD is due to shared genetics or shared environment remains an open question. As this literature review has shown, there is an important and seemingly independent risk increase associated with a family history of CHD. In addition to the need for further investigations into the role that socioeconomic conditions could play, as mentioned above, currently unmeasured genetic factors could offer a strong potential explanation for the association between a family history and the development of CHD (10). More than a decade on from the completion of the Human Genome Project, the genetics of CHD, and CVD in general, is still an area with much uncertainty (34, 35). The INTERHEART study adjusted for some known genetic variants known to be involved in the heritability of CHD. However, the genotype risk score they developed appeared to have a negligible ability to predict risk independent of serum lipid levels. The odds ratio of MI given a combined maternal and paternal history was altered from 2.26 (1.68-3.06) to 2.28 (1.64-3.17) after adding the genotype score to the list of variables that were adjusted for. When interpreting these results, it should be noted that the researchers here directly compare odds ratios in the main and sub-populations directly. And the loci that are currently known only explain a minor proportion of the risk variance concerning CHD. It is probably a fair assumption that the heritability of CHD is through complex genetic mechanisms.

Zöller et al. approached the discussion of nature versus nurture from another angle, where they compared the risk conferred by CHD in a proband for siblings and spouses of the proband. As described above, in contrast to the noticeable risk increase for siblings, there was almost no such increase observed in spouses. Given that spouses share environmental and demographic, except gender in most cases, this difference in risk association suggests that genetic factors or early environmental exposures are of utmost importance.

Twin studies have found a moderate genetic contribution, greater at younger ages of illness, and with greater concordance rates for CHD mortality in monozygotic than dizygotic twins

(14, 36). Genome Wide Association Studies have so far found the genetic base for the atherosclerotic process to be a complex interplay between a few known and many as of yet unknown genes, in what has been described as a "mosaic" compromised of large-effect variants rare in frequency, small-effect variants common in frequency, and environmental influences (34). Studying the interaction between those genetic variants and environmental influences, the emerging field of epigenetics provides another possible mediator for the effect of a family history, with experimental results suggesting an epigenetic impact on both cardiovascular development and disease (37). A Danish adoptees' study found that the biological and not the adoptive fathers' socioeconomic status was associated with higher mortality in the fifth decade of life, possibly lending support to the idea that genetic or prenatal environmental influences shape future pattern of illness more than rearing environment (38).

Self-reported versus validated family history

The studies that have used verified CHD events in relatives to define family history, are keen to promote this as a major advantage compared to those that have used self-reported events (11, 15). There are strong arguments to support this. Given the choice between verified and non-verified events, most researchers will intuitively opt for the former, since it reduces the risk of important sources of error such as recall bias.

Self-reported family history of premature MI has been shown to have both a positive and negative predictive value of above 90%, and self-reported family history of MI at any age to have a sensitivity of around 70%, and a specificity of more than 90% (39-41). The relatively poor sensitivity could mean that a large number of CHD events could go unreported, possibly biasing results towards an underestimation of the effect of a family history. The advantage of self-reported information is the fact that it corresponds to how family history is assessed clinically, making the risk estimates of interest to clinicians.

Family history as a part of risk assessment

We have in this literature review seen that a positive family history may be an independent risk factor for coronary heart disease in the index individuals. Many of the studies have used self-reported family history, which is how family history will typically be assessed in a clinical setting. Thus, enquiring whether there exists any familial aggregation of CHD in the patient's family appears to be salient. However, although a positive family history is used in some risk scoring algorithms, like QRISK, it is not a part of the more widely used Framingham Risk Score (FRS) and SCORE (13). And in the EPIC-Norfolk study (13) reviewed above they found that adding whether or not the index patient has a family history of CHD to FRS, results in only modest improvement in classification of individuals into the correct risk category. This was also the case in another study that investigated the added value of family history for risk classification (42).

However, two key points should be addressed. Firstly, this raises question on the differences between risk on population level compared to risk on an individual level. This discrepancy is seen clearly in the difference between how well the risk scoring calculators predict risk on these two levels of analysis (43). The INTERHEART study found that the population attributable risk of a family history was 12.0% (99% CI 9.2%–15.1%), which fell to 9.8% (7.6–12.5) after adjustment for nine established risk factors (2). However, when family history was added to the information from these other nine risk factors, the overall population attributable risk rose from 90.4% to only 91.4%. The researchers interpreted this as that although family history was an independent risk factor for myocardial infarction, most of the associated risk burden could be accounted for through the other risk factors studied. This

could explain the findings described above, where adding family history to risk score calculators does little to improve the assessment of population level risk. This does necessarily mean that it is not an important risk factor, even after adjustment for these other risk factors, as the other INTERHEART study by Chow et al. described in this review above showed.

Secondly, enquiring into family history is a quick and inexpensive test. Few would argue that it should be performed instead of assessing any of the components that are included in the risk scoring systems, but often it will be one of the first risk factors that the physician reveals in the history taking, and is of particular interest for doctors working in a setting where laboratory facilities are not currently available, or in a an acute setting prior to obtaining the results of the other tests.

CONCLUSION

From the studies included in this literature review, a family history of CHD can be an independent risk factor for developing CHD, however the results suggests that more work is needed on the subject. In most studies the effect is dependent on the exact content and context of the family history and index individual, but there are few findings that are consistent across the various studies. There appears to be greater risk with a premature compared to a non-premature family history and, and that a family history is a more important risk factor if it includes more than one family member, even if a degree of uncertainty persists even for these two factors. Certain sex-specific effects are observed in several studies, but the results differ to such a degree that is difficult to draw any conclusions. This also applies to other questions such as whether sibling or parental history is more important.

Adding family history to existing risk calculators does not appear to improve their predictive value, but sound arguments, such as cost and accessibility, can still be presented for enquiring into family history in clinical practice. But given how the effect estimates varies with the factors listed above, it is necessary to not treat family history as a binary risk factor of yes or no, and to obtain exact details on the number of affected relatives, at what age the CHD event occurred, and possibly even consider the gender of affected relatives and index individual.

Further research is needed into the causative pathways behind the association between family history and CHD. Socioeconomic position is underexplored as a potential confounding factor, and much remains to be discovered on the role played by genetics.

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