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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

Table 1
Relationship of family history of CHD and coronary artery calcium.

Author/Journal/Year	Study population	Main findings	Comments
Nasir et al., 2004 [8]	$N = 8549$ Age = 52 ± 9 years Gender = 69% men Study population: physician referred	The OR (95% confidence interval) for the presence of CAC • Among men with FH of premature CHD in parents only, in siblings only and combined FH were 1.3(1.1–1.6), 2.3(1.7–3.6) and 2.5(1.8–3.3). • Among women the corresponding ORs were 1.3(1.0–1.8), 2.3(1.7–3.6) and 1.9(1.3–3.1) respectively.	The study emphasizes on the highly significant association between FH of premature CHD and the presence and extent of CAC and also shows that sibling history is more strongly associated with subclinical atherosclerosis as compared to parental history of premature CHD.
Taylor et al., 2004 [9]	$N = 1619$ Age range – 40–50 years Sex – all males Study population: community-based	• The prevalence of any CAC in subjects with no family history was 19.3%, the respective values in those with family history in first-degree relatives, second-degree relatives and both being 26.6%, 26.5% and 30.3%. • The multivariable adjusted odds ratios for any CAC in different categories of family history were: 1.49 (1.05–2.11) at $p = 0.026$ for first-degree only, 1.41 (1.002–1.99) at $p = 0.049$ for second-degree only and 1.68 (1.06–2.66) at $p = 0.026$ for both first- and second-degree. All categories of family history were recognized as independent predictors of CAC.	The authors established the importance of FH of premature CHD in second-degree relatives. They suggested that the duration of CV risk exposure in the first-degree relatives of younger individuals might not be sufficient to cause CHD. With the current narrow definition of positive FH, subjects with affected second-degree relatives fall in the low-risk category and are overlooked. Hence, it's important to consider FH in both first- and second-degree relatives for more accurate CHD screening and primary prevention strategies.
Fornage et al., 2004 [14]	$N = 2959$ Sub-groups (N, age at Year 15, men%): 1. African–Americans (1335, 39.66 ± 3.80, 42.40) 2. Caucasians (1624, 40.76 ± 3.36, 48.77) Study population: CARDIA	In the total sample, parental history of MI was significantly associated with CAC status, OR (95% CI) being 2.14(1.62–2.83). In African–Americans, the relationship was not significant after adjustment with traditional cardiovascular risk factors. In Caucasians the relationship was significant and independent, the unadjusted and adjusted ORs being, 2.46(1.74–3.45) and 2.03(1.40–2.95).	They used a well-characterized bi-racial CARDIA cohort of young asymptomatic adults to establish differential associations of parental history of stroke and MI and CAC prevalence in Caucasians and African–Americans. They also studied maternal and paternal histories of stroke and MI separately and correlated them with CAC status in the offspring.
Michos et al., 2005 [11]	$N = 6141$ Age – 55 ± 9 years Gender = 68% men Study population: physician referred	The OR (95% CI) for presence of CAC >0 among those with and without FH of premature CHD was 3.3(2.4–4.7) and 2.4(2.6–3.3). The interaction was statistically significant ($p < 0.05$).	The study demonstrated that a familial propensity to subclinical atherosclerosis interacts with the presence of >2 metabolic risk factors, magnifying the risks for those exposed to both.
Nasir et al., 2007 [10]	$N = 5347$ Age – 62 ± 10 years Gender = 47% men Population = MESA	• The age–gender–race adjusted OR for CAC >0 comparing FH of premature CHD versus no FH of CHD was 1.94(95% CI 1.64–2.29). • The age–gender and race-adjusted prevalence of CAC >0 was significantly higher with the presence of any family history of premature CHD than for people with no family history of premature CHD among individuals classified as low risk (35% versus 23%, $p < 0.0001$) and among those at intermediate risk (70% versus 60%, $p = 0.01$).	The study observed an association between family history of premature CHD and the presence of any CAC as well as advanced CAC independent of other risk factors and Framingham risk score. These findings were seen in multiple ethnic groups.
Philips et al., 2007 [12]	$N = 2743$ Sub-groups (N, age ± SD, sex) 1. Young i.e. men <45 years and women <55 years (1824, 40.4 ± 6.6, 65.7% female) 2. Old i.e. men >45 years and women >55 years (919, 54.8 ± 5.8, 34% female) Study population: Dallas Heart Study	• In young subjects with premature FHMI, the crude and adjusted odds ratios for CAC were 2.1(95% CI 1.4–3.1, $p = 0.0005$) and 1.8(95% CI 1.1–2.8, $p = 0.02$) respectively. There was no significant relationship between CAC and any FHMI in the older subjects. • The relationship between FHMI and prevalent CAC was not significant in young subjects with 0 or 1 CV risk factors. However, FHMI was significantly associated with higher prevalence of CAC in young subjects with ≥2 risk factors ($p < 0.001$). The interaction between the effects of FHMI and presence of multiple CV risk factors on prevalent CAC was significant (adjusted interaction $p = 0.04$).	The authors demonstrated a differential effect of family history of MI on CAC prevalence depending on the presence or absence of cardiovascular risk factors. They proposed an interaction between positive family history and number of cardiovascular risk factors on the severity of subclinical atherosclerosis as assessed by coronary artery calcium.

