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Review

Family history of coronary heart disease and markers of subclinical cardiovascular disease: Where do we stand?

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ABSTRACT

Objective: The goals of this systematic analysis are to determine the association between family history of coronary heart disease (CHD) and markers of subclinical cardiovascular disease as well as to discuss the inclusion of CHD family history in the frequently used coronary risk prediction algorithms.
Background: Individuals with a family history of CHD are at high risk for developing atherosclerosis and events related to CHD, regardless of the presence of other coronary risk factors. They form a target population that might benefit from primary prevention strategies; however, family history data is not a part of the frequently used risk prediction algorithms.
Methods: Medline and PubMed databases were searched for all studies evaluating the relationship between measures of subclinical atherosclerosis and family history of CHD, published till June 2010.
Results: Thirty-two studies met the above criteria and were included in this review. Coronary artery calcium, carotid intima thickness, vascular function, and inflammatory markers including C reactive protein, fibrinogen, and D-dimer were used as measures of subclinical atherosclerosis. Studies differed in design, demographic data of the population, techniques and validation of family history information. Most studies established a statistically significant relationship between the above markers and family history of CAD; further, the association was noted to be independent of traditional risk factors.
Conclusion: Family history of CAD is associated with markers of subclinical atherosclerosis, and this relationship remains statistically significant after adjusting for traditional risk factors. The above data suggest these individuals should be considered strongly as candidates for assessment of subclinical CVD to further refine risk and treatment goals.

Contents

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1. Introduction

Individuals with a family history of coronary heart disease (CHD) appear to be at a significantly increased risk for events related to CHD [1–7]. As such, they form a potential target population for early aggressive primary prevention strategies. The Framingham Risk Score presently incorporates the conventional cardiovascular risk factors (age, total cholesterol, smoking, HDL cholesterol, and systolic blood pressure) only in its calculation of a 10-year global CHD risk score. The Framingham algorithm does not include family history information as a criterion to guide pharmacotherapy primary prevention, and as such may underestimate risk for developing CHD amongst those with the strongest family histories.

In order to incorporate the prognostic significance of family history data into potential risk stratification strategies, it is important to first correlate family history of premature CHD with existing subclinical atherosclerosis in asymptomatic individuals. Markers of subclinical coronary heart disease include coronary artery calcium (CAC), carotid intima–media thickness, inflammatory markers, and measures of endothelial dysfunction, among others. The presence of a significant association between family history of premature CHD and subclinical atherosclerosis would warrant the development of a strategy to include this risk factor into prediction algorithms such as the Framingham risk score, allowing for timely preventive efforts.

2. Methods

We carried out a systematic review of studies evaluating family history and markers of subclinical atherosclerosis. A computerized literature search was performed through MEDLINE and PubMed databases to identify English-language articles published from January 1, 1980, through June 1, 2010. The keywords utilized for the search in all text fields were “family history of coronary heart disease” alone or in combination with “coronary artery calcium”, “carotid IMT”, or “subclinical atherosclerosis”. Search results were analyzed, and studies were included if they provided data assessing the relationship between family history and measures of subclinical atherosclerosis in asymptomatic adult patients. For this meta-analysis, these measures were established as coronary artery calcium (CAC), carotid intima–media thickness (IMT), vascular reactivity to hormonal stimulation, and systemic inflammatory markers including high sensitivity C reactive protein (hsCRP), fibrinogen, tissue plasminogen activator (t-PA), and D-dimer. We limited the search results to full-text studies published in peer-reviewed journals in the English-language. We also checked the reference lists of all identified studies to locate additional articles not found in the initial electronic search that would be useful for this review. Thirty-two studies were found that met the above criteria and were included in this review.

3. Results

3.1. Family history of premature CHD and coronary artery calcification

Table 1 presents summarized results of all studies evaluating the association between family history of premature MI and coronary artery calcium. Nasir et al. [8] demonstrated that sibling history is more reflective of prevalence of subclinical atherosclerosis as compared to parental history of CHD alone; they reported increased odds ratio for the presence of CAC in participants with family history of premature CHD in siblings (odds ratio of 2.3, 95% CI: 1.7–3.6), compared to parents (odds ratio 1.3, 95% CI: 1.1–1.6), with the highest odds ratio for those with a combined family history (2.5, 95% CI: 1.8–3.3). Taylor et al. [9] demonstrated that a family history of CHD in second-degree relatives is similarly associated with increased prevalence of CAC, with comparable odds ratios of 1.49 (95% CI, 1.05–2.11) for first-degree history, and odds ratio of 1.41 (95% CI, 1.002–1.99 at $p = 0.049$) for a second-degree family history of CHD. Additionally, a family history specifically of premature CHD has been shown to be more strongly associated with CAC than late CHD family history, independent of other risk factors [10]. Other studies have shown that family history has a stronger association with CAC in the presence of metabolic risk factors [11,12]. The relationship between family history of CHD and CAC appears to be stronger in younger adults as opposed to older adults [12,13]. There also is evidence for differential relationships of family history and CAC with regards to race; Caucasians with a positive family history of myocardial infarction show a greater odds ratio for presence of CAC than African–Americans [14].

Bamberg et al. used contrast-enhanced 64-slice coronary MDCT to measure non-calcified atherosclerotic plaque (NCAP), which is considered to be a marker of early atherosclerosis [15]. They established a statistically significant relationship between extent of NCAP and family history of CAD ($p = 0.04$) after adjustment for age, gender and traditional risk factors.

3.2. Family history of premature CHD and carotid intima thickness

Studies focused on the relationship between family history of premature CHD and carotid IMT are listed in Table 2. Wang et al. [16] used validated family history information from the Framingham Heart Study to establish that age-adjusted mean internal carotid IMT in subjects with family history of premature CHD was significantly larger in men and women compared to patients without a family history. Jounala et al. [17] found similar results of greater carotid IMT associated with a positive family history of CHD in a population of Finnish young adults. They also demonstrated that in those subjects with positive family history, carotid IMT correlated strongly with increased number of cardiovascular risk factors. Taraboanta et al. [18] demonstrated that first-degree relatives of patients with angiographically proven CAD had increased carotid IMT and plaque burden, with a combined median thickness of 0.76 mm (interquartile range 0.69–1.01) versus 0.69 mm, (interquartile range 0.60–0.88) in controls ($p < 0.001$) after adjusting for risk factors.

In contrast, Zureik et al. [19] did not find a statistically significant association between common carotid IMT and family history of premature death from CHD (0.66 ± 0.11 mm versus 0.66 ± 0.12 mm; $p = 0.76$). However, they did show an association between family history and the prevalence of atherosclerotic plaques. Bensen et al. [20] used the family risk score, a quantitative measure of family history of CHD, to stratify positive family history