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Table 1 (*continued*)

Author/Journal/Year	Study population	Main findings	Comments
Patel et al., 2007 [35]	$N = 2404$ Sub-groups: 1. Young women – n, mean age a) No FHMI – 1162, 40.0 b) FHMI – 165, 41.3 2. Young men – n, mean age a) No FHMI – 977, 40.5 b) FHMI – 100, 40.9 Study population: Dallas Heart Study.	• All subjects with FHMI had a higher prevalence of CAC compared to those without (the respective p values for men and women being 0.029 and <0.0001). FHMI was independently associated with prevalent CAC in women after adjustment for risk factors (adjusted OR, 2.0; 95% CI, 1.0–4.1). In men, the association was moderately attenuated after multivariate adjustment (adjusted OR, 1.7; 95% CI, 0.9–3.2). • FHMI was associated with greater prevalence of CAC in women with FRS estimated 10-yr risk <10% ($p = 0.01$) but not among similar men. In subjects with FRS estimated 10-yr risk ≥10%, there was increased prevalence of CAC with FHMI in men and women, the relationship being statistically significant only in men ($p = 0.01$).	The study demonstrated a significant relationship between FHMI and prevalent CAC in both men and women. The association was independent of cardiovascular risk factors only in women. Also, the difference in cardiovascular risk perception between those with FHMI versus those without was of greater magnitude in men. The authors used these findings to underscore the importance of cardiovascular preventive strategies in women who are often considered as a less susceptible group.
Parikh et al., 2007 [13]	$N = 2035$ Sub-groups (n, mean age, % women): 1. Framingham offspring (797, 63, 56) 2. Third generation (1238, 46, 47) Study population: Framingham Heart Study	• Among the third generation, parental premature CHD as well as CVD was significantly associated with CAC, the respective odds ratios being 2.22(1.22–4.01) and 2.17(1.41–3.33). • Among the Framingham offspring, there was no significant relationship between CAC and parental premature CVD or CHD. • Among the third generation, parental premature CHD was associated with AAC, OR = 1.65(0.99–2.75); $p = 0.05$. There was no such association seen in the offspring. • There was no association between parental premature CVD and AAC in either cohort.	The authors reported a statistically significant relationship of parental premature CHD and CVD with CAC, especially in younger middle-aged adults. They also demonstrated that premature parental CHD was significantly associated with AAC in the same cohort. The study further concluded that paternal premature CVD confers a greater risk compared to maternal disease.
Bamberg et al., 2008 [15]	$N = 195$ Gender: 46.6% females Sub-groups (Age range): 1. No plaque: 49 ± 9 yrs 2. NCAP: 50 ± 6 yrs 3. MCAP: 60 ± 12 yrs 4. CAP: 57 ± 13 yrs	• In linear regression, family history of CAD was significantly associated with the extent of NCAP (β: 0.63, $p = 0.04$) even after adjustment for age, gender and TRF. • The extent of NCAP decreased and the extent of MCAP and CAP increased with age ($p = 0.06$, $p = 0.02$ and $p = 0.13$, respectively).	The authors showed that NCAP (measured by contrast-enhanced 64-slice coronary MDCT) decreased with age, while MCAP and CAP increased. This finding might support the proposition that NCAP is a marker of early atherosclerosis. They further described a relationship between NCAP and family history of CAD.
Rivera et al., 2009 [46]	$N = 1015$ Population: South Korean Age: 53 ± 10 Gender: 64% men	• MDCT was used to measure the presence of coronary artery plaque and characterize any plaque as calcified, mixed, or non-calcified. • In linear regression, family history of CAD was not associated with the presence of plaque, nor was there a significant association with non-calcified plaques.	In analyzing the relation of CHD risk factors with the presence of coronary artery plaques as assessed on 64-slice coronary MDCT, family history did not show a significant association with the presence of any plaque. Extent of NCAP was also not associated with family history in this population.
Scheuner et al., 2010 [37]	$N = 6070$ Gender: 47% men Study population: MESA	• General Cardiovascular Risk Profile (GCRP) accurately predicated CAC in men and women. • Addition of family history data improved identification of individuals with a positive CAC.	In this study, GCRP was used to as a prediction tool for assessing CAC in MESA participants. Inclusion of family history data led to better discrimination and fit of GCRP prediction and also improved the ability to reclassify patients to a higher risk category.

information; they noted a step-wise increase in IMT with increasing FRS in all ethnic groups except African–Americans. The age-adjusted and fully adjusted partial regression coefficients for FRS as an independent predictor of IMT were significant in other ethnic groups but not in African–Americans.

3.3. Family history of premature CHD and inflammatory markers

Family history of premature coronary heart disease has also been linked with inflammatory markers like hsCRP, fibrinogen, and D-dimer (Table 3). Margaglione et al. [21] showed that individuals with a family history of MI had increased odds ratio of 1.72 (95% CI, 1.20–2.45) for plasminogen activator inhibitor-1 4G/4G allele, a gene polymorphism found to be an independent predictor for MI by inactivating endogenous fibrinolysis, and for CRP levels >0.33 mg/L (OR 1.75, 95% CI 1.05–2.91).

Mills et al. [22] demonstrated that adjusted mean values for fibrinogen were higher in healthy male first-degree relatives of individuals with premature CHD, compared to age-matched controls (3.0 g/L versus 2.8 g/L). They also reported that family history of premature CHD remained an independent predictor of increased fibrinogen levels after multiple regression analysis. Robinson et al. [23] evaluated the role of dual family history of MI (at least one parent and sibling) as a predictor of fibrinogen levels. They reported

Table 2
Relationship of family history of CHD and carotid IMT.

Author/Journal/Year	Study population	Major findings	Comments
Zureik et al., 1999 [19]	$N = 1040$ Age = 59–71 years Gender – 40.8% males Study population: elderly volunteers	• Common carotid IMT was not associated with parental history of premature death from CHD (0.66 ± 0.11 mm versus 0.66 ± 0.12 mm; $p = 0.76$) • Age- and sex-adjusted OR of atheromatous plaques (defined as localized echo structures encroaching into the vessel lumen, ≥1 mm thickness) associated with parental history of premature death from CHD was 2.85(95% confidence interval, 1.60–5.08; $p < 0.0001$). Multivariate adjustment for major known CHD risk factors did not markedly alter the results (OR – 2.7; $p < 0.0002$).	The authors established an association between family history of premature CHD death and prevalence of atherosclerotic plaque as assessed by ultrasonography. They also demonstrated that there is no statistically significant relationship between common carotid IMT and family history of premature CHD death.
Cuomo et al., 2002 [47]	$N = 228$ Sub-groups (N, mean age ± SD, gender): 1. Children and adolescents (108, 12.7 ± 3.8, 44.4% males) 2. Young adults (120, 23.8 ± 3.3, 45% males) Study population: Children of patients with premature MI	• Among both age groups, individuals with a parental history of premature MI showed a significantly increased CCA-IMT (mean of combined sites: age 5–18 yrs: 0.45 ± 0.076 mm versus 0.40 ± 0.066 mm in controls; age 19–30 yrs: 0.48 ± 0.077 mm versus 0.45 ± 0.078 mm in controls, $p = 0.007$). • Mean carotid IMT was independently associated with parental history of premature MI in both age groups.	The authors established a significant independent association between parental history of premature myocardial infarction and CCA-IMT. They established that the vascular structural changes transmitted to offsprings from parents with MI could be detected in childhood and adolescence. Validated family history information was used.
Wang et al., 2003 [16]	$N = 1662$ Age (range) = 57(34–83) Gender = 51% women Study population: Framingham Offspring Cohort	• Age-adjusted mean internal carotid IMT in subjects who had at least one parent with premature CHD than in those without a validated parental history of premature CHD were 1.13 mm versus 1.04 mm in men, $p < 0.01$ and 0.92 mm versus 0.85 mm in women, $p = 0.03$. • Fully adjusted mean internal carotid diameters in men and women were 1.12 and 0.92 mm respectively, $p < 0.05$ for both.	The study demonstrated that family history of premature CHD predisposes to enhanced subclinical atherosclerosis as assessed by carotid IMT. They used validated family history information from the original Framingham cohort
Jerrard-Dunne et al., 2003 [48]	$N = 5400$ Age = 55.9 ± 9.7 Gender = 50.6% female Study population: Carotid Atherosclerosis Progression Study	• Positive parental history of stroke was significantly associated with both CCA-IMT and ICA-IMT in the top quartile with odds ratios of 1.32(95% CI 1.10–1.58); $p = 0.003$ and 1.24(95% CI 1.04–1.48); $p = 0.018$ respectively. • In contrast, positive family history of MI is significantly associated with only CCA-IMT in the top quartile, the odds ratios being 1.82(95% CI 1.52–2.19) for all subjects and 2.51(95% CI 1.94–3.25) for subjects ≤60 years; $p < 0.001$ for both.	The study demonstrates a significant association between family history of stroke/MI and IMT independent of conventional risk factors. It also shows the differential effect of family history of stroke versus MI on the specific sites in the carotid arterial tree.
Juonala et al., 2006 [17]	$N = 2265$ Gender = 44.7% males Age range – 24–39 years Study population: community-based	• Individuals with a family history of CHD had higher carotid IMT compared to those without (0.600 ± 0.109 mm versus 0.578 ± 0.089 mm; age- and sex-adjusted P value 0.003). The difference in IMT remained essentially similar after adjustments with current or childhood risk factors. • There were no significant differences in brachial artery FMD and carotid artery compliance in subjects with a family history compared to those without. • Carotid IMT was more strongly associated with the number of risk factors in subjects with family history compared to those without (p for interaction = 0.007).	The authors established that individuals with family history of CHD had a higher carotid IMT compared to those without. They also showed that the effect of traditional risk factors on IMT was enhanced in subjects with a family history of CHD. This observation points towards a significant interaction between genetic and environmental factors.
Bensen et al., 1999 [20]	$N = 12,082$ Age range: 45–64 yrs Sub-groups (n, ethnicity, gender): 1) 1879 African–American females 2) 4944 Caucasian females 3) 1155 African–American males 4) 4104 Caucasian males Study population: ARIC	• Step-wise increase in IMT across the three FRS strata (defined as low <–0.5, mid –0.5 to 0.5 and high >0.5) was seen in all the ethnic-gender groups except African–American men. • The age-adjusted partial regression coefficients for FRS as an independent predictor of IMT were significant in all except African–American males. • Similarly, fully adjusted partial regression coefficients were significant in all except African–American men and women.	The authors demonstrated differential association of CHD FRS and subclinical atherosclerosis as assessed by IMT in various ethnic groups. They suggested that the statistically non-significant association in African-Americans could be attributed to the fact that IMT in this particular ethnic group is probably more so representative of hypertensive changes than atherosclerotic process.

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Table 2 (*continued*)

Author/Journal/Year	Study population	Major findings	Comments
Taraboanta et al., 2008 [18]	$N = 222$, - 65 men, 44.4 ± 11 yrs - 46 women, 44.7 ± 13 yrs Controls: 111 matched controls from M-CHAT, 46.7 ± 10.2 yrs Study population: First-degree relatives of angiographically proven CAD.	• Average total thickness (a combined measure of IMT and plaque burden) was significantly increased in first-degree relatives (FDRs) compared to controls (0.76 mm, interquartile range [IQR] 0.69–1.01 versus 0.69 mm, IQR 0.60–0.88, $p < 0.001$). • Among the non-conventional risk factors, only plasma homocysteine was greater in FDRs than in controls (9.6 mg/L, IQR 8.0–11.1 versus 7.5 mg/L, IQR 6.4–8.7, $p < 0.001$), after adjusting for all confounding variables.	The authors identified an appropriate subject cohort by enrolling the first-degree relatives of patients with angiographically proven early onset CHD. They used matched controls to demonstrate a statistically significant association of increased plaque burden and IMT (both measured by B-mode ultrasound) with family history of CHD.
Chen et al., 2008 [49]	$N = 1073$ Gender: 43% male Population: Young adults from the Bogalusa Heart Study	Internal carotid IMT and composite carotid IMT were greater in patients with a positive parental history of CAD ($p < 0.05$). There was a trend towards greater IMT thickness when patients were divided by race (black and white) for those with a family history of premature CAD.	The authors describe greater carotid IMT among young patients with a positive parental history of CAD, with the greatest significant difference in IMT at the internal carotid site.

significantly higher fibrinogen levels in subjects with dual family history of MI ($p = 0.016$). First-degree male relatives of patients with premature CHD have also been shown to have significantly higher D-dimer, t-PA, and fibrinogen levels compared with controls [24].

3.4. Family history of premature CHD and vascular function

Studies evaluating the relationship between family history of coronary heart disease and endothelial dysfunction are listed in Table 4. Clarkson et al. [25] reported that brachial artery

Table 3
Relationship of family history of CHD and inflammatory markers.

Author/Journal/Year	Study population	Main findings	Comments
Margaglione et al., 2000 [21]	$N = 1048$ Age (range) = 36 (22–66) years Gender = 43.6% males Study population: community-based	Cardiovascular risk factors independently associated with family history of MI in first-degree relatives were age (OR 1.03, 95% CI 1.01–1.05), total cholesterol (OR 1.35, 95% CI 1.11–1.65), plasminogen activator inhibitor-1 4G/4G (OR 1.72, 95% CI 1.20–2.45) and CRP levels >0.33 mg/L (OR 1.75, 95% CI 1.05–2.91).	The authors identified conventional risk factors that were independently associated with family history of MI in a first-degree relative. They studied complex inter-relationships between these factors and concluded that "higher levels of CRP may be a cumulative indicator of the effect of cardiovascular risk factors i.e. hypertension, obesity and hyperlipidemia".
Mills et al., 2002 [22]	$N = 495$ Gender = All males Sub-groups (N, median age): Probands (125, 60 yrs) Relatives (185, 36 yrs) Controls (185, 42 yrs) Study population: community-based	• Plasma fibrinogen levels in male relatives of CHD patients were significantly higher compared to control subjects, (3.0 g/L compared to 2.8 g/L, respectively; $p = 0.01$). • After multiple regression analysis, family history of premature coronary heart disease remained an independent predictor of fibrinogen levels.	The study demonstrates a significant association between family history of premature CHD and plasma fibrinogen levels. The authors did not specify the exact role of fibrinogen in subclinical atherosclerosis. They however stated that fibrinogen might be of particular importance in individuals classified as low risk according to conventional CHD risk scores.
Mills et al., 2002 [24]	$N = 475$ Sex – all males Sub-groups: N, mean age (range): 1. Probands: 125, 60(52–68) 2. Relatives: 175, 36(19–53) 3. Controls: 175, 41(19–64)	• Relatives had significantly higher D-dimer, t-PA, and fibrinogen levels compared with controls ($p < 0.05$ for all), but not PAI-1 levels or insulin resistance • Relative/control status and PAI-1 levels were the leading contributors to t-PA variance, and relative/control status, age and fibrinogen were the only significant contributors in the D-dimer multiple linear regression model.	The authors studied the relationship between markers of the fibrinolytic system and insulin resistance in healthy male relatives of patients with angiographically proven premature CAD. They found elevated levels of fibrin D-dimer, t-PA and fibrinogen in the relatives as compared with controls. The study concluded that fibrinolytic activity is enhanced in healthy relatives of patients with premature CAD.
Robinson et al., 2004 [23]	$N = 170$ Sub-groups – N, mean age(range), % Men: 1. Family history of MI – 34, 61(39–80), 23.5% 2. No family history – 136, 61(39–80), 23.5%	Individuals with a dual family history of MI (at least one parent and sibling) had higher levels of plasma fibrinogen compared to those without any family history ($p = 0.016$). Multivariable linear regression analysis showed that family history of MI ($p = 0.031$) and BMI (0.002) was significant independent predictors of plasma fibrinogen levels.	The study demonstrated an independent and significant association between dual family history of MI and plasma fibrinogen levels. The authors reported that in addition to family history of MI, body mass index was also a significant and independent predictor of plasma fibrinogen levels.
Sailam et al., 2008 [50]	$N = 89$ Gender: 38% men Age: 47 ± 5.3 years Study population: Young adults with premature family history of CHD	Prevalence of hsCRP greater than 3.3 mg/dL was 24% in the study group. The prevalence of a positive CAC score was 38%.	This cross-sectional study of young patients with a low FRS and with a positive family history of premature CHD looked at prevalence of subclinical disease. The authors concluded the degree of burden of subclinical disease was not accurately conveyed by their FRS.
Hamer et al., 2009 [51]	$N = 5946$ Gender: 44.5% men Age: 53.6 ± 12.4 Study population: Scottish Health Survey	Parental history of CVD was associated with greater CRP levels, with dual parental history showing the highest CRP level ($p < 0.001$).	Patients with a positive parental family history showed greater level of established and novel risk factors, including CRP. The study further identified an association with family history and risk for clinical CHD.

flow-mediated dilation (FMD) was significantly impaired in those with a positive family history as compared to controls, (4.9 ± 4.6% versus 8.3 ± 3.5%, respectively, $p < 0.005$). They also noted that the effect of family history was more pronounced when the affected relative had a normal cardiovascular profile ($p = 0.026$).

Gaeta et al. [26] found that subjects with a family history of CHD had reduced flow-mediated brachial-artery reactivity as compared to controls (10.2 ± 6.6% versus 5.7 ± 5%, $p = 0.001$). They also demonstrated that family history subjects had a higher carotid IMT compared to controls (values of combined sites, 0.49 ± 0.08 mm versus 0.44 ± 0.07 mm; $p = 0.004$). Schächinger et al. [27] showed that acetylcholine- (Ach) induced endothelium-dependent blood flow was significantly impaired in patients with family history. However, Hamburg et al. [28] reported that endothelium-dependent brachial artery FMD was impaired only in men with family history of CAD compared with controls (3.2 ± 1% versus 8.1 ± 1.9%, $p = 0.02$), but not in women.

Finally, studies centered on the association of family history with other markers of subclinical atherosclerosis are presented in Table 5. Riley et al. [29] used a young study population to demonstrate a significant and independent relation between family history of MI and increased mean pressure-strain elastic modules, a measure of arterial stiffness. Sdringola et al. [30] used PET scanning to assess the size and severity of myocardial perfusion defects in otherwise asymptomatic individuals and concluded that the perfusion defects were larger in those with family history compared to controls (11 ± 13% versus 1 ± 1%, $p = 0.02$) and larger than those in asymptomatic subjects with comparable risk factors but no family history (11 ± 13% versus 5 ± 6%, $p = 0.02$).

4. Discussion

In this systematic review, we critically evaluated the current body of evidence studying the relationship between FH of premature CHD and subclinical atherosclerosis. Results demonstrated consistent evidence indicating positive FH as an independent predictor of subclinical disease as assessed by several markers such as CAC, carotid IMT, inflammatory markers (CRP, fibrinogen, D-dimer etc.), and flow-mediated dilatation. This suggests that FH of premature CHD may play an important role in screening the asymptomatic population for subsets that might benefit from earlier, more aggressive preventive therapies. There are several barriers,

Table 4
Relationship of family history of CHD and endothelial function.

Author/Journal/Year	Study population	Main findings	Comments
Clarkson et al., 1997 [25]	$N = 100$ Sub-groups (N, age ± SD, male%): 1. Family history subjects (50, 25 ± 8, 64%) 2. Control subjects (50, 25 ± 9, 64%) Study population: community-based	• Brachial artery FMD was 4.9 ± 4.6% in those with a positive family history, compared to 8.3 ± 3.5% in controls ($p < 0.01$). • Among the family history group, those with no risk factors and whose affected relative had normal CV profile had markedly impaired FMD (2.9 ± 3.7% versus 8.3 ± 3.5%). Paired analysis of this group with those whose affected relative had coronary risk factors showed that FMD in the former group was significantly deranged compared to the latter ($p < 0.05$).	The study demonstrated an impaired endothelial dependent dilatation of the brachial artery in individuals with a family history of coronary artery disease. The study also established that endothelial function was greatly impaired in the family history subjects who were free of risk factors and whose relatives had normal cardiovascular profiles.
Schächinger et al., 1999 [27]	$N = 150$ Sub-groups (N, age ± SD, female/male): 1. Negative family history (100, 54 ± 9.6, 34/66) 2. Postive family history (50, 52 ± 12, 19/31)	• The maximal Ach induced coronary blood flow, dose-dependent Ach induced blood flow, and endothelium-independent blood flow increase were significantly impaired in patients with a positive family history ($p < 0.05$ for all). • After multivariate regression analysis only Ach induced endothelium-dependent blood flow was significantly impaired in patients with family history ($p < 0.01$).	The authors established a significant and independent association between positive family history and endothelial dependent coronary blood flow regulation. They also suggested that endothelial dysfunction seen in individuals with positive family history may facilitate progression of atherosclerosis by hampering vascular remodeling, and this process may be mediated by increased plasma homocysteine levels.
Gaeta et al., 2000 [26]	$N = 80$ Sub-groups (N, mean age ± SD, male sex%) 1. Subjects (40, 19.0 ± 5.2, 48%) 2. Controls (40, 19.2 ± 5.3, 48%)	• The individuals with a parental history of premature myocardial infarction had reduced flow-mediated brachial-artery reactivity as compared to controls (10.2 ± 6.6% versus 5.7 ± 5%, $p < 0.01$). • The subjects with family history had a greater carotid IMT compared to controls (values of combined sites, 0.49 ± 0.08 mm versus 0.44 ± 0.07 mm; $p < 0.01$). • Brachial-artery reactivity and IMT were inversely correlated in subjects with family history ($p < 0.01$) but not in controls	The study showed that both brachial-artery reactivity and carotid IMT were significantly and independently associated with a parental history of premature myocardial infarction. The authors established a significant negative correlation between brachial-artery reactivity and carotid IMT in subjects with a parental history of premature MI.
Hamburg et al., 2004 [28]	$N = 62$ Sub-groups (N, age ± SD): 1. Men a) Family History (15, 31 ± 2) b) Controls (13, 33 ± 1) 2. Women a) Family history (19, 30 ± 1) b) Controls (15, 31 ± 1)	• Endothelium-dependent brachial artery FMD was impaired in men with family history of CAD compared with controls ($p < 0.05$), but not in women. • There was a significant interaction between family history and gender ($p < 0.05$).	The study shows a significantly impaired FMD in males with positive family history compared to controls. In contrast, no such association was seen in women with positive family history. Therefore, the authors demonstrated the protective effect of female gender on the endothelial dysfunction seen in those with family history of CAD.
Bulut et al., 2009 [52]	$N = 56$ Age range: 23–31 Gender: 100% male Sub-groups: Positive family history of CHD versus controls Study group: Healthy German male volunteers	• Non-significant trend towards decreased brachial-artery reactivity to hyperemia and nitroglycerin for men with a positive premature family history of CHD. • The positive family history group had an increased circulating endothelial microparticles ($p < 0.05$).	In this study, the authors found young men with a positive family history of CHD had increased circulating endothelial microparticles, a marker for endothelial damage. However, there was no significant difference in FMD in the 2 groups.

Table 5
Relationship of family history of CHD and other markers of subclinical atherosclerosis.

Author/Journal/Year	Study population	Main findings	Comments
Riley et al., 1986 [29]	$N = 109$ Sex – 45.8% males Age range – 10–17 years	• The study subjects were divided into high-risk and low-risk categories by using systolic blood pressure and total cholesterol as the criteria. After controlling for race, sex and age, Ep, the mean pressure–strain elastic modulus (a measure of stiffness) in the high-risk group was 5.1 kPa higher than in the low-risk group (one-sided p value $= 0.03$). • Family history of MI was significantly related to increased Ep levels ($p < 0.05$), independently of race, sex, age, total cholesterol and systolic blood pressure.	The study demonstrated that family history of myocardial infarction is associated with reduced arterial elasticity at a young age. The authors also reported an association between reduced carotid elasticity and traditional cardiovascular risk factors.
Sdringola et al., 2001 [30]	$N = 90$ Sub-groups (N, age): 1. Index cases (10, 50 ± 22) 2. Controls (18, 66 ± 8) 3. Asymptomatic relatives (32, 44 ± 11) 4. No family history (30, 55 ± 8)	• The size of perfusion defects was larger in those with family history compared to controls (11 ± 13% versus 1 ± 1%, $p = 0.02$) and larger than those in asymptomatic subjects with comparable risk factors but no family history (11 ± 13% versus 5 ± 6%, $p = 0.02$). • The severity of perfusion defects did not differ in those with family history compared to matched controls without family history.	The authors worked on the relationship of extent and severity of coronary perfusion defects with family history. They observed that family history of CAD was associated with larger defects but not with increased disease severity.

however, that have precluded the incorporation of FH in the primary prevention guidelines for CAD.

Among the studied markers of subclinical CVD, coronary artery calcium and carotid IMT demonstrated strong associations with FH in terms of the magnitude of odds ratio (approximately 2–3). A majority of the studies demonstrated a significant relationship between FH of premature coronary heart disease and CAC which was independent of conventional cardiovascular risk factors. However, Philips et al. reported that FH was not significantly associated with CAC in older individuals [12]. Nevertheless, they also suggested that their study could have been affected by survivor bias and competing risk leading to the above mentioned results. Fornage et al. showed that although the relation between family history of MI and CAC was significant in both Caucasians and African–Americans, adjustment with CV risk factors attenuated the association in the latter [14]. Those results point towards differential impact of FH and traditional cardiovascular risk factors in different ethnic groups.

Among the studies using IMT as a parameter of subclinical disease, 71% established that FH is a significant and independent predictor of carotid-IMT. Zureik et al. however, did not find any statistically significant association between parental death from MI and carotid IMT [19]. The authors also stated that the results could have been hampered by survivor and self-selection bias in addition to possible misclassification of subjects according to parental history of premature death from MI. Also, Bensen et al. reported that the relationship between family risk score and carotid IMT was largely attributable to traditional risk factors in African–American men and women [20]. They noted that the incongruent finding in a particular ethnic group could possibly be reflective of inaccurate reporting of family composition, medical history or even differences in pathophysiologic mechanisms.

The pathogenesis of coronary heart disease involves an interplay of several biochemical processes, namely lipid metabolism, inflammatory response, endothelial function, platelet function, thrombosis, fibrinolysis, homocysteine metabolism, insulin sensitivity, and blood pressure regulation [31]. Although each process is influenced by environmental factors, it entails systematic function of several receptors, chemical messengers and signaling pathways that can be altered by genetic variation. It is reasonable to state that family history of premature heart disease is indicative of genetic susceptibility to CHD. Individuals from the same family share similar genetic, environmental, behavioral and cultural factors, which might have a bearing on development of CHD [6]. Predilection to develop CHD can be attributed to a multitude of risk factors that are recognized as either established or emerging [6]. Among established risk factors are increased LDL cholesterol, decreased HDL cholesterol, cigarette smoking, hypertension, diabetes and age. The emerging risk factors are so called because of inadequate data describing their potential role as predictors of CHD and include elevated small dense LDL particles, hyperhomocysteinemia, CRP, and IL-6, among several others. However, quantifying the exact risk posed by each factor to CHD development and progression has been difficult. In this setting, family history of premature CHD represents a relatively simple and cost-effective means to identify individuals likely to benefit the most from timely implementation of preventive strategies [32].

According to the current NCEP ATP III guidelines, family history of premature coronary heart disease in a first-degree relative is included among major risk factors that modify LDL-goals [33]. Similarly, the Prospective Cardiovascular Munster (PROCAM) score as well as the Reynolds risk score include premature family history of CHD as a criterion in their risk assessment; however their definition of a positive family history includes only a single-age cutoff for men and women (age 60) and the Reynolds score does not account for sibling history [34,35]. In the European Society of Cardiology and European Atherosclerosis Society guidelines on dyslipidemia, family history of premature CHD is mentioned as a separate and independent risk factor for cardiovascular disease, although it is not included in the main risk function tables [36]. However, family history is conspicuously absent in the universally followed Framingham Risk Score for coronary risk stratification [33]. We have described the findings from 3 large multi-ethnic studies (namely, MESA [10,37], Framingham Heart Study [13,16], and Dallas Heart Study [38]) that reported an independent and statistically significant association between FH of premature CHD and subclinical atherosclerosis. These and other findings presented in our systematic review of relevant literature provide evidence that subjects with a positive family history constitute a higher risk group, and are attractive candidates for more intense primary prevention efforts. The current risk prediction and assessment models, and in turn, the U.S., European, and other world-wide guidelines, should be re-evaluated to more fully reflect this link.

5. Limitations

It is important to consider the potential limitations of family history for its inclusion in risk prediction algorithms. One concern

is the validity of self-reported family history data. Several studies have evaluated self-report of family history with direct validation [32,39,40]. In a large validation study conducted by Bensen at al [39] using relative's self-report as the standard, it was shown that the proband's report was 87% sensitive and 99% specific for spouse's CHD status, 85% sensitive and 93% specific for a parent's CHD status, and 81% sensitive and 98% specific for a sibling's CHD status [41]. Moreover, studies have demonstrated [39,42,43] that variables such as gender, personal history of CHD or having a CHD risk factor such as diabetes, hypertension or hypercholesterolemia do not influence accuracy of family history report [44]. However, older age has been associated with a more inaccurate account of family history [39,43].

Family Risk Score is a method that characterizes family history information in terms of severity by expressing it as a quantitative variable [32]. It requires detailed family history information, which is often considered cumbersome to obtain. Moreover, this data has been typically used to support an already existing diagnosis of CHD [45].

In addition, several lacunae exist in the current information on feasibility, validity and utility of family history data and ethical, legal and social issues that may surface [6]. Further prospective studies are needed to evaluate the efficacy of family history data in engineering preventive strategies that have clear benefits in terms of reduction of CHD incidence.

6. Summary

Family history of coronary artery disease reflects genetic predisposition to CHD and can be utilized as a simple and valuable tool to delineate individuals who may benefit from assessment of subclinical atherosclerosis and who are most likely to benefit from timely prevention strategies. There are nonetheless several gaps in our information on validity, feasibility and utility of family history data. Further research will be helpful in evaluating the application of family history data in reducing cardiovascular events.

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